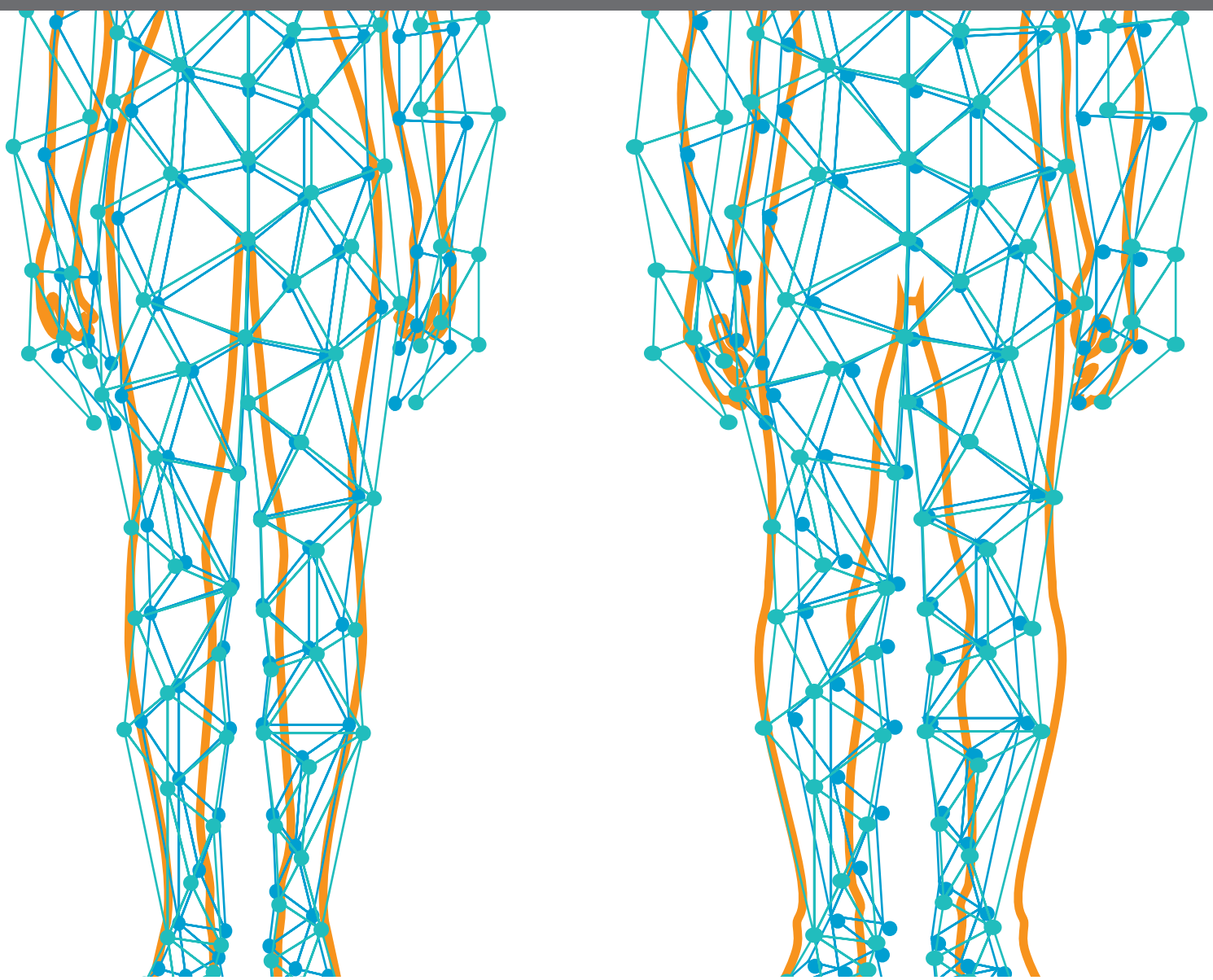
BIOETHICS AMIDST THE COVID-19 PANDEMIC

EDITED BY: Maysa Al-Hussaini, Asem H. Mansour, Haavi Morreim, Ma'n H. Zawati and Thalia A. Arawi

PUBLISHED IN: Frontiers in Medicine, Frontiers in Public Health and Frontiers in Psychiatry



frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88974-078-9
DOI 10.3389/978-2-88974-078-9

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BIOETHICS AMIDST THE COVID-19 PANDEMIC

Topic Editors:
Maysa Al-Hussaini, King Hussein Cancer Center, Jordan
Asem H. Mansour, King Hussein Cancer Center, Jordan
Haavi Morreim, University of Tennessee Health Science Center (UTHSC), United States
Ma'n H. Zawati, McGill University, Canada
Thalia A. Arawi, American University of Beirut Medical Center, Lebanon

Citation: Al-Hussaini, M., Mansour, A. H., Morreim, H., Zawati, M. H., Arawi, T. A., eds. (2022). Bioethics Amidst The COVID-19 Pandemic. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88974-078-9

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frontiers in Medicine

EDITORIAL
published: 26 November 2021
doi: 10.3389/fmed.2021.778146

Editorial: Bioethics Amidst the COVID-19 Pandemic

Maysa Al-Hussaini[1], Asem H. Mansour[1], Thalia A. Arawi[2], Ma'n H. Zawati[3] and Haavi Morreim[4]*

[1] Human Research Participants Protection (HRPP) Office, King Hussein Cancer Center, Amman, Jordan, [2] Faculty of Medicine, American University of Beirut, Beirut, Lebanon, [3] Centre of Genomics and Policy, McGill University, Montreal, QC, Canada, [4] University of Tennessee Health Science Center (UTHSC), Memphis, TN, United States

Keywords: bioethics, COVID-19, resource allocation, clinical trials, do not resuscitate (DNR), cancer, psychological well-being, informatics

Editorial on the Research Topic

Bioethics Amidst the COVID-19 Pandemic

March 2020 witnessed the WHO's declaration of COVID-19 as a global pandemic. It is a date that has imprinted history. Almost 2 years later and the pandemic remains in many ways a global mystery: how did it come to be? Will there be new waves and additional mutations? Is it man-made and thus a form of biological warfare or is it released to trick governments and people into buying vaccines to increase the profit of pharmaceutical companies with trillions of dollars that will be used to subsidize more wars? Almost 2 years now and a plethora of questions continue to be raised in connection to the vaccine: which one is better? Should there be a booster shot? Will it tamper our DNA? Does it really protect from the pandemic? Does it work with new variants?

Scarcity of resources, beds, and ventilators brought to light new moral conundrums for clinicians and ethicists: How should scarce medical resources be allocated? Should the elderly be sacrificed? Is a unilateral Do-Not-Resuscitate (DNR) acceptable from the moral standpoint? etc.

The above were enough for us to see the cruciality of delving more into bioethical concerns during pandemics which led to a call that we issued on May 2020 at the earliest stages of the pandemic. We received global contributions tackling different issues or similar ones from different cultural backgrounds. Their contributions made the content rich with information and triggered more thinking about ethical dilemmas and how to solve them. Most importantly, it made us realize how important bioethics is during pandemics globally and how ethical concerns became more central in medical care globally, regardless of the economic divide, cultural differences, and/or political ideologies.

The contributions were divided into six main entries/themes:

1. *Care offered to patients, regardless of their ailment.* As caring for patients suffering from cancer began as an enigma in the early stages of the pandemic, Al-Tabba et al. address this issue in their article calling for practical measures that are applicable in different settings and with different resource capacities basing their work on the experience of the King Hussein Cancer Center in Jordan.
   In their "Do-Not-Resuscitate and COVID-19; the Ethical Dilemma and Suggested Solutions," Sultan et al. discuss the issue of whether physicians or the healthcare system can take a unilateral decision about withdrawal of life support in situations of resource scarcity. In their "The Care for non-COVID-19 Patients: A Matter of Choice or Moral Obligation?" Hassan and Arawi address the ethical burdens that arise from the need to respond to non-COVID-19 patients who are often left untreated during the pandemic.

OPEN ACCESS

Edited and reviewed by:
Steffen Thirstrup, NDA Advisory Services Ltd., United Kingdom

****Correspondence:***
Maysa Al-Hussaini
mhussaini@khcc.jo

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *16 September 2021*
Accepted: *05 November 2021*
Published: *26 November 2021*

Citation:
Al-Hussaini M, Mansour AH, Arawi TA, Zawati MH and Morreim H (2021) Editorial: Bioethics Amidst the COVID-19 Pandemic. Front. Med. 8:778146. doi: 10.3389/fmed.2021.778146

2. *The moral obligation of healthcare workers amidst moral dilemmas:* Under this theme, Maraqa et al. adopt a "Mixed Method Study to Explore Ethical Dilemmas and Health Care Workers' Willingness to Work Amidst COVID 19 Pandemic in Palestine." As the important role nurses play in the care of patients is often downsided, Alloubani et al. address the issue in their article the ethical role the nurses' play during the pandemic, finding among other conclusions that nurses in the survey believe nurses have an obligation to care for patients regardless of their medical diagnosis. Alahmad et al. tackle the "Ethical Challenges Related to the Novel Coronavirus (COVID-19) Outbreak" after conducting in-depth interviews with health professionals from Saudi Arabia.
3. *The fair allocation of scarce medical resources* appeared as another theme, with Huseynov et al. discussing the "General Public Preferences for Allocating Scarce Medical Resources during COVID-19." In their "Fair allocation of the scarce medical resources, a comparative study from Jordan, Al Hussaini et al. surveyed physicians, medical students, allied health practitioners, religion scholars and laypeople revealing how each group prioritizes the distribution of resources. Using Fuzzy Logic, Saadah et al. propose a framework on "Whom Should Be Saved?" and Alhalaseh et al. discuss the allocation of already scarce medical resources arguing that solutions that might work in countries with limited resources are different from those usually adopted by the better-resourced countries.
4. *Clinical Trials*: This section highlights some of the major obstacles behind the continuity of clinical trials with Hashem et al. address the major obstacles behind the continuity of clinical trials in their article "Obstacles and Considerations Related to Clinical Trial Research during the COVID-19 Pandemic." Abdelhafiz et al. raise the issue of factors affecting participation in trials in their article "Factors influencing participation in COVID-19 clinical trials: a multi-national study" and argue that during the pandemic, willingness to participate in clinical trials was affected by such factors as the scientific and ethical character of the trial, an opportunity to protect the family from the virus, access to additional healthcare, and the ability to return to community normalcy. Li et al. address the "Deficiencies in planning interventional trial registration of COVID-19 in China," observing that the lack of appropriate planning resulted in over-registration of COVID-19 trials in China, with the result that the number of patients needed by the trials was actually greater than the number of newly-diagnosed patients.
5. *Psychological well-being*. The effect of the pandemic, lockdown, and quarantine on the psychological and mental well-being of various sectors in the community, and the ethical obligations toward those who are at risk formed the fifth theme. Guo et al. report the plethora of "Adverse psychological reactions and psychological aids for medical staff during the COVID-19 outbreak in China." This is especially important as the experience of China was leading the world, although anxiety and the psychological impact were similar regardless of the geographic location. Saadeh et al. address this issue in her article on 6,157 Jordanian undergraduate university students, and how large increases in smartphone use becomes a concern, as 27.6 and 57.2% reported an increase and great increase, respectively, of their smartphone, with around 42% using theirs for more than 6 hours a day. Of interest, students' living environment proved significant in this study, as those, e.g., who lived in rural areas or in a home with a garden rather than in an apartment experienced lesser increases in their mobile phone use. Of interest, Yadav et al. also address the "Anxiety and Depression among Health Sciences Students at Home Quarantine during COVID-19 Pandemic in selected Provinces of Nepal" again addressing similarities of concerning issues in different countries. They too found, among other things, that factors such as place of residence significantly affected respondents' levels of depression and anxiety. Saaddeh et al. also look into the "Effect of COVID-19 quarantine on the sleep quality and the depressive symptom levels of university students in Jordan during the spring of 2020," when the long-term lockdown was imposed on the country. The sleep quality of three-quarters of the participants was negatively affected by the extended quarantine. In addition, depressive symptoms were reported in 71% of participants, including 34% with moderate and 37% with high depressive symptoms scores. Meanwhile, Li et al. investigate the "Psychological distress, social support, coping style, and perceived stress among medical staff and medical students in the early stages of the COVID-19 epidemic in China." Guo et al. elegantly performed a systematic review and meta-analysis on the "Depression and coping styles of college students during COVID-19 epidemic." The number of articles under this theme clearly indicates the ethical obligation toward implementing effective measures to help mitigate the psychological effect of the imposed quarantine and lockdown, particularly among college and university students.
6. *The role states and governments played during the pandemic*. Some of these interventions were ethically disputed. Dave and Gupta address an essentially debatable issue of policies mandating tracking systems that were used during the pandemic and how ethical these were. Through deploying the Faden-Shebaya framework, which is used to justify public health interventions, the authors argue that while theoretically justified, it is difficult to defend a mandatory policy in practice. Freitas et al. write A reflection on the main ethical obstacles related to the strategic action "o brasil conta comigo." Edlinger et al. ask "Is it legitimate for society to intervene in the way citizens live their lives when the cost of health care has to be borne by the general public?—General considerations and special implications during the Covid-19 pandemic."
Lastly, Odeh et al. came up with an interesting classification "iOntoBioethics: A Framework for the Agile Development of Bioethics Ontologies in Pandemics, Applied to COVID-19," a unique and unprecedented work that will set the stage toward an artificial intelligence-based classification of the (bio)ethical published literature, which might contribute toward setting the stage for "Bioethics Informatics."

It was an immense pleasure for us to co-edit this Frontier's issue. Nonetheless, bioethical dilemmas continue to arise almost every day along with ethical discussions, and debates. As long as

the pandemic is still active, there will always be emerging new bioethical issues, the latest of which is related to the vaccine itself. We contend that several of the aforementioned themes can be extrapolated to fit discussions related to the vaccine, including the fair prioritization of this invaluable medical resource, the anxiety and hesitancy among some to receive the vaccine, and the role of governments in enforcing vaccination among its citizens.

We hope you will find this issue useful and enlightening.

AUTHOR CONTRIBUTIONS

MA-H, AM, TA, MZ, and HM contributed to the article and approved the submitted version.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

PERSPECTIVE
published: 07 October 2020
doi: 10.3389/fmed.2020.561168

Ethical Considerations for Treating Cancer Patients During the SARS-CoV-2 Virus Crisis: To Treat or Not to Treat? A Literature Review and Perspective From a Cancer Center in Low-Middle Income Country

Amal Al-Tabba'[1†], *Maysa Al-Hussaini*[2,3†], *Razan Mansour*[4], *Hala Sultan*[5], *Hikmat Abdel-Razeq*[5,6] *and Asem Mansour*[3,7*]

[1] Independent Researcher, Amman, Jordan, [2] Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, Amman, Jordan, [3] Human Research Participants Protection Office, King Hussein Cancer Center, Amman, Jordan, [4] Office of Scientific Affairs and Research, King Hussein Cancer Center, Amman, Jordan, [5] University of Jordan School of Medicine, Amman, Jordan, [6] Department of Medical Oncology, King Hussein Cancer Center, Amman, Jordan, [7] King Hussein Cancer Center, Amman, Jordan

Providing routine healthcare to patients with serious health illnesses represents a challenge to healthcare providers amid the SARS-CoV-2 pandemic. Treating cancer patients during this pandemic is even more complex due to their heightened vulnerability, as both cancer and cancer treatment weaken the immune system leading to a higher risk of both infections and severe complications. In addition to the need to protect cancer patients from unnecessary exposure to SARS-CoV-2 infection during their routine care, interruption, and discontinuation of cancer treatment can result in negative consequences on patients' health, in addition to the ghost of rationing healthcare resources in high demand during a global health crisis. This article aims to explore the ethical dilemmas faced by decision-makers and healthcare providers caring for cancer patients during the SARS-CoV-2 pandemic. This includes setting triage criteria for non-infected cancer patients, fairly allocating limited healthcare resources between cancer patients and SARS-CoV-2 patients, prioritizing SARS-CoV-2 treatment or vaccine, once developed, for cancer patients and non-cancer patients, patient-physician communication on matters such as end-of-life and do-not-resuscitate (DNR), and lastly, shifting physicians' priorities from treating their own cancer patients to treating critically ill SARS-CoV-2 infected patients. Ultimately, no straightforward decision can be easily made at such exceptionally difficult times. Applying different ethical principles can result in very different scenarios and consequences. In the end, we will briefly share the experience of the King Hussein Cancer Center (KHCC), the only standalone comprehensive cancer center in the region.

Keywords: pandemic, ethics, cancer care, guidelines, SARS-CoV-2, COVID-19

OPEN ACCESS

Edited by:
Mette Due Theilade Thomsen, PIP Adviser, Denmark

Reviewed by:
James Whiteford McBlane, Medicines and Healthcare Products Regulatory Agency, United Kingdom
Frits Lekkerkerker, Consultant, Netherlands
Samir Sami Amr, Istishari Hospital, Jordan

***Correspondence:**
Asem Mansour
amansour@khcc.jo

[†] *These authors have contributed equally to this work*

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *11 May 2020*
Accepted: *03 September 2020*
Published: *07 October 2020*

Citation:
Al-Tabba' A, Al-Hussaini M, Mansour R, Sultan H, Abdel-Razeq H and Mansour A (2020) Ethical Considerations for Treating Cancer Patients During the SARS-CoV-2 Virus Crisis: To Treat or Not to Treat? A Literature Review and Perspective From a Cancer Center in Low-Middle Income Country. Front. Med. 7:561168. doi: 10.3389/fmed.2020.561168

INTRODUCTION

In December 2019, the World Health Organization (WHO) in China was informed of cases of pneumonia of an unknown cause detected in Wuhan City, Hubei Province, now known as the novel coronavirus or SARS-CoV-2 (1). As of 07th August 2020, the virus had made its way to 188 countries causing a pandemic with almost 20 million confirmed cases (2). This rapid spread of the virus around the world spared healthcare providers and healthcare systems very little time, resulting in multiple medical and ethical mysteries, they are still struggling to unravel. Cancer care amidst the pandemic is in itself a mystery; as patients with cancer carry a higher risk of SARS-CoV-2 infection, Intensive Care Unit (ICU) admissions or even death compared with other patients (3). For example, after applying universal microbiologic screening for asymptomatic cancer patients in one hospital in the United Arab Emirates (UAE), 8.24% (7 out of 85) of the tested patients were positive for SARS-CoV-2 (4).

"What a terrible time to have cancer," read the headline of an article at The Guardian written by Heather Chaney in her weekly column, describing difficulties in the treatment journey in the middle of the SARS-CoV-2 pandemic (5). Cancer patients and their families experience substantial concern and fear of this virus.

Just like cancer and its treatment may decrease the patient's ability to fight the infection, protective measures against the virus and limitation of health resources may also cause a delay in cancer treatment too. Thus, many ethical questions arise including how to sort cancer patients into prioritized and agreed-on categories? Who is to be treated first, patients with urgent medical needs, or those with the best chances of survival? Are there specific guidelines for cancer care during crisis and shortage of supplies? And what specific guidelines are there for healthcare providers treating cancer patients?

LITERATURE REVIEW

Thereupon, some strategies and guidelines were proposed for cancer patients amid the SARS-CoV-2 crisis (6, 7). Triaging patients was of the most concerning challenge as identification of symptomatic patients with a suspicion of infection is crucial for the protection of other patients and healthcare providers. Screening points were allocated to entry sites of some cancer centers for patients, visitors, and even healthcare providers. Limitation of the number of visitors and providers was also recommended, and early-detection screening appointments were deferred. Regarding outpatient clinic visits, many were rescheduled or substituted with telemedicine when possible.

One controversial strategy was the intentional postponing of adjuvant chemotherapy, radiotherapy, stem cell transplant procedures and elective surgeries, which raises a question on how to balance a delay in cancer management against the risk of infection with SARS-CoV-2. This becomes even more baffling in certain aspects of cancer treatment. For example, hematologic malignancies require prompt diagnosis and treatment, whereas, most solid cancers may have longer treatment windows. Is it ethical to delay treatment in older patients and patients with metastatic disease where time is critical and delay may lead to worsening status and loss of the opportunity to treat? Additionally, should these decisions be unilateral, even when patients and physicians do not meet face-to-face?

Some cancer patients, in particular, are at a higher risk of becoming seriously ill if infected with SARS-CoV-2, these include patients receiving immunosuppressive therapy, targeted cancer treatments, recent bone marrow or stem cell transplants, or who are still taking immunosuppressive drugs in addition to patients with hematological malignancies (8). Revisiting the treatment plan for such patients is advisable. Patients and their healthcare providers should discuss whether the risks of beginning or continuing their cancer treatment could outweigh the benefits (8).

Moreover, as the number of SARS-CoV-2 cases is exponentially increasing, hospitals and cancer centers should expect a surge of cases into their wards, depleting its beds, equipment, and resources. Healthcare providers and patients will be faced with difficult choices. Therefore, setting an ethical triage criterion for non-infected cancer patients is of utmost importance.

TRIAGING

Several triage strategies can be followed, each is based on a different ethical justification. **Table 1** lists the different triaging strategies that could be followed as per the WHO (9).

Applying different triaging strategies to the same population (i.e., non-infected cancer patients) will give very different results all of which can be considered ethically justifiable. Health status and comorbidities, site and stage of cancer, and type of treatment and prognosis, all have to be weighed against the ethical principle adopted. For example, if a "protect the most vulnerable" strategy was applied, older patients with more aggressive cancer types and late-stage diagnoses whose treatment will only prolong their life expectancy for a limited time will be prioritized, albeit with potential consumption of the limited available medical resources, which may otherwise be directed to treat and save larger numbers of patients with better overall survival and better chances of benefiting from the treatment of their cancer in the long term. On the contrary, in the "save the greatest number of people" strategy, cancer patients with early stages, less aggressive cancer types, less complicated treatment regimens and higher chances of survival will be at the top of the list, which in the long run would result in more lives saved. For example, an old female patient with breast cancer with metastasis and co-morbidities would serve a good example for the third scenario i.e., protecting the most vulnerable. Whereas a young, otherwise healthy breast cancer patient with localized disease who stands a good chance of benefitting from an early treatment would fit into the first scenario; saving the most lives. Patients who have not yet been diagnosed or have been newly diagnosed and have not started treatment will be neglected in the "first come, first serve" strategy regardless of how life-saving the treatment can be to their case.

The United Kingdom's (UK) National Health Services (NHS) has issued its clinical guideline for the management

TABLE 1 | Different triage strategies (9).

Triage criteria	Ethical justification
1-Save the greatest number of people	This criterion directs us to give priority in allocation decisions to the category or categories of people that will result in the most lives saved. This usually involves allocating resources on the basis of a patient's prognosis and the amount of resources and/or personnel that will be required to sustain life.
2-First come, first served	This criterion directs us to give priority in allocation decisions to whoever accesses the resource first, independent of the severity of medical need or the needs of others. This criterion is based on the assumption that everyone has an equal ability to access the relevant resource—a presumption that is questionable during an emergency.
3-Protect the most vulnerable	This criterion directs us to give priority in allocation decisions to the most vulnerable category or categories of people in an emergency. Depending on the nature of the emergency, the most vulnerable groups could include infants, elderly people, pregnant women or people with particular medical conditions (e.g., obesity). If this criterion is chosen, we should give priority for live-saving interventions to members of vulnerable groups.
4-Equal access	This criterion directs us to give everyone (or at least similar categories of people) equal access to the benefit(s) of a resource when it is distributed, or at least an equal chance of accessing the benefits. If this criterion is chosen, no person should be given priority over another: each person is as important as any other, and all have an equal claim to access the resource. This differs from the "first come, first served" criterion in that its aim is to provide equal access to as many people as possible, not just those who access it first. Another version of this criterion is that if equal access cannot be given, an equal chance to access the benefits should be given; for instance, through a lottery process in which people who will receive a resource are chosen randomly.
5-Priority for the most important	This criterion directs us to allocate resources in such a way as to ensure that the individuals who are most important for society are given priority for access. The importance of individuals is usually understood in terms of who contributes most to the stability and protection of society (e.g., first responders, health care workers). If this criterion is chosen, individuals judged as having such a social function are given priority over those who do not.

of non-coronavirus patients requiring acute cancer care on 23rd March 2020. The guideline discussed different priority levels for categorizing patients undergoing surgery, patients on systemic anti-cancer treatments and patients on radiation therapy (**Table 2**) (8). It can be assumed that the NHS guidance has followed the "protect the most vulnerable" strategy for patients undergoing surgery as this would be judged based on the "emergency status" but a "save the greatest number of people" strategy for patients on systematic anti-cancer treatments as this would "result in the most lives saved" and a mix of both strategies for patients on radiation therapy.

The American Society of Clinical Oncology (ASCO) has created a series of Frequently Asked Questions (FAQs) to guide oncologists in their clinical practice during the SARS-CoV-2 pandemic (7). Other organizations have released guidance for specific cancer types, such as the American Society of Breast Surgeons (10, 11), the American Society of Hematology (12), and

TABLE 2 | National Health Services (NHS) clinical guidelines for the management of non-coronavirus cancer patients (8).

Priority level	Patient group
	Patients undergoing surgery
Priority level 1a	Emergency—operation needed within 24 h to save life
Priority level 1b	Urgent—operation needed with 72 h Based on urgent/emergency surgery for life-threatening conditions such as obstruction, bleeding, and regional and/or localized infection permanent injury/clinical harm from the progression of conditions such as spinal cord compression
Priority level 2	Elective surgery with the expectation of cure, prioritized according to surgery within 4 weeks to save life/progression of disease beyond operability based on • urgency of symptoms • complications such as local compressive symptoms • biological priority (expected growth rate) of individual cancers
Priority level 3	Elective surgery can be delayed for 10–12 weeks will have no predicted negative outcome.
	Patients on systemic anti-cancer treatments
Priority level 1	• Curative therapy with a high (>50%) chance of success. • Adjuvant (or neo) therapy which adds at least 50% chance of cure to surgery or radiotherapy alone or treatment given at relapse
Priority level 2	• Curative therapy with an intermediate (20–50%) chance of success. • Adjuvant (or neo) therapy which adds a 20–50% chance of cure to surgery or radiotherapy alone or treatment given at relapse
Priority level 3	• Curative therapy of a low chance (10–20%) of success • Adjuvant (or neo) therapy which adds 10–20% chance of cure to surgery or radiotherapy alone or treatment given at relapse • Non-curative therapy with a high (>50%) chance of >1 year of life extension.
Priority level 4	• Curative therapy with a very low (0–10%) chance of success. • Adjuvant (or neo) therapy which adds a <10 chance of cure to surgery or radiotherapy alone or treatment given at relapse • Non-curative therapy with an intermediate (15–50%) chance of > 1-year life extension.
Priority level 5	• Non-curative therapy with a high (>50%) chance of palliation/temporary tumor control but <1-year life extension.
Priority level 6	• Non-curative therapy with an intermediate (15–50%) chance of palliation or temporary tumor control and <1-year life extension.
	Patients on radiation therapy
Priority level 1	• Patients with category 1 (rapidly proliferating) tumors currently being treated with radical (chemo)radiotherapy with curative intent where there is little or no scope for compensation of gaps. • Patients with category 1 tumors in whom combined External Beam Radiotherapy (EBRT) and subsequent brachytherapy is the management plan and the EBRT is already underway. • Patients with category 1 tumors who have not yet started and in whom clinical need determines that treatment should start in line with current cancer waiting times.
Priority level 2	• Urgent palliative radiotherapy in patients with malignant spinal cord compression who have a useful salvageable neurological function.
Priority level 3	• Radical radiotherapy for Category 2 (less aggressive) tumors where radiotherapy is the first definitive treatment. • Post-operative radiotherapy where there is known residual disease following surgery in tumors with aggressive biology.

(Continued)

TABLE 2 | Continued

Priority level	Patient group
Priority level 4	• Palliative radiotherapy where the alleviation of symptoms would reduce the burden on other healthcare services, such as hemoptysis.
Priority level 5	• Adjuvant radiotherapy where there has been complete resection of disease and there is a <20% risk of recurrence at 10 years, for example most ER positive breast cancer in patients receiving endocrine therapy. • Radical radiotherapy for prostate cancer in patients receiving neo-adjuvant hormone therapy.

the Society of Surgical Oncology (13). Similarly, the European Society for Medical Oncology (ESMO) issued several guidelines on the management of various types of cancers, including for example, breast (14), lung (15), colorectal (16), and pancreatic carcinoma (17). Prioritizing cancer patients is based on a tiered framework that incorporated both the information on the value-based prioritization and clinical cogency of the interventions into a high, intermediate and low priority that would guide the surgical, medical, radiation interventions based on consensus recommendations from international experts.

Other parts of the world have made some efforts to develop recommendations to guide oncologists in providing cancer care during the SARS-CoV-2 in developing countries. Examples include collaborative work initiated through international collaboration, including contributions from some Arab Countries (18).

ALLOCATION OF LIMITED RESOURCES

The current pandemic has stretched healthcare resources in many ways. However, ventilators have stolen much of the show (19). If a SARS-CoV-2 infected cancer patient is competing with another SARS-CoV-2 infected, otherwise healthy, individual for a ventilator, how can one determine who gets the ventilator? A more complex situation can emerge for non-infected cancer patients who need the ventilator for their standard cancer care or terminally ill cancer patients who are already on ventilators; would such groups rank at the bottom of the list? In settings of scarcity such as these, it is important to consider not only what is ethically justifiable but also what is ethically unacceptable. Some may argue that removing terminally ill cancer patients already on ventilators to be used for SARS-CoV-2 infected patients with high chances of survival is ethically permissible, however, others may argue that it is ethically unacceptable especially without the consent of the patient or his/her family.

Since the emergence of SARS-CoV-2 pandemic, scientists are working day and night to find a potential treatment or vaccine to prevent the spread of the virus. Many anticipate the success of these treatments/vaccines to put an end to this tragic pandemic (19). However, this will not put an end to the currently faced ethical dilemmas. The significant question now will be who will have the priority to receive such treatments or vaccines? The dilemma of ventilators might propagate in case of establishing an effective treatment or an antiviral vaccine. For new vaccines, will priority be given to the most vulnerable to the infection/at higher risk of morbidity or mortality due to SARS-CoV-2 infection or to those who are most likely to benefit from immunization? In other words, will cancer patients be finally prioritized and seen as more vulnerable or will administer it to healthcare providers working in the frontline and interacting with hundreds of infected individuals on daily basis be more justifiable?

TABLE 3 | American Medical Association (AMA) Code of Medical Ethics Opinion 11.1.3, Allocating Limited Health Care Resources (20).

Individually and collectively through the profession, physicians should advocate for policies and procedures that allocate scarce health care resources fairly among patients, in keeping with the following criteria:
(a) Base allocation policies on criteria relating to medical need, including the urgency of need, likelihood and anticipated duration of benefit, and change in the quality of life. In limited circumstances, it may be appropriate to take into consideration the amount of resources required for successful treatment. It is not appropriate to base allocation policies on social worth, perceived obstacles to treatment, patient contribution to illness, past use of resources, or other non-medical characteristics.
(b) Give first priority to those patients for whom treatment will avoid premature death or extremely poor outcomes, then to patients who will experience the greatest change in the quality of life, when there are very substantial differences among patients who need access to the scarce resource(s).
(c) Use an objective, flexible, transparent mechanism to determine which patients will receive the resource(s) when there are not substantial differences among patients who need access to the scarce resource(s).
(d) Explain the applicable allocation policies or procedures to patients who are denied access to the scarce resource(s) and to the public.

Whether it is a ventilator, antiviral medication, or vaccine, the consequences of a particular treatment decision can be afflictive for those excluded from benefit by that decision. Thus, no single person should be burdened to take such hard decisions. The value of well-educated, trained and experienced medical ethicists surfaces here. They are most-fit to balance such choices and guide the medical community to make the most justifiable ethical decisions governed by such specific circumstances. In addition, a clear ethical framework should be generalized and followed on a national level to ensure fairness of treatment. Fairness does not necessarily mean that every patient is provided with the same resources, rather differences in resource allocation, treatment and prioritization of patients is based on ethically justifiable criteria.

The American Medical Association (AMA) Code of Medical Ethics has provided foundation guidance in response to the SARS-CoV-2 pandemic (20). **Table 3** lists the AMA Code of Medical Ethics Opinion 11.1.3, which gives guidance for allocating limited health care resources (21). It can be noticed that such guidance is framed broadly and intended to be applicable across a range of settings. A more specific framework is needed specifically to guide and unify the care provided for cancer patients during the current SARS-CoV-2 pandemic.

Acting and communicating ethically sound decisions should be a priority for healthcare providers during such hard times, and it becomes vital not only to communicate, but to provide

resources of education for patients to help them make decisions regarding their treatment. However, during a crisis, the stakes grow higher, and the ethical challenges of communicating both accurately and strategically can be very complicated. Informed consents can be especially challenging. Additionally, in cases of scarce resources, physicians might need to play a proactive role and have premature end-of-life and DNR discussions with their cancer patients (6).

Another complex situation is when healthcare providers caring for cancer patients are called to care for critically-ill SARS-CoV-2 infected patients outside of their specialty and routine clinical practice, especially in a national health crisis (19). Here, physicians are left with a hard paradox of conscience leaving their own cancer patients, who they have been treating for years, juggling with their chances of survival after a long journey of painful procedures and treatment cycles, to fulfill yet another noble role and save many infected patients lives' giving them the opportunity to go back to their lives as healthy as they were before with no permanent negative consequences on their health.

SITUATION IN JORDAN

On the 15th March 2020, Jordan had only one confirmed case of SARS-CoV-2 infection (22). Nonetheless, this did not stop healthcare institutions from starting to prepare for a potential health crisis, already witnessed in several countries worldwide at that time. No national guidelines for treating cancer patients were developed, leading individual institutions to take the initiative to develop their own internal policies.

Situation at King Hussein Cancer Center

King Hussein Cancer Center (KHCC) is a standalone cancer center located in Jordan's capital, Amman. It provides comprehensive cancer care for the citizen of Jordan and neighboring countries. The center treats over 6,000 new cases annually; one quarter of which are non-Jordanians.

Given the unprecedented current outbreak and the lack of proper predictions on when such pandemic can be controlled, the diagnosis and treatment of malignant tumors should be carried out in an orderly and safe manner. Guidelines and recommendations on how to manage cancer patients during this pandemic do exist (18, 23). To meet challenges and to optimize quality care, KHCC had put into effect several measures:

Drive-Thru Screening

To avoid exposing our patients and our healthcare workers to SARS-CoV-2 infection, patients and their companions were screened twice; the day before their scheduled appointments to outpatient clinics, chemotherapy, radiotherapy, or elective diagnostic imaging, patients were screened over the phone by nurse coordinators about any exposure or clinical symptoms that may suggest SARS-CoV-2 infection. On the day of the appointment, all patients arriving at the center were screened again in a specially-designed "Drive-Thru" system where brief history and vital signs were measured.

Telemedicine

During the first 2 months of the pandemic, the center decided on adopting "Tele-Clinics." All scheduled patients were notified the day before not to report to the hospital and that their clinic visits will be made via phone calls by their nurse coordinators and clinicians. During this "Tele-Clinic," the team assessed patients clinically for all issues related to their cancer or its therapy. Occasionally, patients were requested to report to the hospital for a clinic visit, a drop-in clinic or even to the emergency room (ER). Such clinical encounters were documented in patients' electronic medical records.

Additionally, the center enforced and upgraded a previously established call center. Patients may call 24/7 inquiring about new complaints or issues related to their cancer or its therapy. Senior oncology nurses, who have access to all oncologists and other consultant physicians, operate this call center. Messages were also sent to all KHCC patients not to come to the ER before contacting the call center. Unnecessary ER visits were prohibited using this approach.

Limited Medical Services

During the first few weeks, KHCC limited elective surgeries and limited chemotherapy sessions to potentially curable cancers utilizing regimens not known to cause prolonged immunosuppression. Fortunately, these arrangements were temporary and resulted in minor delays in patients' active therapy. Likewise, the Hospital Ethics Committee updated and approved new modifications to the DNR policy to allow a team of physicians to make DNR decisions if more ICU beds or ventilators were needed (24). Fortunately, such situations were never encountered.

Medication Home Delivery

To avoid difficult commuting to the hospital and to minimize exposure, the center adopted a delivery plan to patients, to distribute newly prescribed and refilled medications. This service was welcomed by both patients and physicians alike. Special arrangements were made to refill narcotics as local rules and regulations prohibit delivering such medications.

Healthcare Workers

Learning from the experience encountered in some European and neighboring countries, the center decided to work during the early months with reduced staffing. Staff not on-duty were asked to stay home to avoid any accidental exposure and lengthy quarantines. An incidence of a single exposure at our center put aside more than 30 healthcare workers including physicians, nurses, dieticians, respiratory therapists, clinical pharmacists, housekeeping, and many others.

CONCLUSIONS

As the current SARS-CoV-2 pandemic continues to evolve worldwide, many ethically challenging decisions must be made. This includes treating cancer patients, which might be easily overlooked at such difficult times. Much attention should be given to provide guidance for healthcare providers on

delaying or altering cancer treatment plans, allocation of limited resources and patient-physician communication in addition to the importance of on-going discussions between medical ethicists and healthcare providers. The role of qualified medical ethicists and consultants is of paramount importance as they can ensure ethical medical practice during such critical times. However, in Jordan, such expertise are not abundant and the role of medical ethicists is still slowly emerging.

Finally, we provided a summary of the insight from the experience of KHCC, a comprehensive cancer center in this particular region. Overall, it appears that KHCC opted to adopt extreme measures to ensure the safety of patients and healthcare workers alike. As per the recommended triaging strategies (**Table 1**) it would appear that KHCC followed a mixture of "protecting the most vulnerable" and "prioritization of the most important."

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

AA-T: literature review and collection of data, writing the first draft, review, and final approval. MA-H and AM: inception of the idea, critical review of the first draft, critical review, and final approval. RM and HS: literature review, reviewing, and editing the first draft, and final review and approval. HA-R: literature review, reviewing, editing the revised draft, and final review and approval. All authors are accountable for the content of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

OPINION
published: 29 October 2020
doi: 10.3389/fmed.2020.564038

The Care for Non-COVID-19 Patients: A Matter of Choice or Moral Obligation?

Bashar Hassan[1] *and Thalia Arawi*[2*]

[1] Faculty of Medicine, American University of Beirut, Beirut, Lebanon, [2] American University of Beirut Medical Center, Beirut, Lebanon

Keywords: COVID-19, coronavirus, SARS-CoV-2, non-COVID-19 patients, ethics, elective surgeries, psychological interventions, mental health

INTRODUCTION

A male patient Sam (not his real name), suddenly unable to walk, presented to Addington Hospital in Durban, South Africa, a couple of days before the president declared a national state of disaster due to SARS-CoV-2. An MRI scan at Inkosi Albert Luthuli Hospital was needed to establish the suspected diagnosis of Tuberculosis (TB); however, he was told he had to wait for months or even a year, due to the huge strain the aforenamed hospital was facing because of the corona virus. Therefore, Sam was not provided with a clear diagnosis, and thus no proper treatment. He was told that he will not be able to walk again and sent back home to an overcrowded hostel where his family and hundreds of other underprivileged people could contract the disease if it really was TB (1). From South Africa to Canada, due to the massive burden of COVID-19 on the health care systems, Sydney Loney had her mastectomy, which was originally scheduled in mid-March, postponed indefinitely (2). Due to the scarce medical resources SARS-CoV-2 has left hospitals with, patients with deadly infectious diseases like TB, cancers that can metastasize, and numerous other conditions, are being denied medical care. In addition, thousands of elective surgeries are being canceled (3). In this article, we shed light on the ethical challenges imposed by SARS-CoV-2 regarding non-COVID-19 patients and raise the possibility of establishing more considerate regulations and specific psychological interventions for this subset of patients.

SARS-CoV-2 is the newly discovered infectious virus responsible for Coronavirus disease (COVID-19) (4). Owing to the immense burden of COVID-19 pandemic on health care systems, the Centers for Medicare and Medicaid Services, the U.S. Surgeon General, the American College of Surgeons (ACS) and many other medical specialties and societies have put guidelines for the temporary cancelation of elective surgeries (5, 6). The ACS has even thanked the surgeons who already stopped performing them (6). These recommendations and guidelines are still being constantly updated as to how surgeons should choose whether or not to perform a certain operation (6). Over decades, the scientific literature has been flooding with incessantly updated guidelines on providing the best medical care for patients, as well as conducting surgeries. It is morally perplexing, as a budding medical professional and junior physician, to see guidelines released to restrict medical care and delay surgeries instead (5, 6).

ETHICAL CHALLENGES RELATED TO NON-COVID-19 PATIENTS

COVID-19 and the aforementioned guidelines emanating from it challenge the basic ethical principles of medicine such as the universal right to healthcare, beneficence, non-maleficence, justice, to mention but a few core ones (5, 6). On the other hand, having specific guidelines for elective surgeries (5, 6), may ensure equality among non-COVID-19 patients, only if all hospitals

OPEN ACCESS

Edited by:
Mette Due Theilade Thomsen, Shionogi Limited, United Kingdom

Reviewed by:
Sigurd Lauridsen, University of Southern Denmark, Denmark

****Correspondence:***
Thalia Arawi
ta16@aub.edu.lb

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *20 May 2020*
Accepted: *02 October 2020*
Published: *29 October 2020*

Citation:
Hassan B and Arawi T (2020) The Care for Non-COVID-19 Patients: A Matter of Choice or Moral Obligation? Front. Med. 7:564038. doi: 10.3389/fmed.2020.564038

agree to abide by these guidelines (which is very unlikely). Many hospitals do not follow the aforementioned published guidelines, which raises the possibility of unfair treatment and different handling of two patients with the same medical condition requiring the same "elective" surgery, if they had gone into two different hospitals, placing the patient who have been denied surgery at a disadvantage. It also puts the healthcare institution, which does not offer a valid moral justification for its "triaging," in a difficult situation in terms of trust and reputation.

Aside from published guidelines, many other factors have contributed to the cancellation of elective surgeries, and some perhaps were contributing factors to establishing these guidelines. For example, the shortage of PPEs and beds necessary for operations, and even medical personnel who have been summoned to work on COVID-19 floors, has put COVID-19 patients at risk of not receiving the appropriate medical care (7). Also, some insurance companies are not paying except for urgent operations, which may in turn delay elective surgeries of non-COVID-19 patients. Some of these patients may themselves refrain from seeking medical care fearing that they may contract the COVID-19 virus.

Allocating hospital resources to COVID-19 patients should not mean leaving potentially fatal or impedingly dangerous cases untreated. This may perhaps be achieved through more considerate regulations that give equal, or at least greater, considerations for non-COVID-19 patients. We see this particularly important building on the fact that delaying medical treatment for non-COVID-19 patients may be more harmful to health care systems on the long run with the rising numbers of non-COVID-19 patients, thus placing health care systems in an endless cycle of medical care shortage. To explain this further, we take TB as an example. TB is the number 1 cause of death from an infectious disease (8); therefore, both diseases, COVID-19 and TB, can be fatal and are contagious. Untreated TB patients might further spread the disease, ending up with more non-COVID-19 patients in need of medical care, and thus exacerbating the existing situation. Hence, regarding TB as less important than COVID-19, in our opinion is counterintuitive, as it defeats the purpose of reserving medical care for COVID-19 patients and may in fact increase the burden on health care systems and the risk of an impending health catastrophe.

This is particularly important in certain populations like that of Nigeria. Experts have declared that the focus of Nigeria should be to tackle TB rather than COVID-19, as the former is worse than the latter (9). They based their recommendations on the fact that TB kills over 3,000 people daily in Nigeria, at a time when COVID-19 kills 60 people a day (9). The Head of TB unit at the World Health Organization (WHO) expressed that the treatment of TB in Nigeria is hugely lacking proper funding, which mainly comes from US agencies (9). Because many funds are diverging into COVID-19 research and resources, this is another reason COVID-19 exacerbates other conditions, like TB.

Following the same line of thought, the COVID-19 pandemic has strongly contributed to delaying acute care of strokes and myocardial infarctions, routine monitoring, preventive protocols, childhood vaccinations, and cancer, diabetes, and lipid disorders treatments (10). Such delays may have significant future population-based consequences (10), what we note will lead to a health catastrophe. Although the above may be seen as a public health priority, to us focusing on a blooming disease rather than a greater burden for a certain population, or ending up with people dying because of delaying proper screening or preventive measures, is ethically challenging as it undermines the basic bioethics principles of medicine and the notion of humane medicine.

The consequences of curtailing surgeries and medical care are not only limited to the present health risks we are currently facing, but also to the future health risks that will arise from canceling or refraining from a plethora of surgical procedures, screenings, and prevention. These anticipated health risks will most probably not only be physical, but also mental.

MENTAL HEALTH OF NON-COVID-19 PATIENTS

The specter of COVID-19 has been hovering for months now. Many family members are not being able to see their hospitalized loved ones. While some countries offer virtual solutions, many find this a cold way of "being" with their loved ones, leading to feelings of helplessness. Other persons are subjected to great distress for not holding proper funerals and burial rituals for their beloved family members (11). Healthcare workers are under a lot of mental and physical stress; some even opted to end their lives (12). Adding those to the social distancing afflicted by the Coronavirus, we see the world going into a pandemic of a mental health nature.

In light of an already deteriorating mental health, this impact of COVID-19 is often exacerbated in those who are sick yet denied medical care, proper treatment, and elective surgeries. Psychological interventions have been designed to deal with COVID-19 patients, survivors, and other people in quarantine (13). To our knowledge, however, there is scarce data on the psychological interventions for non-COVID-19 patients who have been denied elective surgeries, proper medical care, access to the hospital, etc. We would like to encourage greater consideration of this particular subtype of patients in newer guidelines and raise the possibility of designing specific psychological interventions for them to protect their threatened mental health and psychological well-being. We contend that this is an issue of paramount importance that should be addressed by the national bioethics committees of different countries, as mental health is as important as physical health.

As a conclusion, to mitigate consequences of the COVID-19 pandemic, regular monitoring, screening tests, preventive measures, and quality care should resume as soon as possible to non-COVID-19 patients who have been denied proper care during the pandemic. This may be a challenging task as it requires that hospitals keep a track record and contact the "rejected" or "postponed patients" who might have undergone the treatment/procedure elsewhere. Also, psychological interventions should target COVID-19

patients, survivors, those who lost their loved ones, and non-COVID-19 patients whose management has been delayed. We reckon that all patients have the same right to proper medical evaluation, care, and treatment. Although the new guidelines prioritize COVID-19 patients, other patients are still patients, and we as health care professionals have a duty toward all.

AUTHOR CONTRIBUTIONS

BH is the main contributor and writer and edited accordingly. TA revised the article, raised several remarks, titled the article, and made the final edits. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

PERSPECTIVE
published: 02 December 2020
doi: 10.3389/fmed.2020.590265

Mandating the Use of Proximity Tracking Apps During Coronavirus Disease 2019: Ethical Justifications

*Riya Dave and Rashmi Gupta**

Cognitive and Behavioural Neuroscience Laboratory, Department of Humanities and Social Sciences, Indian Institute of Technology Bombay, Mumbai, India

The rise of the coronavirus disease 2019 (COVID-19) in a digital world has expectedly called upon technologies, such as wearables and mobile devices, to work in conjunction with public health interventions to tackle the pandemic. One significant example of this integration is the deployment of proximity tracking apps on smartphones to enhance traditional contact tracing methods. Many countries have adopted proximity tracking apps; however, there is a large degree of global differentiation in the voluntariness of the apps. Further, the concept of a mandatory policy—forcing individuals to use the apps—has been met with ethical concerns (e.g., privacy and liberty). While ethical considerations surrounding deployment have been put forth, such as by the World Health Organization, ethical justifications for a mandatory policy are lacking. Here, we use the Faden–Shebaya framework, which was formed to justify public health interventions, to determine if the compulsory use of proximity tracking apps is ethically appropriate. We show that while theoretically justified, due to the current state of proximity tracking applications and societal factors, it is difficult to defend a mandatory policy in practice.

Keywords: ethical framework, digital health, COVID-19, ethics, contact tracing

OPEN ACCESS

Edited by:
Maysa Al-Hussaini,
King Hussein Cancer Center, Jordan

Reviewed by:
Domenico Criscuolo,
Italian Society of Pharmaceutical Medicine, Italy
Peter Arányi,
Medical Research Council, Hungary

****Correspondence:***
Rashmi Gupta
rash_cogsci@yahoo.com

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *31 July 2020*
Accepted: *02 November 2020*
Published: *02 December 2020*

Citation:
Dave R and Gupta R (2020) Mandating the Use of Proximity Tracking Apps During Coronavirus Disease 2019: Ethical Justifications. Front. Med. 7:590265. doi: 10.3389/fmed.2020.590265

INTRODUCTION

The rise of coronavirus disease 2019 (COVID-19) during a digital technology boom has led the world to integrate various technologies with health strategies to curb the pandemic. Amongst such integrations, the use of smartphones in conjunction with traditional contact tracing methods has been proposed as a key way to augment public health surveillance (1–3). To do so, digital proximity tracking apps—location tracking applications downloaded onto smartphones—have been globally issued. Proximity tracking apps measure the signal strength between smartphones to determine whether two devices were close enough for a long-enough duration for there to have been virus transmission. If an individual is infected, those within proximity of the infected individual will be notified. Appropriate next steps to reduce health risks are then given to the suspected individual (1–5).

The proposed benefits of proximity tracking apps have encouraged many countries to design and deploy such tools quickly (1). However, there is large global differentiation in their voluntariness, as some countries mandate that individuals download the app (3, 5, 6). While app usership has proposed benefits, mandating their use has led to ethical concerns over the infringement of individual rights (liberty and privacy). Noting the tradeoff, the World Health Organization (WHO) has outlined ethical suggestions for how governments and private institutions could design and

deploy proximity tracking apps (1). Recent studies have also put forth their ethical considerations as frameworks for app implementation (3, 6, 7).

Although considerations and suggestions have been put forth, ethical justifications for a compulsory intervention are lacking. Is it ethically appropriate to mandate the use of proximity tracking apps despite violations to individual rights? Given the global differentiation in the voluntariness of proximity tracking apps and their proposed benefits to public health (8), we believe that an investigation of the ethical appropriateness of mandating their use is highly necessary.

FRAMEWORKS FOR THE ETHICAL JUSTIFICATION OF PUBLIC HEALTH INTERVENTIONS

To justify the mandatory implementation of digital proximity tracking apps, we can turn to frameworks that determine the ethical appropriateness of public health interventions. Amongst frameworks, there is differentiation in the themes emphasized: For example, Kass (9) and Childress et al. (10) highlight the intervention efficacy plays in justifying public health intervention (11), while Upshur (11) and Faden and Shebaya (12) believe the straightforward application of the principles of biomedical ethics—autonomy, beneficence, nonmaleficence, and justice—is too limited in scope.

The "Faden–Shebaya framework" further differs from other frameworks in that it argues against frameworks that provide broad, moral warrants, such as "to maximize public good" or "advance social justice" (12). The "Faden–Shebaya framework" does not deny that the underlying tension of a health policy surrounds hurting individual rights, but they do not disproportionately weigh "human flourishing" to justify any violations to autonomy (12, 13). In other words, the framework incorporates factors, as discussed below, in addition to public and individual health benefits into the core of their ethical debate. Given the focus of the framework across channels and the emphasis on more than the scientific efficacy of the policy, we use the "Faden–Shebaya framework" to justify whether mandating the use of proximity tracking apps is ethically appropriate. To do so, we critically analyzed four justifications they have put forth: (1) collective action, (2) overall health benefit, (3) distribution of burdens, and (4) harm to others (Mill's harm principle) (12). Before delving into the framework, we first discuss the individual rights that may be violated. We then explain the justifications of the framework in detail. Finally, an ethical analysis that incorporates these elements is provided.

IMPLICATIONS OF A MANDATORY POLICY ON INDIVIDUAL RIGHTS

In the event of any mandatory intervention, three individual rights are known to be violated: liberty, privacy, and informed consent (13).

With this intervention, liberty is violated as individuals do not have the ability to reject the policy. Privacy regards data misuse, such as the transfer of personal information outside the defined goals of the app, imperfect anonymization of the data, or security loopholes in the app that put individual data at risk (14). Without informed consent, the agent in charge of the dataset could collect and repurpose data from the app without the user's knowledge (3, 6, 14). Questions then surround: how long will the agent hold the data? When will it be deleted? The WHO suggests that data be deleted from proximity tracking apps after the pandemic subsides. Given the large uncertainty of when that could be, if individuals are forced to abide by such a compulsory policy, they lose their ability to not only consent to how data is collected and where it may go but also the duration of that collection (1, 3).

Further, the data collected should be anonymized and typically is even in countries that have mandatory interventions, such as in India. However, recent studies have shown that machine learning can, somewhat easily, re-identify data, which puts an individual's right to privacy on a tenuous support (15). Lastly, a mandatory policy would force individuals to face the consequences of any product malfunctions in safeguarding data. As case examples, countries such as South Korea and Qatar have been scrutinized due to security issues found in their tracking apps that put their population at risk (16).

THE FADEN–SHEBAYA FRAMEWORK

Collective Action

Collective action is the idea that if an individual or a large group of individuals refute a public health regulation on the grounds that it does not directly benefit them or align with their beliefs, the consequences extend to society. A classic example of this concept is an outbreak of measles that resulted from under-vaccination of children by parents (17). In other words, collective action asserts that in order for an intervention to be successful, participation must encompass the entire society, as without full cooperation, neither the individual nor the society can reap the benefits of the intervention. Collective action, therefore, sets the grounds for supporting a mandatory health intervention (12, 13). Without collective action, there is also a high possibility that the "free-rider" problem will rise, where those individuals who are omitted from the intervention still gain some benefits (13).

Fairness in the Distribution of Burden

Public health "burdens" are understood as both the burdens of the illness and the burdens of the intervention itself (13). On the grounds of fairness in the distribution of burdens, individuals may be asked to bear public health burdens that do not directly benefit them in an attempt to make the disease burdens more equitable. For instance, between 1962 and 1994 in Japan, children were also asked to be vaccinated against seasonal influenza to protect the elderly (who were harshly impacted by the illness) (12, 13).

Overall Benefit to Society

Proponents of intrusive public health interventions often argue that such interventions are justified because of the overall benefits to society (12, 13, 17). For example, by mandating that everyone get a vaccine or requiring an HIV positive patient to disclose

sensitive information on previous sexual partners, it is believed that society will benefit as a whole (13). However, in order to reap any benefits, the intervention must be effective in producing an advantageous outcome.

Harm to Others (Mill's Harm Principle)

According to Faden and Shebaya, the "harm principle" is often viewed as the most compelling justification for public health policies that interfere with individual liberty (12). Mill's harm principle argues that harm should be prevented from occurring to others. This logic has been used to justify drastic actions such as quarantines and other compulsory treatment for highly infectious diseases (13).

ETHICAL ANALYSIS OF MANDATORY POLICY

We segmented the analysis into two parts. The first is a theoretical justification of the intervention, followed by a review of the application of the policy in practice. We argue that while the policy may be theoretically justified, in practice, it does not hold.

Theoretical Justification of the Intervention

The WHO states that at least 60% of a country's population needs to use the app in order to stop transmission and contain the virus (1, 4). Thus, not downloading the app will do harm to society, and by Mill's principle, the harm done to the public (contracting the virus) could have been prevented through app usage. Thus, a mandatory policy would ensure that a majority uses the app, minimizing any physical harm from illness.

The mandatory policy could be further justified on the grounds of collective action and overall health benefit, as a negative consequence of not having full participation is a suboptimal, or ineffective, contact tracing app (1). Thus, to prevent "free riders" and reap the overall health benefit, a mandatory policy would be theoretically appropriate.

Lastly, on the grounds of fairness in the distribution of burdens, a policy mandating the use of proximity tracking apps may be justified here. In general, the disease places a greater burden on the elderly: those above the age of 65 have an 80% mortality rate from the virus (COVID-19), making them an age group that is hit disproportionally more than younger generations by the virus (18). This group also has the lowest smartphone penetration rate than other generations (19). With a mandatory policy, younger generations would take on the burden of complying with the intervention (sacrificing their autonomy) in order to be in fair alignment with the disease burden placed on the elderly.

Justifications in Practice

However, even with a mandatory policy, there are uncertainties, product concerns, and societal parameters that limit the theoretical implementation of a mandatory policy.

The impact will only go as far as the number of people that own smartphones with GPS/Bluetooth capabilities for tracking. In other words, while the policy may be theoretically justified, it is not in practice because it may be inherently impossible for everyone—or the majority—of a country to meet the user threshold suggested for app efficacy. For example, in India, 26% of the population own smartphones. While benefits may still be reaped at this percentage for that group that participates as well as others (4), this would contribute to the "free-rider" problem and contribute to skewed data (13). In addition, if this percentage lies largely within wealthier classes, then the data yielded from the app that are analyzed for alleviation purposes, such as resource allocation, would inaccurately paint an understanding of virus spread—or "hotspots" (5, 6). On the other end, this 26% would give away their autonomy but not gain a true indication of when they may be around infected people, which violates the principle of reciprocity (11, 12). Further, even if a country had the capacity to reach the needed threshold, we must also take into account cultural differentiation. From a draconian government that may lead citizens to more readily accept a compulsory policy to a prevailing religious view, such as to limit the use of technology, that may hinder acceptance of that same policy, there is no guarantee that citizens of a certain country will, in fact, follow without resistance or protest. Thus, while cooperation from all individuals in the society would eliminate any discrimination or data bias, the app's effectiveness only holds true if there is an even distribution of smartphones, a willingness to accept the policy, and a high smartphone penetration rate.

It is true that app usage is proposed to hinder virus transmission and thus control the virus spread (achieve overall health benefit). However, these benefits are contingent on a baseline requirement: that the policy proves effective in producing societal benefits. In its current state, those dependencies are not guaranteed.

The dependencies can be divided into two categories: (1) the technology itself and (2) societal parameters. With respect to the technology itself, currently, we cannot guarantee that the proximity apps will be effective and accurate in augmenting contact tracing. There is little scientific evidence of their efficacy to date (1, 3). As a result, proximity tracking apps are being deployed in many countries after few, if any, pilot studies or risk assessments published (20). In the absence of official validation tests and protocols, there can be no indicator of accuracy and effectiveness (3, 20). Other limitations include an inability to account for factors that are specific to the environment, such as wind direction or the presence of ventilation (21). In addition, while GPS and Bluetooth technologies can determine proximity, one loophole includes barriers between people, such as walls or windows, that will not automatically be factored into risk profiles. Moreover, individuals may be spatially distanced but occupy the same GPS coordinate, leading to false positives for notifications (3, 21).

Further, there are various societal parameters necessary to ensure app success, such as a high smartphone penetration rate, feasibility and reliability of testing, and individual adherence to suggested protocols. As discussed previously, to reach the proposed efficacy, the country must have a majority using GPS/Bluetooth-enabled smartphone devices (3). If we take a country such as Pakistan, which has a smartphone usership of 16%, while there would still be benefits to a compulsory policy, it could be argued that societal benefit is not being maximized for

all of society, and thus, the policy is not ethically appropriate by the justification of societal benefit (22).

The next hindrance to the effectiveness of a mandatory policy is the feasibility and reliability of testing. Without the ease of testing and quick testing-response rates, the app's efforts will be thwarted. Similarly, if the testing is unreliable, then the app will not present an accurate representation of the spread of the virus. According to research done by Johns Hopkins Medical School, there was a 38% chance of a false negative, which changes to 20% if an individual was tested 8 days after infection (23). Further, the policy also requires that society members adhere to suggested protocols and self-report symptoms (if applicable). If an individual receives a notification that they were in proximity with an infected individual, but do not follow requested protocols (self-quarantine, report any symptoms later or get tested), then the app's goal will not be realized, making the collection of data and forced use come at a high cost and little societal benefit (1). Thus, while the mandatory policy can be theoretically justified on the grounds that it is benefiting public health, the uncertainty that surrounds the success of the intervention and the technology in producing public good makes it difficult to defend its implementation (3).

While the physical harm to others may be minimized through app deployment, we must not omit other forms of harm that could be placed on society members as a result of a mandatory policy. Harm, such as security threats or psychological harm from being coerced into an act against will, must be weighed (13). It is evidenced through South Korea and Qatar that a rush to design the app with minimal validation tests has led to security issues (3, 15). Faulty technology is more susceptible to data breaches, which places the individuals forced to use the app at high risk of being identified (21). In its current state, it is difficult to justify the mandatory implementation of the app under the principle that it will reduce the harm done to others by protecting them, as the app's efficacy is yet questionable. Nonetheless, to determine a justification based on harm principles, all forms of negative impact must be weighed.

CONCLUSION

Here, we applied the "Faden–Shebaya framework" to determine if and how the mandatory use of contact tracing apps could be ethically appropriate. We went through their framework and critically analyzed each justification for its application to the current pandemic.

Faden and Shebaya (12) state that more than one justification can and should be used when making health policy decisions (12). While the concept of equitable distribution of burden holds in theory and in practice, when weighed with evidence from the other justifications, it is difficult to defend the policy. Therefore, we argue that while the policy could theoretically be appropriate, given the current context, such as the feasibility of testing or app limitations, it is difficult to justify a mandatory policy in practice at the expense of individual rights.

To better balance theoretical and practical justifications, there are actions that those in charge of developing and deploying such apps could take. Developers could form policies, similar to a Hippocratic Oath, to ensure that the patient is always valued first and treated ethically. This would support guidelines on data use from the app, safety testing for security loopholes, and data anonymization. Those in charge of deploying the app could take the time to continuously weigh the individual risk with societal benefit to determine the worth of deploying such apps. While there is no perfect system or answer, especially given the large cultural differentiation between countries, steps can be taken to bring about an ethical justification for a country that balances the theoretical with the practical and the individual with society.

While each health intervention taken during the pandemic, from mandatory use of masks to social distancing requirements to the prohibition of gathering, can be relayed, they each warrant their own system of justifications and cannot be treated equally. Thus, further discussion of the mandatory use of contact tracing apps is critical. What this article can conclude is that a system of checks and balances is needed before any health intervention is justified.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

ORIGINAL RESEARCH
published: 11 December 2020
doi: 10.3389/fpubh.2020.587423

General Public Preferences for Allocating Scarce Medical Resources During COVID-19

Samir Huseynov[1]*, *Marco A. Palma*[1] and *Rodolfo M. Nayga Jr.*[2]

[1] Texas A&M University, College Station, TX, United States, [2] University of Arkansas, Fayetteville, AR, United States

COVID-19 has overwhelmed healthcare systems across the globe with an unprecedented surge in the demand for hospitalizations. Consequently, many hospitals are facing precarious conditions due to limited capacity, especially in the provision of ventilators. The governing ethical principles of medical practice delineated in (1) favor prioritizing younger patients, largely because of their relatively higher expected life years. We conduct a survey of the general public in the United States to elicit their preferences for the allocation of a limited number of ventilators. The results show that the general public views align with the established ethical principles, which favor younger patients.
JEL Classification: C91.

Keywords: scarce, ventilators, triage, principles, ethics

OPEN ACCESS

Edited by:
Ma'n H. Zawati,
McGill University, Canada

Reviewed by:
Zhiwei Xu,
The University of Queensland, Australia
Alexander Bernier,
McGill University, Canada

***Correspondence:**
Samir Huseynov
samirhuseyn@gmail.com

Specialty section:
This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health

Received: *26 July 2020*
Accepted: *23 November 2020*
Published: *11 December 2020*

Citation:
Huseynov S, Palma MA and Nayga RM Jr (2020) General Public Preferences for Allocating Scarce Medical Resources During COVID-19. Front. Public Health 8:587423. doi: 10.3389/fpubh.2020.587423

The catastrophic consequences of COVID-19 to human health have been felt on a global scale. The virus has already impacted the health of millions and claimed the lives of several hundred thousand people across 215 countries (2). Even in developed nations, the pandemic has overwhelmed healthcare systems with an unprecedented increase in the demand for hospitalizations. Disruptions in the global supply chain for healthcare equipment, which plays a vital role in the replenishment of health-provision, have consequently left many hospitals in precarious conditions due to limited capacity and urgent needs for medical resources (1, 3, 4). The most severe shortages have been experienced in the provision of ventilators, which are essential medical equipment for treating coronavirus patients (5). This situation is exacerbated in developing countries where the public health systems tend to have more limited capacity constraints.[1] Many countries report that medical personnel have been forced to make difficult rationing decisions regarding which patients will be assigned to ventilators or other life-saving equipment (1, 6, 7). Hospitals operating beyond capacity and severe shortages of essential resources raise the importance of the ethical considerations in determining the underlying principles and values for the fair allocation of medical treatment during COVID-19. Historically, these ethical decisions have mainly taken place during extraordinary times of warfare or heavy armed conflicts (8). The derived lessons from the COVID-19 experience can provide invaluable insights in the event of future pandemics, natural disasters or other phenomena that creates excessive burdens in the healthcare system.

1. PRINCIPLES FOR FAIR ALLOCATION OF SCARCE MEDICAL RESOURCES

There is a growing interdisciplinary literature on the investigation of the main governing principles for limited medical resource allocations during pandemics (9–11). Especially, the

[1]https://www.un.org/development/desa/dpad/publication/un-desa-policy-brief-66-covid-19-and-the-least-developed-countries/

vast medical literature identifies four main governing principles: (1) *Treating patients equally*, (2) *Prioritizing the worst-off*, (3) *Maximizing social benefits*, and (4) *Maximizing individual benefits* (1). Since the fatality rate of the coronavirus greatly varies across age groups and comorbidities, treating patients equally can only be applied among patients who have similar prognosis (1, 12). The principle of "Prioritizing the worst-off" or the allocation of limited medical resources to the sickest patients can be operationalized when it maximizes the expected post-treatment life-years (1, 13). In the context of COVID-19, this concept favors younger patients when it helps to contain the virus (assuming that younger patients are more mobile and can widely spread the virus), or the sickest patients if it maximizes survival years after the treatment. The "Maximizing social benefits" principle favors patients who provide direct benefits to communities, such as healthcare workers or research participants.[2] However, determining which patient can provide the highest benefit to society can be extremely difficult, particularly during the course of urgent clinical decisions (1). Nevertheless, having more expected life years also increases the expected social benefits from the treated patients and favors younger patients. In contrast, older patients should be prioritized in vaccination, as the survival rate of younger patients is higher for the same waiting period (1). The principle of "Maximizing individual benefits" requires using scarce resources either for increasing the number of lives saved or for increasing post-treatment life-years, both of which generally favor younger patients (1, 14, 15).

Based on the four mentioned principles, Emanuel et al. (1) recommend that if patients have similar severity of COVID-19 symptoms, life-saving equipment and resources should be allocated to younger patients who are estimated to have the same prognosis as older patients. This resource allocation approach will maximize the benefit from post-treatment life-years (1). However, relying on on-site prognosis estimations can be problematic. Previous work has shown that physicians consistently demonstrate inaccurate prognosis estimations, which makes incorporating their judgments of survival probabilities into triage decisions very questionable (16). Therefore, in this study we simplify our context to exclusively focus on severity of observed symptoms as the main decision criteria in the allocation of scarce medical resources. Emanuel et al. (1) also highlight the importance of scrutinizing these values with the affected parties, including the general public, to ensure consensus for the fair allocation of scarce medical resources. Information about the general public's preferences for allocation of scarce medical resources such as ventilators is important and can help guide public health experts and policy makers. Our study answers to this important call and investigates public preferences over the fair distribution of limited medical resources.

2. SURVEY DETAILS

Our study answers (1)'s call by using a survey to measure the U.S. general public views on the fair allocation of ventilators among patients who have similar morbidities and experience similar severity of COVID-19 symptoms. We employed the consequentiality method to increase the truthfulness of survey responses (17). Specifically, we partnered with public health organizations and informed survey participants that their feedback would be communicated to relevant Government offices and would affect their decisions. We conducted an online survey with 586 U.S. participants using the MTurk platform on April 6, 2020, when the COVID-19 pandemic was spreading rapidly across the United States. We restricted our online survey target audience to U.S. residents who were at least 18 years of age. We inquired responses from 600 MTurk users, and after the elimination of 14 incomplete survey entries, we ended up with the data of 586 respondents. Our sample constitutes a wide range of socio-demographic characteristics (see Table A1). The final sample has a larger proportion of males (60%) and the average age of survey respondents is 37. We controlled for gender in our regression analyses to disentangle the noise stemmed from the overrepresentation of males in our sample.

The participants were presented with a hypothetical scenario, in which 1,000 COVID-19 patients, with a similar level of severity of observed symptoms, were seeking treatment in a hospital. Since the current state of the medical ethics literature overwhelmingly prioritizes patients based on age considerations, our main focus is the age of the patients. Each respondent was asked to allocate 100 available ventilators among patients with similar symptoms that differed in age across 10 age categories, ranging from "0 to 10" years old to "90 or older" groups (see Figure A1). We partnered with public health officials and emergency disaster responding agencies and informed participants that their aggregate responses would be shared with Government officials.[3] Providing respondents with an opportunity to voice their opinions to policy-makers over the utilization of limited medical resources enabled us to incentivize participants to respond truthfully regarding their opinion on the fair allocation of scarce medical resources during COVID-19.

3. MAIN FINDINGS

Figure 1A shows the average number of ventilators allocated across age groups. Notice that the principle of *Treating patients equally* requires the allocation of exactly 10 ventilators to each age group since in the presented scenario, all patients have similar levels of severity of detectable symptoms. The other three principles would require allocating more ventilators to younger patients conditional on the assumption that younger patients have more post-treatment life-years. The results of the survey indicate that our respondents allocate more ventilators to the "0–10," "10–20," "20–30," and "30–40" age groups and less ventilators for patients 60 years old or older. This finding suggests that the general public favors allocating more ventilators to younger patients, which is in conformity with the clinical ethical procedures suggested by the majority of the medical literature

[2]https://www.cdc.gov/flu/pandemic-resources/national-strategy/planning-guidance/index.html

[3]This study was approved by Texas A&M University IRB2020-0400M and based on the IRB approved protocol requirements, personnel identifiers are removed from individual response data. Therefore, only aggregate results are reported.

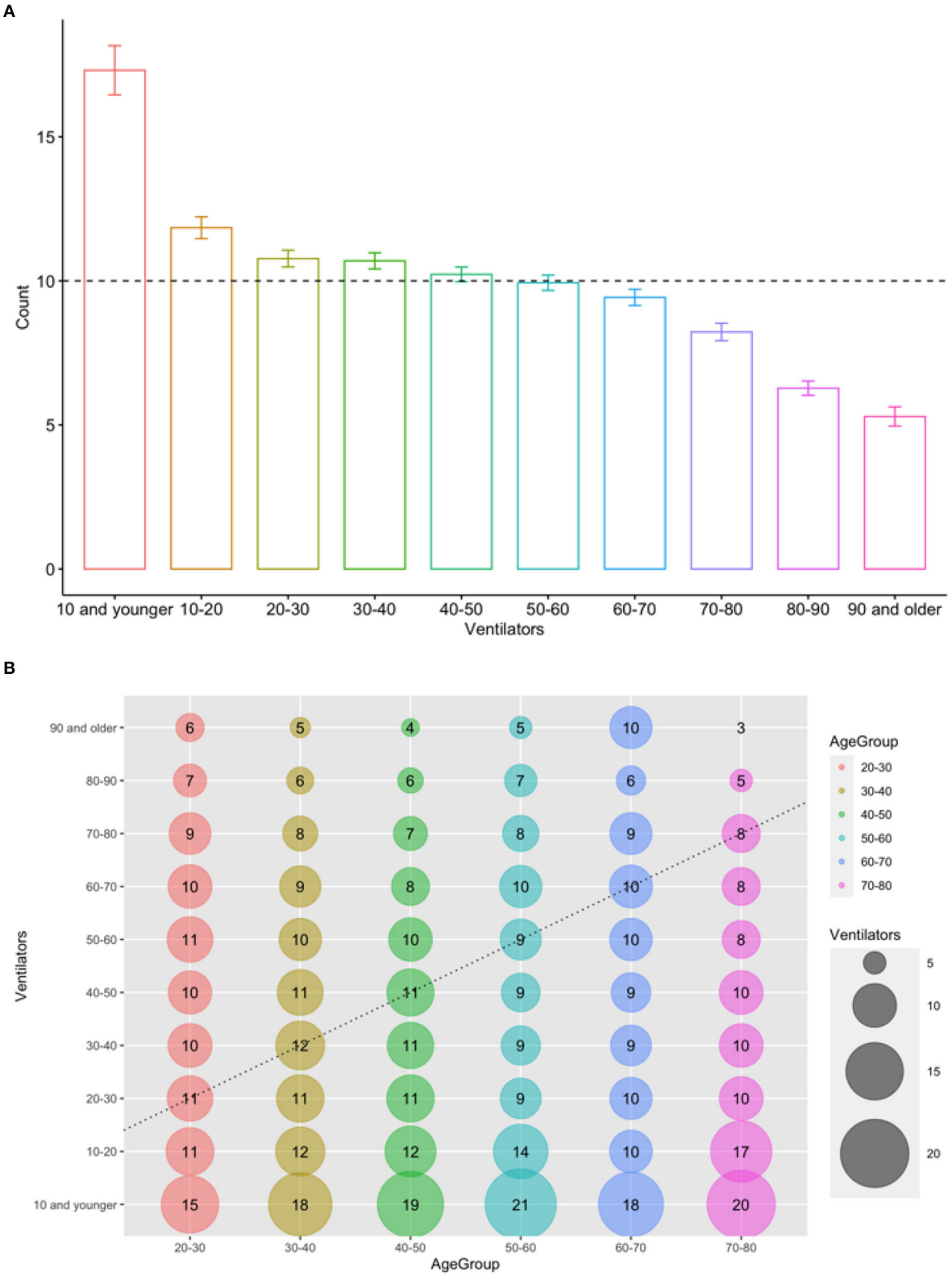

FIGURE 1 | Allocations of ventilators across age groups. **(A)** The average number of ventilator allocations across patient age groups. **(B)** The average number of allocated ventilators. The x-axis represents the age groups of decision-makers (i.e., respondents), and the y-axis shows patient age groups.

[see (1) for details]. Moreover, this result shows that the general public supports the ethical values adopted by some practitioners operating beyond capacity during COVID-19 (18).

Figure 1B shows that, on average, participants from all age groups allocate more ventilators to younger patients, especially to patients younger than 10, while allocating around 10 ventilators to their "own age group." This result shows that while respondents adhere to egalitarian principles when treating their own age group (i.e., allocating around 10 ventilators), they tend to show a favoritism for the youngest age group (i.e., 10 or younger). It is noteworthy that even patients 60 or older, who receive the lowest allocation of ventilators, also favor participants who are 20 years old or younger. Table A2 shows that most socio-demographic factors and current psychological mood measures are not strong predictors of preferences over the utilization of scarce medical resources. Females demonstrate a stronger preference for allocating ventilators to younger patients, while pro-democratic participants favor younger patients with a relatively lower magnitude (19). The underlying principles followed in the construction of the allocation index by age are discussed in the **Appendix**.

4. CONCLUSION

COVID-19 has increased the demand for public health resources to levels unprecedented since World War II (20). Across several countries, healthcare workers had to apply strict rationing and ethical principles to efficiently utilize limited medical resources. Although the existing medical literature predominantly favors ethical rules that prioritize younger patients in terms of receiving access to scarce medical resources, the number of studies documenting the general public's views on daily clinical procedures is scant. Emanuel et al. (1) urge for the added perspective of other affected parties in the determination of existing ethical values. Our study speaks to this literature, and documents that, indeed, the general public predominantly favors younger patients, when it comes to allocation of limited number of ventilators among COVID-19 patients with similar severity of observed symptoms. We find that this result is robust to the age of the decision-makers and some other socio-demographic variables. An important limitation of our study is that we do not explicitly model the role of prognosis in medical resource allocations in our analysis. Future studies should also focus on the impact of prognosis estimations on triage decisions.

The mentioned four basic ethical principles have a binary nature and it is very likely that they may demonstrate contradictory points during practical applications. Some studies elaborate decision trees or scoring rules based on principal ethical principles that enable practitioners to use more comprehensive and unified empirical tools to maximize benefit for the greatest number of patients (21, 22). Prospective studies can develop a more comprehensive operationalization of the fundamental principles via simple decision-aiding methods. While in reality the ethical question is more complex, since patients do not always present the same severity in symptoms, our results provide useful information that aligns the general public views with the ethical standards set by the medical profession governing principles.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Texas A&M University IRB2020-0400M. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SH, MP, and RN: study design, running the study, analyzing the data, writing the first draft, and writing the final draft.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2020.587423/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

REVIEW
published: 23 December 2020
doi: 10.3389/fmed.2020.598038

Obstacles and Considerations Related to Clinical Trial Research During the COVID-19 Pandemic

Hasan Hashem[1]*, *Mohammad Abufaraj*[2], *Abdelghani Tbakhi*[3] and *Iyad Sultan*[1]

[1] Division of Pediatric Hematology Oncology, Department of Pediatrics, King Hussein Cancer Center (KHCC), Amman, Jordan, [2] Division of Urology, Department of Special Surgery, Jordan University Hospital, Amman, Jordan, [3] Department of Cellular Therapy and Applied Genomics, King Hussein Cancer Center (KHCC), Amman, Jordan

The response to the COVID-19 pandemic from the research and science community has been vigorous, with information being released faster than that of any other event in human history. Articles related to the virus were being rapidly published by January 2020. A small fraction of these publications comprised reports of prospective clinical trials (0.25%), and many of these trials have imparted conflicting conclusions, leading to confusion among the public and the scientific community. Additionally, the pandemic has raised many serious scientific and ethical concerns related to clinical research. In this review, we divided the conduct of clinical research trials into three steps and critically reviewed each step, along with the challenges and obstacles arising amid the ongoing crisis. The clinical research steps we reviewed include (1) clinical trial design factors such as social and scientific value, feasibility, single vs. multicenter trials, randomization, control groups, endpoints, off-label and compassionate use of medications, data analysis, and verifying the integrity of data; (2) ethical issues such as committee approvals, efficiency, virtual visits and remote monitoring, informed consent, shipping investigational products, and external monitoring and audits; and (3) publication and sharing of preprints, press releases, social media, and misinformation. The COVID-19 pandemic is adversely affecting existing clinical trials for other ailments and diseases, including cancer, with most trials being delayed or deferred. Although urgency is needed to communicate effective treatment and prevention strategies for COVID-19, research efforts should maintain the same high-quality core ethical principles that governed human subject research before the pandemic. Despite the catastrophic devastation caused by the pandemic, the adoption of more flexible, cost-effective methods of conducting clinical trials (without compromising ethical conduct, safety, or data integrity, while maintaining research efficiency) represents a potential silver lining. Streamlining clinical research will help to congruently address other important health issues, despite the ongoing COVID-19 crisis.

Keywords: COVID-19, SARS-CoV-2, clinical research, clinical trials, ethics, misinformation

OPEN ACCESS

Edited by:
Ma'n H. Zawati,
McGill University, Canada

Reviewed by:
Rolf Bass,
Retired, Berlin, Germany
Peter Arányi,
Medical Research Council, Hungary

***Correspondence:**
Hasan Hashem
hh.08847@khcc.jo

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *23 August 2020*
Accepted: *24 November 2020*
Published: *23 December 2020*

Citation:
Hashem H, Abufaraj M, Tbakhi A and Sultan I (2020) Obstacles and Considerations Related to Clinical Trial Research During the COVID-19 Pandemic. Front. Med. 7:598038. doi: 10.3389/fmed.2020.598038

INTRODUCTION

SARS-CoV-2, the causative agent of COVID-19, was identified in Wuhan, China, in early December 2019. It rapidly spread throughout China with highly efficient human-to-human transmission and has now circumnavigated the globe, becoming a worldwide pandemic. The World Health Organization (WHO) first declared it a public health emergency and subsequently a pandemic (1–3). The response to the COVID-19 pandemic by the scientific community was vigorous and with unprecedented speed. Nevertheless, the COVID-19 pandemic has disrupted all aspects of academic medical center research, raising serious concerns (4, 5).

By the time of this writing, 2145 SARS-CoV-2 studies have been registered on the ClinicalTrials.gov website (**Table 1**). These studies cover a wide spectrum of potential therapeutics, ranging from repurposed antibiotics, antimalarials, and antiparasitic medications to various monoclonal antibodies, targeted antiviral drugs, and stem cell therapeutics. Although the WHO has established a blueprint for performing clinical research during the pandemic, many of these studies suffer from overlapping methodologies and a distinct lack of synergy. This is particularly important because the required numbers of study subjects for these trials irrationally fluctuate, rendering some of these studies impossible to complete. The results of these studies may also later affect the design of hundreds of other studies, and ethical concerns are rising as these studies circumvent rigorous scientific standards to achieve results. Such studies and their reporting serve only to muddle facts with contradictory information and are a general disservice to clinicians practicing evidence-based medicine (EBM). Examples of contradictory information resulting from such studies include the benefit or lack thereof of incorporating corticosteroids for patients with moderately severe disease and the changing perspective of chloroquine/hydroxychloroquine efficacy and toxicity.

SUMMARY OF RESEARCH PUBLISHED DURING THE COVID-19 PANDEMIC

A Medline search using the keywords COVID19, COVID-19, and SARS-CoV-2 identified all citations until October 31, 2020. Citations were then categorized according to the type of reference, month of publication, and language. The same keywords were used to search for citations that also included drugs in each category listed in **Table 1**. An automated search method using R (Version 4.0.2) and Easy PubMed package (v 2.13) was used to automatically retrieve citations for different categories.

By October 31, 2020, 71,004 articles were cataloged by the National Library of Medicine. The number of articles increased sharply since January 2020: 428 published in January, 689 published in February, 2269 published in March, 7109 published in April, 11,206 published in May, 13,056 published in June, 14,199 published in July, 12,717 published in August, 13,061 published in September, and 11,495 published in October. The majority (95%) of articles were written in English, followed by Chinese and French (1% each). Only 180 (0.25%) studies out of 71,004 comprised clinical trials including randomized controlled trials (RCTs). A small proportion of publications also reported observational studies ($n = 559$), systematic reviews ($n = 1072$), and meta-analyses ($n = 349$). Editorials and letters represented nearly one-fourth of COVID-19 publications ($n = 16{,}561$, 23%) (**Figure 1**). As of October 31, 2020, The United States published the highest number of studies, followed by France and China (**Figure 2**).

EXAMPLES OF MAJOR FLAWS AND MISINFORMATION PUBLISHED DURING THE COVID-19 PANDEMIC

Although the pressure and urgency for conducting COVID-19 research abounds during this worldwide crisis, this should not preclude scientific principles and ethics (6). Pandemics raise difficult scientific and ethical questions for research in this climate. Therefore, understanding what ethical concerns remain the same and what differs is important for conducting clinical trials during pandemics. For example, the first case report of presymptomatic transmission published in the *New England Journal of Medicine* (*NEJM*) was based on incorrect information because the researchers did not interview the patient, believing her to be asymptomatic during the period in which she exposed others to the virus. However, when German investigators subsequently interviewed her, she reported having symptoms at the time of transmission (7). Additionally, some patient experiences were reported in more than one publication, as described by the editors of the *Journal of the American Medical Association* (8). In a study published in *NEJM* describing critically ill patients who received remdesivir, the time to clinical improvement was calculated as a time event without considering death as a competing risk. This inflated public belief of the drug's benefits because deceased patients do not have an equal chance of improvement and thus cannot be censored (9).

In the following sections, we list and dissect the steps of conducting clinical research in terms of challenges and obstacles that researchers experience and propose solutions to achieve ethically adherent and scientifically sound research (**Figure 3**).

DESIGNING SCIENTIFICALLY SOLID RESEARCH

Scientific and Social Value

All research or clinical trials should embody certain concepts and principles to be considered informative and valuable. Research generally begins with a hypothesis. The aim of this hypothesis and its testing should be important, clinically meaningful, and of value to study participants. The interventions selected for testing should consist of the most promising therapies, as determined by existing data. The value of clinical trials depends on the quality of information produced and the relevance of the data to address public health needs. Nevertheless, there are many less-developed countries that do not have well-prepared medical infrastructure and little or no experience in conducting trials. Moreover, there is

TABLE 1 | Categories of drugs under Investigation for COVID19 Treatment or Prevention (2,145 interventional studies registered on ClinicalTrials.gov as of October 31, 2020).

Category	Studies	Drugs	PubMed	Published clinical trials	Phases of studies							Status of studies					
					1	1/2	2	2/3	3	4	Others	Active, not recruiting	Not yet recruiting	Recruiting*	Completed	Suspended	Terminated/ withdrawn
Antimalarials	196	8	1,917	27	10	3	52	26	69	21	15	15	39	85	21	11	30
Anti-inflammatory	141	24	1,399	8	10	2	33	25	45	12	14	13	30	83	17	2	4
Immune-modulators	138	4	1,320	5	20	9	51	13	17	2	26	9	18	85	16	0	2
Antivirals	122	27	869	27	3	3	56	17	30	5	8	10	30	81	9	5	6
Plasma Infusion	117	39	857	11	4	0	56	16	29	6	6	15	28	80	10	5	5
Antibiotics	83	25	615	8	4	3	20	3	21	7	25	3	26	81	5	1	5
Stem cell therapies	75	6	550	5	4	1	24	7	29	4	6	5	18	81	6	8	8
Dietary/vitamins	71	14	4,097	3	17	16	5	2	24	6	1	13	13	83	1	0	0
Others	70	17	543	93	21	21	17	1	2	1	7	7	18	82	5	0	1
Antiparasitic	66	5	114	1	1	2	23	13	15	4	8	2	23	81	8	0	0
Antibodies	64	19	608	4	2	2	13	7	21	13	6	2	19	82	1	0	2
Anticoagulant	55	31	5,388	4	4	8	20	2	9	7	5	5	11	81	2	1	1
Steroids	51	7	761	9	0	1	13	6	15	9	7	2	10	80	6	1	4
Cardiovascular/antihypertensive	49	25	648	1	1	1	26	10	8	2	1	7	10	80	4	2	2
Vaccines	43	15	182	14	2	3	19	6	6	4	3	2	6	80	2	1	4
Targeted therapies	40	7	119	3	3	4	20	3	8	1	1	5	14	80	0	0	1
Cytokines	32	5	706	17	2	1	15	1	6	5	2	2	8	83	5	1	0
ACE receptor targeted	24	11	789	1	3	0	8	3	3	5	2	0	8	81	2	1	1
Neurologic/anesthetic	21	13	116	3	2	0	7	2	3	3	4	3	8	80	0	0	1
Hormonal (other than steroids)	20	12	1,095	12	3	1	8	2	4	2	0	2	6	80	0	0	1
Traditional/herbal	13	9	746	10	0	2	2	5	2	0	2	0	2	80	1	2	0

Data extracted from ClinicalTrials.gov on October 31, 2020; PubMed search (October 31, 2020) shows hits of drugs in each category in combinations with the following search world (COVID OR COVID-19 OR COVID19 OR SARS-COV-2 OR SARS-COV2); Rows may not add up to the expected total due to some missing or unknown (e.g., status "No longer available" or "Active Not Recruiting"). Columns may not add up to the expected total number due to the overlap in some drugs (e.g., targeted therapies and antibodies) and inability to categorize some studies (e.g., studies of medical devices).

**Recruiting studies include studies recruiting by invitation.*

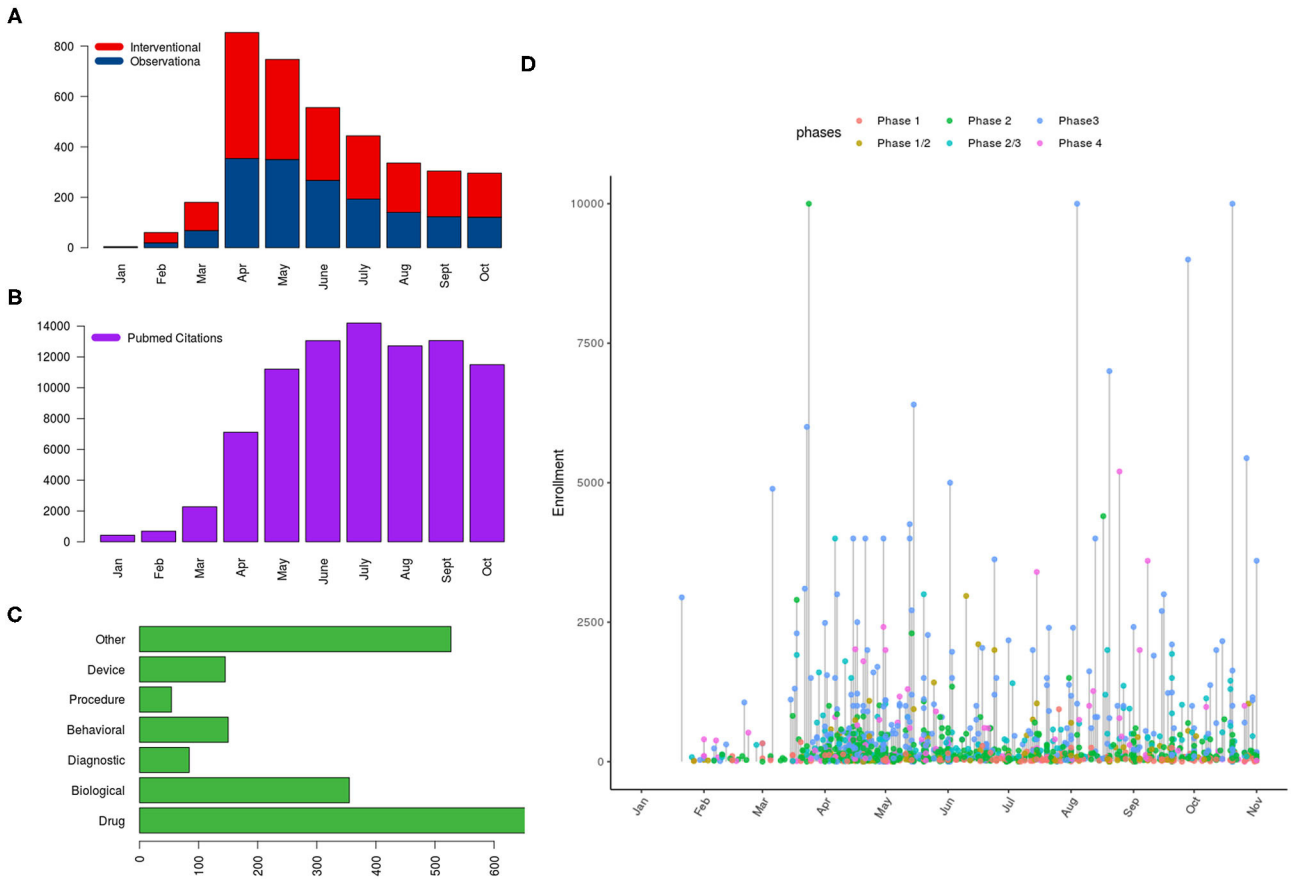

FIGURE 1 | Distribution of clinical trials registered on ClinicalTrials.gov and PubMed citations referring to COVID-19 as of October 31, 2020; the panels show **(A)** the distribution of studies according to type and month of posting, **(B)** number of PubMed citations per month, **(C)** the type of intervention in interventional trials, and **(D)** a lollipop graph showing the anticipated number of subjects to be enrolled on interventional trials with the horizontal axis indicating the date of first posting of studies (year 2020) and the *y* axis indicating the required number of subjects to be enrolled (capped at 10,000); color of the points indicates the phase of trial.

considerable heterogeneity across countries and even within each country, when it comes to health care systems. This may result in some differences in many aspects starting from the review process itself to all the other steps of conducting trials such as data monitoring and patient safety. Accordingly, these regional differences should be closely monitored when conducting clinical trials. Clinical trial design should be rigorous and analyzed with full integrity. The knowledge gained should be reported completely, promptly, and consistently. These trials should meet all regulatory standards and conducted in an effective and safe manner. Sound scientific research principles should not be compromised even during pandemics (10, 11).

Resource Allocation

As the COVID-19 pandemic unfolds, preparedness programs are taking precedence over non-clinical activities deemed non-urgent. Research is a key aspect of responding to pandemics, yet it should never impede response efforts, such as maintaining personnel, equipment, and facilities for treating patients (12). Health care systems are frequently overwhelmed during pandemics because all resources are allocated and diverted to quell the pandemic. All countries share the common constraint of finite budgets and resources for combating pandemics, which is particularly true for the current COVID-19 pandemic (13). Such restricted resources are challenging for multiple steps of conducting clinical research. For example, study feasibility may be affected, leading to a sense that the study may never be completed. For that reason, researchers, sponsors, and regulators must make exceptional efforts to cooperate and collaborate to concentrate resources in the most efficient way while concomitantly ensuring that the standards of scientifically sound research are not relaxed (14). This may be accomplished by testing multiple interventions in collaborative multi-institutional trials. Nevertheless, there are many challenges in multicenter large-scale clinical trials. First, complex protocols will increase pressure on the coordinating center to maintain oversight and avoid deviations. Second, lack of workflow standardization across research sites. Third, data collection and protocol adherence could be challenging due to differences in laws and regulations among different countries. Collaborative efforts among national policy makers, the pharmaceutical industry, opinion leaders, patient advocacy groups, and regulatory agencies are imperative

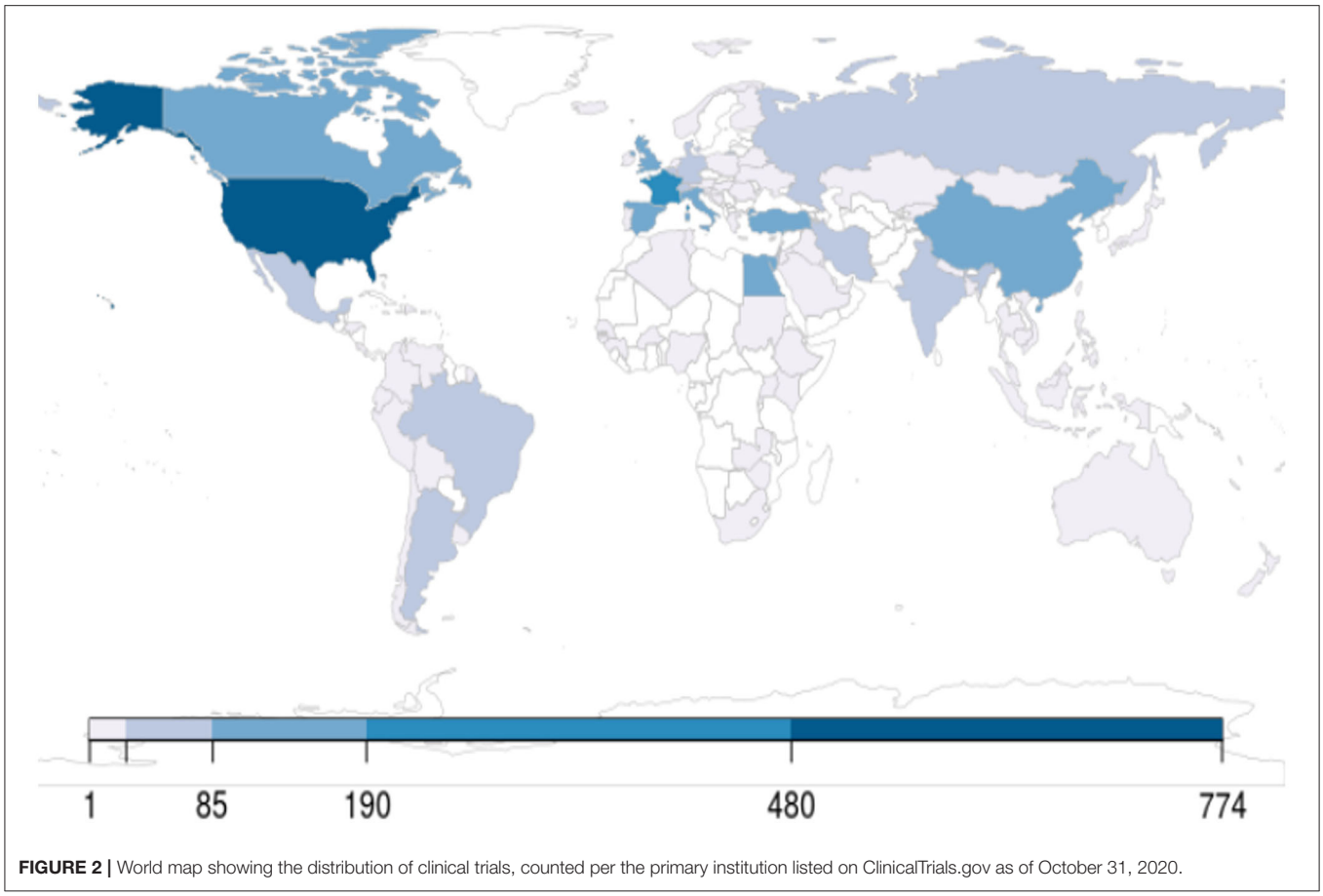

FIGURE 2 | World map showing the distribution of clinical trials, counted per the primary institution listed on ClinicalTrials.gov as of October 31, 2020.

for containing the pandemic because of their oversight roles, which should be used to expedite trials that meet all of the standard core ethical and scientific requirements but also minimize and prevent duplicated and underpowered studies.

Drug Repurposing

Drug repurposing is an attractive strategy for treating a novel disease because it offers lower costs and reduced time to reach the market. This strategy alleviates some clinical trial steps, especially those concerning the strenuous diligence and time required for phase 1 and 2 trials (15). Because the safety profiles of repurposed drugs are established, using previously existing therapeutic agents designed to treat other diseases and pathologies, especially those similar to SARS-CoV-2/COVID-19, is a particularly appealing approach (16, 17). Moreover, this approach may be the only practical method for establishing a rapid response to an emerging pandemic. Indeed, existing pharmaceutical supply chains are available for formulation and distribution.

Evidence vs. Emotional-Based Medicine

EBM is not and should never be emotion-based medicine. "Listening to your gut," administering unsubstantiated treatments in a panic response, and conducting hasty science are regressive approaches. The unprecedented speed of concept-to-implementation RCTs in only a few weeks provides proof of concept that properly conducted RCTs can be promptly initiated in the middle of a pandemic. Abandoning sound scientific principles in the face of pandemic simply because we are overwhelmed is clearly unacceptable (18).

INSTITUTIONAL REVIEW BOARD AND ETHICAL APPROVAL

Ethics in Research During the COVID-19 Pandemic

Planning and conducting clinical research during pandemics elicit a number of ethical issues that must be addressed. To this end, some stakeholders debated whether it is ethical to conduct research at all in the midst of a pandemic. Some were skeptical of activities that may draw efforts away from the mission of providing clinical care to patients affected by the pandemic. However, some argued that the pandemic presents the best opportunity to conduct COVID-19 clinical research. Indeed, the WHO Research Ethics Review Committee stated that conducting research is an ethical obligation. Despite the sense of urgency elicited by the pandemic, research is still subject to the same core ethical principles that govern research on human subjects. Specifically, clinical research must minimize harm by saving lives and ensuring that informed consent is always obtained, despite

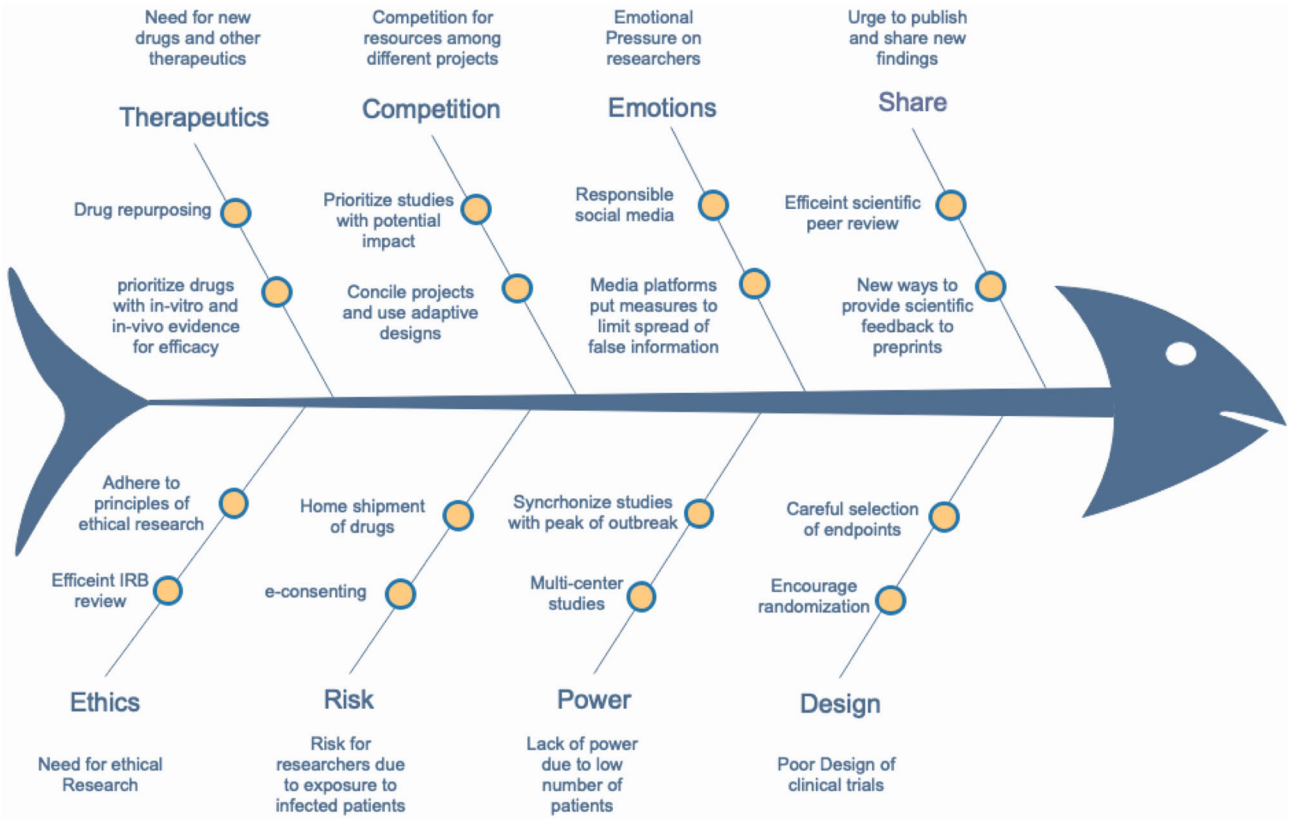

FIGURE 3 | A fishbone diagram showing the main obstacles for conducting efficient COVID-19-related research and some suggested solutions.

the pandemic, while ensuring efficient use of resources (19). However, a paltry amount of studies focusing on ethical guidance for conducting research during pandemics are published (20–23). Nevertheless, the way we currently conduct research must be adaptable and evolve as the current pandemic unfolds because it can provide us with a new understanding and discovery of methods that can make conducting research faster, safer, and more efficient. Maintaining ethics in research is imperative to providing answers for questions in which no black-and-white answers are available. One such question is how to ethically allocate scarce resources for research when health care systems are stretched beyond capacity. Another such question is how to ethically balance the public health resources needed to combat the pandemic with those needed by research designed to find potential remedies for the same pandemic (24).

Institutional Review Board Efficiency

Thousands of clinical trials were registered in the first few months after COVID-19 was declared a pandemic. If ethics committees cannot review such a large number of clinical trials and ensure that they maintain a high standard, many high-risk and low-benefit drugs may potentially be used to treat patients with COVID-19. Not only will these patients be at risk for unknown complications but valuable resources may also be unallocated for more meaningful research. The ethical review for COVID-19 research at this time occurs under exceptional circumstances. Institutional review boards (IRBs) should particularly consider such issues as strict inclusion and exclusion criteria, participant compensation, and clearly defined risks of the trial to vulnerable patients (25). Moreover, IRBs must ensure that the standard of ethical review is not relaxed (26). To improve IRB expediency during pandemics, pre-study documents should be available and generally easy to complete as quickly as possible. Such documents include signed protocols by principal investigators, financial disclosure forms, conflict of interest disclosure forms, letters of agreement with sponsors, and informed consent forms. Template case report forms (CRFs) should be made available for modification and online entry. IRBs should be continuously informed of research progress. Notifying IRBs about form modifications may also help to expedite the review process.

Virtual Visits and Remote Monitoring

Travel bans, quarantines, and stay-at-home measures have been implemented to variable degrees throughout the world. Moreover, the risk of transmission of infection not only for participants (if they are healthy) but also for research staff who should be aware of the added risk of infection during in-person visits is an important consideration during pandemics. This introduces limitations on scheduled study assessments and

procedures for patients. Therefore, careful risk assessments must be performed before applying for IRB approval to establish in-person visit purpose, frequency, and extent of monitoring needed for proposed clinical trials (27, 28). To mitigate the likelihood of infection, remote monitoring in the form of telephone and/or video visits is strongly recommended but should be limited to essential core data and kept to a minimal frequency to avoid unnecessary burden on the investigator and trial team. These essential data include screening for inclusion and exclusion criteria, investigational drug doses and dose regimens, and serious adverse events. Using patient local facilities for laboratory investigations and imaging are also alternative approaches for regular study assessments. However, such modifications depend on the type of research, as some studies require frequent monitoring and require face-to-face encounters (29, 30).

Shipments of Investigational Products

To ensure the safety and well-being of participants and to ensure the continuation of clinical trials according to their protocols during the COVID-19 pandemic, it may be necessary to send investigational drugs directly to trial participants. Pharmacovigilance remains of paramount importance to ensure the security, accountability, traceability, and compliance of participant-administered investigational drugs. To maintain patient privacy and data confidentiality, delivery of investigational products directly from trial sites to patients may be necessary. Shipments should occur in a manner that allows tracking of both transport and delivery, and participants should acknowledge receipt of shipments. Written instructions on the storage and use of the investigational drugs should be provided to participants. Moreover, documentation of all communication between providers and patients and instructions remains vital (29).

Informed Consent

Since the medical guidelines established by the Nuremberg Code and later the Declaration of Helsinki were introduced, informed consent became a common and fundamental part of clinical research. The quality of the consent process greatly depends on the time constraints of the procedures. Obtaining informed consent is usually performed with paper forms explaining the research purpose, procedures, and potential adverse effects, which are signed by participants. During pandemics, researchers must consider the risk of transmission of infection through paperwork. Because data acquisition, capture, and storage are often performed electronically, electronic acquisition of informed consent is logical. Verbally attained consent for patients under quarantine can be obtained first in the presence of a witness followed by written consent when the participants are released from quarantine. An alternative approach to minimizing the risk of infection while maintaining all principles of informed consent is through virtual e-consents (31). However, the electronic system for virtual e-consents must include a method to verify identity. Study personnel should also ensure that the information presented to participants is understandable in a language they comprehend. This may be addressed by a checkbox (i.e., "I understand and agree"). Study personnel may help navigate the consent process by clicking on links for the participants. Study participants should also be provided with enough time to meaningfully complete the informed consent process. This may be challenging for sick and critically ill patients; therefore, a surrogate decision maker or legally authorized representative can obtain consent. Ideally, a uniformly accepted procedure should be adopted for all investigators performing research with critically ill subjects (32–34).

External Monitoring/Audits

Oversight responsibilities should be maintained during pandemics to ensure the quality of the research. Temporary alternatives for external monitoring should take into account appropriate oversight and site capacity. Such alternatives may include postponing of on-site monitoring visits, extending the period between visits, and implementing video or phone visits supplemented with centralized monitoring and review. Audits should be postponed and, when conducted, should follow social distancing roles. As the pandemic ends, robust visits and monitoring should return to the pre-pandemic processes. We acknowledge that the COVID-19 pandemic will most likely introduce protocol deviations; these deviations should be managed according to standard procedures in a manner that is in the best interest of the participants without exposing them to unnecessary risks (35).

CLINICAL TRIAL DESIGN/CONDUCT

Single vs. Multi-Center Trials

The urgency of the international response to the COVID-19 pandemic has challenged research coordination and collaboration, resulting in hundreds of independent efforts to test various interventions (13). To achieve rapid yet scientifically sound results, research duplications and competition for recruitment should be avoided (14). Nevertheless, data collection in multicenter trials is challenging. By engaging multiple sites, timely insights into important design and feasibility issues of the recruitment rate and protocol adherence can be acquired. Data collection that is internet-based may facilitate these scenarios. The COVID-19 pandemic has underscored the need for trust in science and global collaboration. Many national regulatory authorities have set up streamlined and fast-track clinical trial approval processes. However, the lack of harmonization between national regulations is slowing down the implementation of international clinical trials. Governments and key regulatory authorities are encouraged to seize the opportunity provided by the current exceptional situation to significantly advance the international harmonization of multiple aspects of clinical trial regulations. There are few examples of international efforts such as working with the International Council for Harmonization (ICH), which has developed a number of guidelines such as MedDRA (Medical Dictionary for Regulatory Activities) for the harmonization of the technical requirements for pharmaceutical products and could facilitate discussion on regulatory standardization. Another example is CARE (Corona Accelerated R&D in Europe), a new consortium supported by the Innovative Medicines Initiative (IMI) public–private partnership

announced to accelerate the discovery and development of urgently needed medicines to treat COVID-19.

Large vs. Small Trials

Adequately powered trials are essential for making important discoveries. A study that enrolls thousands of patients can answer vital questions with confidence, such as whether or not COVID-19 is treatable. However, these studies involve very complex logistics and are consequently very expensive, reducing the ability to screen an adequate number of drugs. If a drug is truly capable of treating COVID-19, this should be evident in a small sample. Endpoints should be designed to capture this difference. For example, achieving a 50% reduction in the time to clinical improvement requires a smaller cohort of patients who need to be treated (NNT) than does a drug achieving a 20% reduction in the time to clinical improvement. The former is more clinically relevant, but the latter is more sensitive and is more likely to avoid premature withdrawal. The NNT cost should be balanced to the available resources and number of agents to be tested. An adaptive approach that permits dynamic changes in the NNT and endpoints according to interim analysis results is being used more commonly during the pandemic (36, 37).

Feasibility

Studies must be feasible and thereby designed so that they can be completed within a time frame that the findings are still relevant. Priority should be given to interventions that reflect the specific needs of the patient population and are readily implementable. For patients in low-income countries, interventions should be affordable and rapidly available. During a pandemic, greater flexibility is needed for conducting clinical trials. A move toward decentralized clinical trials conducted across satellite sites may improve the adaptability of such trials (38, 39). In decentralized clinical trial models, data can be collected at remote locations *via* modern virtual methods. However, barriers and challenges to this model include a greater reliance on data security and increased complexity in supply chain logistics. The solution to these challenges is a hybrid model incorporating decentralized components only during times of crisis, but a greater degree of risk sharing than is currently acceptable is necessary.

Randomization

COVID-19 trials should have a rigorous design; they should be adequately powered and well-designed to generate clinically meaningful data. RCTs are the gold standard for providing efficacy data (18). During pandemics, the temptation to make unproven therapies widely available and not waiting for rigorous clinical trial data to be generated is understandable (25, 40). However, RCTs can be conducted quite rapidly. Thousands of new patients with COVID-19 seek care each day worldwide; therefore, patient accrual requirements, an often rate-limiting step of clinical trials, can be met quickly for COVID-19 clinical trials. However, the sense of urgency to discover efficacious treatments for COVID-19 should not circumvent high standards of research because this could prove detrimental to their quality. The moral mission of research remains the same—to reduce uncertainty and enable caregivers and health care systems to address individual and public health matters. Randomization between low- and high-dose drug treatment arms or between short and long drug durations is only useful after the investigational drug is found to be more efficacious than the standard of care. The rush to offer unproven treatments outside of well-designed clinical trials undermines high-quality science and condemns us to repeat age-old errors.

Many factors can contribute to the fallacy of research exceptionalism (10). First, some evidence, even if flawed, may be preferable to those seeking immediate treatments than is expanding resources on more demanding studies whose benefits will only materialize later. The rapid results generated by hasty research are generally less adherent to the established protocols and quality controls required to produce sound science. Second, some may view that randomizations and placebo comparators conflict with clinician care obligations in urgent conditions. Third, researchers and sponsors may be assumed to be free to exercise broad discretion over trial design. However, most small non-controlled or non-randomized studies are arguably built upon preclinical research findings that are often not confirmed in subsequent well-designed trials. The case for and against hydroxychloroquine is a notable example of this (41). It is important for researchers to realize that every patient treated in an uncontrolled trial is someone being subjected to experimentation without the possibility of contributing to the body of scientific knowledge. Adaptive-designed RCTs should be prioritized during the COVID-19 pandemic and future pandemics. Such RCTs permit investigators to accept or reject multiple experimental therapies throughout the trial, dropping those showing the weakest efficacy and adding new promising treatments, while remaining adequately powered (36, 37, 42).

Off Label, Compassionate Use, and Historical Controls

During the Ebola outbreak in 2014, numerous therapies were tested. Ultimately, however, none were found to be efficacious. Because nearly all of these studies comprised single-arm trials with no concurrent controls, no definitive conclusions emerged (43). The world is now facing a similar situation with the COVID-19 pandemic, with no proven therapies materializing after 6 months from the start of the pandemic. Administering unproven drugs as a last resort incorrectly assumes that the chance of it benefiting the ill is higher than the chance of harming them. In the absence of a control group, it is impossible to know whether patients are benefited or harmed. Furthermore, determining whether adverse effects occurring in patients are caused by the investigational drug or the disease is irresolvable (44). Other methods of comparison, such as historical control data, are unlikely to produce reliable results because supportive care approaches frequently evolve. A common but untrue interpretation of compassionate and off-label drug administration is that if patients die, it is of their disease, but if they survive, it is because of the drug. Discovering new drugs while simultaneously ensuring that they will most likely help to relieve disease symptoms over than of alternatives is imperative; otherwise, therapies for future

coronavirus pandemics are not guaranteed, risking another worldwide standstill in the future (45, 46).

Endpoints

Surrogate measures are not intrinsically beneficial to patients but are designed to be easier and faster to measure than clinically meaningful outcomes. Surrogate endpoints trade the advantage of reducing the time needed to conduct clinical trials for the disadvantage of treatment effect uncertainty. However, during the tumultuous events unfolding during pandemics, when pressure constantly runs high, does this same strategy still hold true? Whether this trade-off is beneficial or detrimental to patients deserves further scrutiny. French investigators were the first to report promising hydroxychloroquine data, although their study was underpowered and six patients were removed from analysis because of unfavorable outcomes (47). Their erroneous positive findings were due to using surrogate measures, i.e., SARS-CoV-2 clearance. Determining the extent in which randomization should have in trials of new interventions is an important consideration. It is also important to consider the endpoints being measured. For example, survival or 28-day morality would be useful endpoints for clinical trials of ventilated patients who have high mortality rates. In contrast, seven-category ordinal scales, which are recommended by the WHO, may be more useful primary endpoints for trials of mild-to-moderate cases because these patients have a much lower risk of death. Moreover, seven-category ordinal scales may minimize potential bias between different trials and sites for their definitions of severity (48).

DATA ANALYSIS AND INTEGRITY

In any clinical trial, information should be collected, recorded, and handled in a way that allows for accurate reporting, interpretation, and verification. Trial success depends on the quality and management of the collected data. Subject privacy should be protected by identification numbers or other methods. Patient folders should contain completed informed consent forms, screening sheets clarifying inclusion and exclusion criteria, patient CRFs, laboratory values, and a record of all communication with the subject. Data safety monitoring boards with relevant clinical expertise, completely independent of the investigators, should be available to evaluate interim data to ensure that participants are not exposed to additional risks (35). During the COVID-19 pandemic, participants have been hesitant of going to hospitals. Therefore, alternative methods, such as telehealth-mediated patient visits, are encouraged to obtain data. These designs should be pre-specified in protocols, prospectively registered, and analyzed accordingly.

PUBLICATION AND SHARING

Peer Review and Preprints

Researchers are ethically obligated to share information as soon as it is quality controlled for release (i.e., peer-reviewed). This may add pressure to the peer-review process to increase efficiency during pandemics. Because reviewers are a scarce resource, especially during pandemics, this can lead to an influx of low-quality publications. Moreover, depositing positive findings to preprint servers earlier than negative findings can introduce bias and may be misleading. Although preprints may expedite communication of notable findings, they also entail certain risks. Many preprints are later rejected or changed to state different conclusions that were initially stated. The publication process must adhere to the principles of publication ethics to promote integrity, accuracy, and value of scholarly publications. These principles are as follows: (1) ensure scientific accuracy and validity through peer review, (2) provide social value, (3) protect participants and affected communities by ensuring that reviewers respect and maintain patient confidentiality and ethics, (4) disclose conflicts of interest and limitations of the data, and (5) hold researchers and journal editors accountable for published data (49, 50). The pressure to publish COVID-19-related articles has led to fast-tracking the peer-review and publication process, resulting in six- to eightfold faster reviews and subsequent online publications than before the COVID-19 pandemic (51). Because the review process is often criticized as a lengthy process that is less efficient than the needs of the scientific community before the pandemic, lessons from this experience should be extended after the pandemic ends.

Social Media, Press Releases, and Misinformation

At the time of this writing, many dubious COVID-19 cures and miracle remedies have spread across social media, reaching vast audiences every day. Social media and online sites are the primary platforms from which false, inaccurate, and misleading information is disseminated because they facilitate rapid and large-scale sharing with little to no adherence to the traditional mechanisms of quality control and gate-keeping outside of the scientific community (52, 53). Misinformation, in which misleading stories are circulated generally in good faith, can propagate outright falsehoods. The demonization of vaccinations on the basis of shoddy and untrue data is a well-known example of misconstrued medical and health care information, culminating in the "anti-vax" movement (54). Therefore, it is not surprising that the COVID-19 pandemic has also been inundated with misinformation. Despite the lack of an effective cure for COVID-19 and thousands of clinical trials registered on ClinicalTrials.gov, misleading news of many potential therapies continues to spread on social media, building hype toward them without acknowledging that many trials will most likely result in negative findings and provide no use toward ending the pandemic. The WHO warned in February 2020 that the COVID-19 pandemic is coupled to an infodemic, i.e., an overabundance of information and misinformation masquerading as truth. The consequences of such infodemics are the spread of uncertainty, fear, and anxiety (55, 56). To mitigate the harm caused by the infodemic, the WHO created a section on its website devoted to myth-busting and debunking false information. As of August 2020, the WHO has been publishing daily reports to provide the population with reliable data. Moreover, search engines such as Google and social media platforms such as Facebook, Twitter,

and YouTube have established measures to both limit the spread of false information and direct users to reliable sources (57).

EFFECT OF THE COVID-19 PANDEMIC ON NON-COVID-19 RESEARCH (CANCER RESEARCH AS AN EXAMPLE)

The complexity of cancer research has been further complicated by the COVID-19 pandemic. COVID-19 has interrupted the launching of new clinical trials because of reduced resources (29, 58). Many patients were enrolled in clinical trials before the pandemic, and as the pandemic progressed, investigators were forced to limit patient visits and constrain their research to essential laboratory studies, causing delays in data collection and reporting (59). The COVID-19 pandemic is halting subject recruitment and hampering the speed and quality of data collection and analysis. To minimize the impact of the pandemic on research, clinical trials investigating potentially life-saving drugs should be prioritized. Investigators conducting clinical trials during the pandemic must be wary because increased protocol deviations can be expected, potentially affecting general patient safety due to missing or late reporting of adverse events (24). The Centers for Disease Control and Prevention and National Institutes of Health have both released guidelines for continuing research during the COVID-19 pandemic (60, 61). Trial sponsors should expect missed follow-ups and report them as deviations. Establishing contingency plans and maintaining sponsor and contract research organization alignment are some of the key issues for continuing cancer research (62–64).

CONCLUSION

The international scientific community must review and self-criticize its response to the COVID-19 pandemic. With more than 40 million people affected and 1 million deaths, efforts should not concentrate on any single aspect of conducting clinical trials but should rely on high-quality standards to demonstrate which therapeutic strategies are the most beneficial for patients. Although we cannot reliably predict which intervention will be most effective for treating COVID-19, well-designed, unbiased clinical trials are necessary to elucidate these interventions. Genuine knowledge can only be gained through objective scientific methods rather than personal or emotionally driven methods, such as mere conjecture or empiricism. Adapting more efficient and cost-effective methods for conducting clinical trials, without compromising ethical conduct, safety, or data integrity, should be the lesson learned from this catastrophe. We will repeat these mistakes in the next pandemic if we do not implement what we have learned in our future research endeavors.

AUTHOR CONTRIBUTIONS

HH and IS designed the study, reviewed the literature, and wrote the manuscript. MA and AT wrote the manuscript. All authors approved the final manuscript.

ACKNOWLEDGMENTS

The authors thank Yaseen Sultan for reviewing and proofreading the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 05 January 2021
doi: 10.3389/fmed.2020.576820

Mixed Method Study to Explore Ethical Dilemmas and Health Care Workers' Willingness to Work Amid COVID-19 Pandemic in Palestine

Beesan Maraqa[1,2]*, *Zaher Nazzal*[3]* and *Therese Zink*[4]

[1] Primary Health Directorate, Ministry of Health, Ramallah, Palestine, [2] Family Medicine Residency Program, Faculty of Graduate Studies, An-Najah National University, Nablus, Palestine, [3] Department of Family and Community Medicine, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine, [4] Department of Family Medicine & School of Public Health, Brown University, Providence, RI, United States

Background: The high potential risks involved in working in a healthcare setting during a pandemic and the associated fear that may affect health care workers' (HCWs') willingness to work are important to understand to eliminate potential barriers to working. This study aimed to assess Palestinian HCWs' willingness to work and the related factors as well as to explore their ethical dilemmas during the coronavirus disease 2019 (COVID-19) pandemic.

Materials and Methods: Quantitative (survey questionnaire) and qualitative (semi-structured interviews) data were collected. Frontline HCWs ($n = 550$) received an online survey link via closed institutional networks. Frequencies summarized the data, and chi-square compared variables and outcomes. Odds ratios (ORs) and multivariable analysis examined predictors for willingness to work. Fifteen HCWs (physicians, nurses, and lab and radiology technicians) were purposefully sampled and agreed to interviews to explore their thoughts, motivations, and worries. Thematic analysis focused on ethical dilemmas to enhance the breadth and the depth of the study.

Results: Almost 25% of surveyed HCWs were not willing to work during the pandemic. Logistic model results showed that physicians and nurses had higher willingness to work than others ($p = 0.004$, Adj. OR = 3.5). Lower stress levels and longer professional experience were predictors of more willing to work ($p = 0.03$, Adj. OR = 2.5; $p = 0.03$, Adj. OR = 2.6, respectively). Interviews showed that willingness to work did not preclude HCWs from fulfilling their duties despite grueling workloads and grave fears about safety and security. HCWs felt poorly prepared, unappreciated, and frustrated by unfair work distribution. The occupation presented additional safety issues.

Conclusion: Physicians and nurses were more likely to comply with a commitment to their professional ethics and the duty or obligation to work. Stress levels could be mitigated in the future with better leadership, adding supports to address mental health and psychosocial challenges to enhance HCWs' well-being and improve quality of care. The realities of the occupation added additional threats and uncertainty.

Keywords: COVID 19, ethical dilemmas, willingness to work, duty to work, health care workers, Palestine

OPEN ACCESS

Edited by:
Ma'n H. Zawati,
McGill University, Canada

Reviewed by:
Frits Lekkerkerker,
Consultant, Enschede, Netherlands
Michael Lang,
McGill University, Canada

***Correspondence:**
Beesan Maraqa
dr.beesan.maraqa@gmail.com
Zaher Nazzal
z.nazzal@najah.edu

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *27 June 2020*
Accepted: *25 November 2020*
Published: *05 January 2021*

Citation:
Maraqa B, Nazzal Z and Zink T (2021) Mixed Method Study to Explore Ethical Dilemmas and Health Care Workers' Willingness to Work Amid COVID-19 Pandemic in Palestine. Front. Med. 7:576820. doi: 10.3389/fmed.2020.576820

INTRODUCTION

The coronavirus disease pandemic of 2019 (COVID-19) was an unprecedented challenge for health care systems across the globe. Frontline health care workers (HCWs) were in the midst of contradictory and limited information about the type, severity, infectiousness, and necessary precautions required during the outbreak.

The COVID-19 pandemic with the rapid spread especially in Europe and United States (US) caused significant concerns as to how best to provide health care in emergency conditions and scarcity of resources (1, 2). The need goes even deeper in the Middle East and North Africa region (MENA), where the existing infrastructure is under stress, which likely intensifies the uncertainty and widens the gaps between those with more robust digital capability and those without (3).

Palestine is one of the countries struggling with compounding challenges of uncertainty, fragility, social mobility, and poverty. In addition, the pandemic reveals "triple tragedies," composed of the COVID-19 pandemic, the politics of continued occupation by Israel, and the challenge of Intra-Palestinian dissent (4). The health care system in Palestine is divided into three levels: primary, secondary, and tertiary. The primary level represents the gateway into the health care system, and the secondary and tertiary consist of hospitals and rehabilitation centers. The four main health service providers working in the Palestinian Territories are the Ministry of Health (MOH), United Nations Relief and Works Agency (UNRWA), non-governmental organizations (NGOs), and the private sector. The key providers of primary care services are MOH and UNRWA. The primary suppliers of secondary services are the MOH and NGOs. The private sector is the largest source of tertiary care. For this pandemic, the major workload was on primary health care (PHC) workers who had to trace contacts and screen high-risk groups and emergency departments at major hospitals, in addition to newly established COVID-19 hospitals that added a challenge for the scarce PHC personnel and resources. It is believed that those delivering health care have a strong obligation to perform, often in the face of personal danger—a duty that is enshrined in the professional codes of conduct (5). However, any emergency event involving contagion or contamination, as with the COVID-19 pandemic, has the potential to alter HCWs' willingness to work for different reasons (6). A recent Cochrane review of previous pandemics reported lack of training about the infection itself and how to use personal protective equipment (PPE), shortage of and low-quality PPE supplies, as well as increased workloads and fatigue among HCWs, ambiguous work settings, and rapidly changing guidelines as the tip of the iceberg during prior experiences, whereas HCWs' fear of catching infection themselves or infecting their families and the psychosocial burden of the pandemic were hidden below the surface (7).

In severe acute respiratory syndrome (SARS) outbreak on 2003, frontline HCWs found themselves in the midst of conflicting and confusing reports and reflected ethical issues such as trust, truth-telling and relationships with colleagues, resource allocation, and public health and infection control (8). Major ethical dilemmas that HCWs could face during this pandemic are balancing their ethical duty to care for their patients against their concerns of contracting COVID-19 and spreading it to their patients and families. Limited availability of PPEs, inequitable distribution of available equipment, and limited and constantly changing recommendations could increase such concerns (9).

Regarding the COVID 19 pandemic, a variety of critical ethical concerns arising from fair allocation of scarce medical resources such as ventilators and resuscitation services (10, 11) to challenges facing HCWs during their duty to treat in extreme circumstances is recognized (12). Cross infection worries place HCWs at a challenging intersection in their duty to work whether to relieve themselves of their work duties if possible or to respond to the ethical sense of duty to patients and community (13). However, studies addressing ethical problems are scarce in the Eastern Mediterranean region, where the trend of mortality and morbidity in COVID-19 varies from that of the European and American regions.

Taking into consideration the potential risks involved in working in a health care setting during a pandemic, and the associated fears, it is important to explore how motivated HCWs are to continue to work during such a crisis and what factors might influence their decisions (14). HCWs' willingness to work in a pandemic ranged from 23.1% at Hong Kong's influenza A (H1N1) pandemic in 2009 to 95.8% in US medical students targeting a hypothetical influenza pandemic. Females were less willing and able to work than males. By working group, physicians were more likely to be willing to work, followed by nurses and other HCWs. Personal safety at work and perception of the risk of a pandemic have been described as factors influencing the willingness to work as well as the availability of PPE and previous training (15). Careful management of these factors can make it possible to implement strategies to address the concerns and fears of HCWs and to eliminate potential barriers to working. No existing literature on the willingness to work on COVID-19 pandemic has been identified. In addition, no one discussed the willingness to work related to ethical concerns. In this study, we aimed to assess Palestinian HCWs' willingness to work and the related factors. Additionally, we intended to explore the ethical dilemmas of concern during the COVID-19 pandemic.

MATERIALS AND METHODS

Study Design

The research involved the combined use of qualitative (interviews) and quantitative (questionnaire) data collection to assess the willingness to work among frontline HCWs and contributing factors. Data were collected in two phases. First, a quantitative cross-sectional study using an online questionnaire that targeted frontline HCWs (physicians, nurses, and lab and radiology technicians) working in hospitals and PHC centers was utilized, and a second phase used semi-structured interviews to enhance the breadth and the depth of the study.

Quantitative Phase

Data Collection and Sampling

A self-administered questionnaire was constructed and refined from previous studies (16, 17) to address the study objective. It was designed using the Web-based application Google Forms, then the questionnaire link was distributed to HCWs through closed institutional (WhatsApp) groups. This method takes advantage of the high rates of Internet use among Palestinians and allowed us to reach as many frontline HCWs as possible given the COVID-19 quarantine and social distancing guidelines. 2 weeks later, a follow-up reminder was sent to HCWs, and a final reminder was sent after another 2 weeks. The questionnaire was completed during the 2nd month of the COVID outbreak in Palestine. Respondent anonymity was preserved using the Web-based survey method for data collection and collation. Web-based tools (such as Google Forms) protect information confidentiality when returning the questionnaire and prohibit other participants from accessing information. Furthermore, no identifying questions were included in the survey.

Sample size calculations for the quantitative part were based on the formula: [Necessary Sample Size $= Z^2$ * expected willingness prevalence * (1- expected willingness prevalence)/(margin of error)^2]. Using an expected proportion of 50%, a 95% confidence interval (CI), and a 5% absolute precision on either side of the proportion, the minimum required sample size was 340 HCWs. This was inflated by 60% to compensate for the expected non-response rate and sent to 550 HCWs using a convenience sampling method.

Instrument

The questionnaire is composed of two parts. The first part assessed participants' basic demographic information: age, sex, experience, work setting (PHC vs. hospital), and having children. Whether or not they lived with family during the outbreak and dealt with positive COVID-19 cases was explored. Willingness to work was assessed using a direct yes/no question, "Are you willing to work during this COVID-19 pandemic?" The second part assessed their stress level, attitudes, and disappointments during their work duty amid the COVID-19 outbreak with a Likert scale of 0 to 5. A direct question has been asked about HCWs' feeling of stress during the pandemic "I feel stressed because of the COVID-19 outbreak," and a group of questions have been asked about factors that may affect their stress, such as fear of being susceptible or transmitting the disease to their families and lack of experience and preparedness. A rank of more than three was used as a cut point (**Supplementary Material 2**).

The questionnaire was pretested for its validity and reliability. Three experts in the field reviewed the instrument for face and content validity, and we piloted it on 20 HCWs with similar sociodemographic and professional characteristics to the study population. This helped us reframe and reword some questions and provided feedback on the feasibility of the Google Forms questionnaire link. Reliability was measured by the internal consistency of the questionnaire with a Cronbach Alpha of 0.90, which indicates excellent reliability.

Statistical Analysis

Quantitative data analysis was completed with the Statistical Package for the Social Sciences software (SPSS version 20.0). Categorical sociodemographic data were summarized by frequencies and percentages of occurrence. The chi-square test was used to compare between categorical variable and the study outcome; associations are presented as odds ratios (ORs) and 95% confidence intervals (95% CIs). Multivariable analysis was conducted to assess for predictors of willingness to work and to control for confounders. A p-value of 0.05 was used to determine statistical significance.

Qualitative Phase

Data Collection and Sampling

Second, a qualitative study using semi-structured interviews explored HCWs' thoughts, worries, fears, reasons, and motivations related to the duty to work during the pandemic. The interview guide was developed from literature review, and the preliminary knowledge of the quantitative findings allowed us to explore areas such as participant motivations in greater depth (13, 18, 19). Initial questions explored HCWs' thoughts about their duty to work during the COVID-19 pandemic, factors motivating them to work, how they perceived their relationships with their colleagues, the barriers they faced, and their most challenging issues. A final question probed their perceptions of the risks and fears about working in the current circumstances (**Supplementary Material 1**).

Fifteen frontline HCWs (physicians, nurses, and lab and radiology technicians) were purposively sampled (20). Interview participants were chosen for various geographical locations on the West Bank (North, Center and North), taking both gender and job requirements into account. They were approached toward the end of the third month of the COVID outbreak *via* e-mail or text. If the HCW agreed to be interviewed, informed consent was obtained verbally and confidentiality was affirmed. HCWs were interviewed in a private place of their choice. Interviews were conducted face-to-face when possible or by telephone to those working in quarantined areas. The interviews were audio recorded and lasted an average of 30 min.

Interview Analysis

Transcripts were transcribed word for word, reviewed against the transcripts in order to ensure accuracy, and translated into English. One researcher (TZ) sorted data into topical categories for further analysis and identification of patterns and themes and assigned codes. These were discussed with the interviewer/researcher (BM) and further organized into themes and subthemes with a focus on the different bioethical dilemmas participants faced. Discussion occurred until consensus was reached and appropriate quotes were selected. The analysis methods used are defined by Creswell and Poth (21).

Ethics Statement

Ethical approval was secured from the institutional review board (IRB) at An-Najah National University. All participants were informed about the purpose of the study, the voluntary nature,

TABLE 1 | Participants' background characteristics and the association with willingness to work.

Variable	Total ($n = 357$) N (%)	Willing to work		*P*-value*
		Yes (%) 268 (75.1)	No (%) 89 (24.9)	
Age				<0.001
<35 years	166 (47.2)	109 (56.7)	57 (34.3)	
≥35 years	186 (52.8)	154 (82.2)	32 (17.2)	
Sex				0.056
Female	197 (55.3)	140 (71.1)	57 (28.9)	
Male	159 (44.7)	124 (79.9)	32 (20.1)	
Work setting				0.036
PHC	203 (56.9)	161 (79.3)	42 (20.7)	
Hospital	154 (43.1)	107 (54.6)	47 (30.5)	
Job title				0.024
Physician	156 (43.7)	120 (76.9)	36 (23.1)	
Nurse	161 (45.1)	125 (77.6)	36 (22.4)	
Others	40 (11.2)	23 (57.5)	17 (42.5)	
Experience				<0.001
<10 years	154 (43.1)	98 (63.6)	56 (36.4)	
≥10 Years	203 (56.9)	170 (83.7)	33 (16.3)	
Having children				0.015
Yes	269 (73.6)	211 (78.4)	58 (21.6)	
No	87 (24.4)	57 (65.5)	30 (34.5)	
Living with family				0.48
Yes	316 (89)	235 (74.4)	81 (25.6)	
No	39 (11)	31 (79.5)	8 (20.5)	
Dealt with COVID-19 case				0.3
Yes	129 (36.1)	101 (78.3)	28(21.7)	
No	228 (63.9)	167 (73.2)	61 (26.8)	

*Chi square test.

TABLE 2 | Health care workers' attitudes and factors related to willingness to work.

Factors/attitude	Willing to work		*P*-value*
	Yes (%) 268 (75.1)	No (%) 89 (24.9)	
Stress from catching infection			0.007
Yes	222 (72.5)	84 (27.3)	
No	46 (90.2)	5 (9.8)	
Feeling safe			0.001
Yes	90 (87.4)	13 (12.6)	
No	78 (70.1)	76 (29.9)	
Fear from transmitting infection to family			0.27
Yes	243 (74.3)	84 (25.7)	
No	25 (83.3)	5 (16.7)	
Perceive susceptibility			0.002
Yes	220 (72.1)	85 (27.9)	
No	48 (92.3)	4 (7.7)	
Perceive severity of COVID-19			0.009
Yes	228 (72.8)	85 (27.2)	
No	40 (90.9)	4 (9.1)	
Lack of experience in such pandemic			0.002
Yes	199 (71.3)	80(28.7)	
No	69 (88.5)	9 (11.5)	
Fear from isolation/ quarantine			0.003
Yes	168 (70.3)	71 (29.7)	
No	100 (84.7)	18 (15.3)	
Availability of PPE			0.60
Yes	162 (76.1)	51 (23.9)	
No	106 (73.6)	38 (26.5)	
Stress			<0.001
Low	86 (90.5)	9 (9.5)	
High	182 (69.5)	80 (30.5)	
Feeling disappointed			0.048
Yes	144 (70.9)	59 (29.1)	
No	124 (80.5)	30 (19.5)	

*Chi square test.

and anonymity, and confidentiality was assured before they gave their consent.

RESULTS

Quantitative Survey

We targeted 550 HCWs and received 400 filled questionnaires, a 73% response rate. However, 43 were incomplete, so we had 357 valid questionnaires. Of the respondents, 43.7 and 45.1% were physicians and nurses, respectively. The mean age was 36.7 years, and 52.8% were older than 35 years. More than half of participants were female (55.3%) and worked in PHC centers (56.9%). Most had children (73.6%) and lived with their families during the pandemic (89%). Thirty-six percent dealt directly with positive COVID-19 cases (**Table 1**).

One quarter of study participants (24.9%) were not willing to work during the pandemic. The results of the univariate analysis, elucidating associations with willingness to work during COVID-19 pandemic, are shown in **Table 1**. More than 80% of HCWs ≥35 years of age showed significantly higher willingness to work (*p*-value 0.001). PHC workers, physicians and nurses, were more willing to work during the pandemic with significance, *p*-value 0.036 and 0.024, respectively. Finally, 78% of those reported to have children had significantly higher willingness to work (*p*-value of 0.015).

HCWs' willingness to work in relation to their attitudes and other factors were assessed using the chi square test. Willingness to work was higher among HCWs who did not report stress about catching the infection and felt safe ($p = 0.007$ and 0.001, respectively). Perception of susceptibility and severity of COVID-19 disease showed significant association with willingness to work ($p = 0.002$ and 0.009, respectively). Lack of experience in a pandemic and fear about isolation or quarantine were also significantly associated with willingness to work ($p = 0.002$ and 0.003, respectively). HCWs with higher stress levels and those who were disappointed reported less willingness to work (**Table 2**).

TABLE 3 | Multivariable model of factors independently associated with willingness to work.

Variable	SE	*P*-value*	Adjusted OR	95% CI
Age				
<35 years†	0.43	0.8	1.1	0.5–2.5
≥35 years				
Work setting				
PHC	0.28	0.5	1.2	0.7–2.1
Hospital†				
Job title				
Physician				
Nurse	0.3	0.4	1.3	0.7–2.4
Others† ‡	0.4	0.004	3.5	1.5–8.3
Experience				
<10 years†	0.4	0.03	2.6	1.1–6.1
≥10 Years				
Having children				
Yes†	0.4	0.5	0.8	0.4–1.5
No				
Stress				
Low	0.4	0.03	2.5	1.1–5.5
High†				
Quarantine fear				
Yes†	0.3	0.2	1.5	0.8–2.9
No				
Infection fear				
Yes†	0.6	0.1	2.6	0.8–8.4
No				
Perceived severity of COVID-19				
Yes†	0.6	0.1	1.7	0.7–3.9
No				
Lack of experience				
Yes†	0.4	0.2	1.5	0.8–2.9
No				

*†Reference Group, ‡lab and radiology technicians; *Significance level ≤0.5; OR, odds ratio; CI, confidence interval.*

Variables significantly associated with willingness to work were entered into a multivariable regression model in an enter mode manner. After controlling confounders, physicians and nurses reported significantly higher willingness to work than others ($p = 0.004$, Adj. OR = 3.5). Those with lower stress levels were two times more willing to work than higher stressed participants ($p = 0.03$). Additionally, willingness to work was significantly related to professional experience; HCWs with more than 10 years' experience were more willing to work than juniors. No significant associations with age, having children, quarantine or infection fear, perceiving of disease severity, and lack of experience existed (**Table 3**).

Qualitative Interviews

Fifteen HCWs were interviewed. The average age was 41 years (range 27–56), with more than half female (60%), and the occupation distribution was seven physicians, six nurses, and two other HCWs (lab and radiology technicians). Themes we focused on for this research include duty to work, perceived stressors, and issues related to the occupation. Each is presented.

Duty to Work

Participants universally felt a duty to work. One expressed a patriotic commitment "because I love Palestine." The laboratory technician was altruistic, stating:

> *"I knew no one will work in PCR lab with the highly contagious virus... so I volunteered to help. I felt it is my responsibility because I have the skills and also my personal responsibility to help people in my community."*

While participants felt obliged to work and Ministry of Health (MOH) prohibited vacations, many knew colleagues who refused to work. One said, "Let me tell you there are no ethics in this pandemic." Several were troubled by coworkers and supervisors who did not share the same sense of duty. A nurse said, "I have conflict with a physician because he refused to work with a patient." A technologist stated, "Colleagues lacked professional ethics. Everyone wants to discharge himself from work and that caused a huge workload for the others." As described by the technologist, some participants were frustrated with their colleagues, but a few described positive experiences. One said, "There was a huge sense of cooperation, we worked together as a team and supported each other." Whether HCWs were in this "working together" or "felt alone and unappreciated," all described incredible stress.

Perceived Stressors

A 33-year-old physician said, "This is the hardest experience in my life." Most found the hours long and grueling, their duties taxing and at times beneath them such as contact tracing or physicians delivering food to quarantined patients. One physician complained, "My colleague and I worked alone to collect half of a random community sample for 1,500 in the district in 48 h... It was unfair, we were exploited."

Working conditions felt unsafe due to inadequate and cheap PPE and no training. One reported, "Some colleagues were exposed to positive cases with no adequate PPE." Another described the PPE "as cheap and not safe. When we were sprayed with water, it soaked through. The virus is much smaller than a water drop, so logically it was not safe." Another explained, "We didn't have any orientation about this situation, no presentations or workshops or anything. Only YouTube videos oriented us what to do... that I had to find." That included how to wear PPE, how to collect nasal swabs, etc. A female nurse said, "The lack of preparedness caused a huge workload, fear, and extreme floundering."

In addition, many were frustrated by the lack of recognition for their efforts: "two months and not even verbal thanks." In fact, MOH withheld pay. "Instead of reward, they [MOH] announced that 2 days will be discounted from our salary to support governmental actions."

The challenge of how to work and meet family obligations was especially challenging for female HCWs who bore the brunt

of children and elderly parents. A female physician said, "The biggest challenge as a female is the unavailability of a nursery as a result of the country lockdown. I don't know what to do with my kids." A few needed accommodations due to personal health issues or family obligations such as caring for an ill parent. A female physician explained:

> *"I approached the ministry officially asking about 'A' shifts only because my father has a pulmonary embolism and I am the one responsible for looking after him and giving his medications... but they refused!"*

HCWs also described the emotional toll, including not seeing family, the fear of infecting family members, or getting sick themselves. A female physician explained, "Due to the quarantine and lockdown, I can't see my family and I miss their support." Another who did go home said, "When I return home, I take off all my clothes at the door and do all the possible disinfection before entering to see my kids."

Demonstrating the burden HCWs carried, one participant told the interviewer, "You covered all the issues hidden in my heart. Thank you for bringing them up."

While the novel virus was a challenge around the globe and securing PPE and understanding about the diagnosis and management were evolving, some stressors might have been mitigated by better leadership. Participants reported limited support from supervisors. The lack of preparation and training is described above. Guidelines about who should not work due to health risks and arranging fair work distribution were largely missing. Supervisors "played favorites" and "there was no transparency." Another explained that "duties were not distributed fairly, some were not asked to do fieldwork and only had to do prestigious work." A female physician who had had cancer the year before said,

> *"I thought I have to discharge myself from the duty to work in this pandemic, but when my physicians and my senior manager told me that this will not be accepted as an excuse to be discharged from duty, I cried a lot..."*

Her colleagues lobbied for her, and she was eventually dispensed from her direct care duties.

These leadership inadequacies contributed to the stressors outlined above. One HCW concluded: "It is our duty and obligation [to work]. But those with chronic or immunosuppressive disease should have been relieved from duty, but this was not the case here."

The Occupation

The lockdown restricted travel and made it difficult for some to get to work or to see their families during periods of work. This was above and beyond the usual traffic patterns related to the occupation where checkpoints obstruct traffic flow and Palestinian access roads wind around Israeli freeways to and from settlements and Israeli cities. Normally, this adds substantial time to travel because only cars with certain license plates can use the Israeli roads. During the lockdown, this was even worse, and some found it easier to walk to work, but even that was difficult. One participant reported, "walking hours each way." Walking was easier than driving because Palestinian forces closed roads for security reasons and checkpoints controlled by the Israeli Defense Forces had more erratic hours than usual, opening and closing without warning. Finally, the realities of the occupation force some Palestinians to work in Israel due to a lack of job opportunities in Palestine. This caused another layer of complication and potential COVID exposure that HCWs in those locations had to deal with. One explained:

> *"After the agreement between the two governments (Palestinian and Israeli) to let the Palestinian workforce in Israel stay there for a one-month period, we were surprised that they returned back illegally from places other than the checkpoints provided by Israelis. This caused a huge challenge. We were waiting at the checkpoint 24/7 but most of the workers entered illegally supported by Israeli coverage. They infected their families which increased the work burden on us and challenged MOH capabilities."*

The occupation added another layer of uncertainty and burden to the challenges of staying safe and caring for patients during the pandemic.

DISCUSSION

Frontline Palestinian HCWs faced extremely challenging work settings during the initial phase of the COVID-19 pandemic. Their ability to manage and cope with the huge work overload affected their willingness to work. The deontological and utilitarian approaches, judging actions as good or bad according to a clear set of rules, appeared to dominate health practice during the early months of the pandemic and raised many ethical dilemmas for our participants. In fact, most felt the duty to work but raised concerns about their safety, questioning the Hippocratic principles under which HCWs generally behave.

Almost one-fourth of Palestinian HCWs were unwilling to work during the pandemic. However, qualitative work demonstrates that unwillingness did not preclude HCWs from working. Attitudes about working seemed to be a continuum from a sense of duty, professionalism, and obligations to MOH and communities on one end and serious concerns about the high risk of personal safety on the other. During other pandemics, the more severe the pandemic, the higher HCW absenteeism and the less willingness to work (22). This further magnified the challenges in a country like Palestine, where limited resources, budget constraints, and conflict are ongoing realities.

The literature shows a wide range in outcomes (15), nevertheless, many studies demonstrated comparable results (23, 24). The debate on duty to care has been reported since the emergence of HIV/AIDS (25). Traditionally, it has been argued that physicians should have high standards of altruism and beneficence and hence have a duty to care for patients even at a risk to themselves (26). But during previous infection outbreaks, HCWs caring for sick people thought about dropping their work duties even though it was ethically unacceptable to them (14, 27). Additionally, a proactive approach, which explored the

willingness to work in the case of infectious disease outbreak or bioterrorism among a large sample of American primary care physicians, revealed one fifth prevalence of unwillingness to work in such settings (28). As the pandemic has continued with additional peaks, pandemic fatigue has become more of a concern (29).

Fears of safety and security were evident in both our quantitative and qualitative data. PPE availability did not show a significant association with willingness to work, but interviews explored the quality and limited availability, which were of grave concern to many. Inadequate safety precautions increased Palestine HCWs' stress level and reflected on their willingness to work. While adequate PPE and evolving guidance may be difficult given the limited resources of MOH and the emerging understanding of the novel virus, better leadership despite the uncertainty might have mitigated some of the stressors.

Thought leaders on managing burnout in the health care workforce outlined the areas where US HCWs wanted support during the current pandemic: hear me, protect me, prepare me, support me, and care for me (30). This parallels much of what we heard from our participants, who were both stressed and disappointed, due to inadequate PPE, poor preparation and training, lack of guidelines about who should avoid exposure to the virus (age and health history), and limited efforts to create fair work assignments. Instead, many supervisors played favorites and were unwilling to accommodate family care needs, especially for women. In addition, for the most part, HCWs felt unappreciated and supervisors' efforts to build teams and a sense of mission in spite of uncertainty were missing. These are domains of good leadership. Research shows that good leadership is imperative in a pandemic (31) and even more important as the pandemic continues (30, 32). This is something MOH can and should address with their leadership teams in both hospital and ambulatory settings.

While childcare obligations were a reported barrier to HCWs' willingness to work in pandemics (22), our survey results (more than 55% female) showed that Palestinian HCWs were more willing to work if they had children. We may expect this finding in a conflict area like Palestine where tragedies and challenges at the political, economic, and social levels force people to struggle to provide for their families. Work may be considered an obligation to meet life's demands and to live with dignity. In fact, many interviewees expressed their duty to work as an obligation; some stated administration forced them to work and MOH forbid any type of vacations. However, the financial realities may be a hidden and unexpressed element.

While three quarters of the survey sample and all interviewees were willing to work, the stress and anxiety were high (72%), but those with less perception of stress and more professional experience were more willing to work. Emotional turmoil is mitigated by support, and institutional programs that address HCWs' mental health issues and focus on their psychosocial well-being to increase their resilience and reduce the magnitude of expected stress on quality of health care services are recommended by the World Health Organization (33, 34). Chinese efforts to address staff mental health needs during the current pandemic showed favorable results and helped HCWs improve the care they provided (35). Public health and policy makers should consider implementing this as we continue to struggle with COVID-19.

As an occupied territory, Palestine confronts COVID-19 from the perspective of the existing Israeli occupation, which weakens the Palestinian Authority's and the Palestinian people's ability to respond effectively to the deadly virus (36). COVID-19 does not distinguish borders, and the Palestinian and Israeli economies are intertwined. As many as 60,000 Palestinians are working in Israel and returning to their homes on a daily basis. While many conflict countries, in line with the current situation, have ceased fire and eased political tension, Israel's occupation has multiplied threats on Palestinians and aborted provisions to limit the transmission of COVID-19 as was expressed in our interviews.

Our study has many strengths. The sample size was large enough to focus on HCWs by profession and distinguish their responses based on place of work. The study took place during the beginning and the peak of cases of the outbreak in Palestine when the uncertainty and potential risks to self and family were the highest. The mixed design provides additional understanding, explanations, and interpretations of the quantitative findings.

The study, however, has cross-sectional study design limitations. The self-administered structure of the questionnaire may be prone to social desirability bias, as HCWs may elucidate positive responses to preserve their figures or as a result of potential perceived coercion from superiors. On the other hand, although the response rate for sample population (HCWs) is considered high, it leaves potential for non-response bias where non-respondents may have characteristics that vary from survey respondents. Besides, the fact that the research was performed in a public health emergency situation could also have limited the opportunity for the busiest and overburdened health workers to participate. The willingness to work among HWCs in Palestine may be either over or underestimated. Despite these realities, this study sheds light on the challenges of COVID-19 pandemic in a region with limited research to date.

In conclusion, Palestinian HCWs reported unwillingness to work amid the COVID-19 pandemic. Physicians and nurses were more likely to comply with a commitment to their professional ethics and the duty or obligation to work. However, stress levels and disappointment were high and could be mitigated in the future with better leadership, in spite of the uncertainty, and adding supports to address mental health and psychosocial challenges and enhance well-being. Finally, the political situation in Palestine creates budget constraints and fragmentation of the Palestinian Authority's response. Israel imposes further restrictions on the freedom of movement, and the lack of cooperation between Palestine and Israel further threatens the health security of Palestinians during this pandemic (36).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Al-Najah National University Institutional Review Board (IRB) Ref: F. Med June /20/7. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BM contributed to the literature search, conceptualization and study design, development of questionnaire, data collection, analysis, data interpretation, and manuscript writing. ZN contributed to the conceptualization and study design, development of questionnaire, analysis, data interpretation, and manuscript writing. TZ contributed to the development of questionnaire, data interpretation, and manuscript writing. All authors have seen and approved the final version of the manuscript for submission.

ACKNOWLEDGMENTS

We were extremely grateful to all health care workers who took part in this study despite the huge pressure they are facing in the COVID-19 outbreak. Great thanks to Palestinian Ministry of Health for approving the study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.576820/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 12 January 2021
doi: 10.3389/fmed.2020.603406

The Fair Allocation of Scarce Medical Resources: A Comparative Study From Jordan

Muhannad H. Yousef[1†], Yazan N. Alhalaseh[2†], Razan Mansour[3], Hala Sultan[1], Naseem Alnadi[1], Ahmad Maswadeh[1], Yasmeen M. Al-Sheble[1], Raghda Sinokrot[1], Khawlah Ammar[3], Asem Mansour[4,5‡] and Maysa Al-Hussaini[5,6‡]*

[1] School of Medicine, University of Jordan, Amman, Jordan, [2] Department of Internal Medicine, King Hussein Cancer Center, Amman, Jordan, [3] Office of Scientific Affairs and Research, King Hussein Cancer Center, Amman, Jordan, [4] King Hussein Cancer Center, Amman, Jordan, [5] Human Research Protection Program, King Hussein Cancer Center, Amman, Jordan, [6] Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, Amman, Jordan

OPEN ACCESS

Edited by:
Sandor Kerpel-Fronius,
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Reviewed by:
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Frits Lekkerkerker,
Consultant, Amsterdam, Netherlands

***Correspondence:**
Maysa Al-Hussaini
mhussaini@khcc.jo

[†] These authors have contributed equally to this work and share first authorship

[‡] These authors have contributed equally to this work and share last authorship

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: 06 September 2020
Accepted: 08 December 2020
Published: 12 January 2021

Citation:
Yousef MH, Alhalaseh YN, Mansour R, Sultan H, Alnadi N, Maswadeh A, Al-Sheble YM, Sinokrot R, Ammar K, Mansour A and Al-Hussaini M (2021) The Fair Allocation of Scarce Medical Resources: A Comparative Study From Jordan. Front. Med. 7:603406. doi: 10.3389/fmed.2020.603406

The allocation strategies during challenging situations among the different social groups is based on 9 principles which can be considered either individually: sickest first, waiting list, prognosis, youngest first, instrumental values, lottery, monetary contribution, reciprocity, and individual behavior, or in combination; youngest first and prognosis, for example. In this study, we aim to look into the most important prioritization principles amongst different groups in the Jordanian population, in order to facilitate the decision-making process for any potential medical crisis. We conducted an online survey that tackled how individuals would deal with three different scenarios of medical scarcity: (1) organ donation, (2) limited hospital beds during an influenza epidemic, and (3) allocation of novel therapeutics for lung cancer. In addition, a free-comment option was included at the end of the survey if respondents wished to contribute further. Seven hundred and fifty-four survey responses were gathered, including 372 males (49.3%), and 382 females (50.7%). Five groups of individuals were represented including religion scholars, physicians, medical students, allied health practitioners, and lay people. Of the five surveyed groups, four found "sickest-first" to be the most important prioritization principle in all three scenarios, and only the physicians group documented a disagreement. In the first scenario, physicians regarded "sickest-first" and "combined-criteria" to be of equal importance. In general, no differences were documented between the examined groups in comparison with lay people in the preference of options in all three scenarios; however, physicians were more likely to choose "combination" in both the second and third scenarios (OR 3.70, 95% CI 1.62–8.44, and 2.62, 95% CI 1.48–4.59; $p < 0.01$), and were less likely to choose "sickest-first" as the single most important prioritization principle (OR 0.57, CI 0.37–0.88, and 0.57; 95% CI 0.36–0.88; $p < 0.01$). Out of 100 free comments, 27 (27.0%) thought that the "social-value" of patients should also be considered, adding the 10th potential allocation principle. Our findings are concordant with literature in terms of allocating scarce medical resources. However, "social-value" appeared as an important principle that should be addressed when prioritizing scarce medical resources in Jordan.

Keywords: scarce medical resources, FAIR, COVID-19, Jordan, justice

INTRODUCTION

Ethical dilemmas have always been ingrained in the practice of medicine, despite the belief that the right to maximum healthcare should not be compromised (1). However, under certain circumstances, like the shortage of medical resources during crises, when the demand for healthcare services exceeds the supply, this right might be waived (2–4). Pandemics, conflicts and war, and natural disasters are all settings where medical resources can become scarce, posing several challenges (5), albeit resources can be scarce and the decisions to prioritize them can still be faced in daily practice in most health systems. These challenges often leave healthcare providers in conundrums they cannot solve without jeopardizing their commitment to an ethical framework of fairness, equity, and equality (6, 7).

This particular encounter has become an imminent reality during the COVID-19 pandemic. The higher mortality rates for older patients and limited hospital beds and ventilators, in addition to the shortage and exhaustion of healthcare workers left physicians facing tough decisions (8). Multiple studies attempted to alleviate this burden by the construction of an ethical framework for prioritizing patients in the setting of resource scarcity. Other studies have developed ethical approaches for evaluating healthcare decisions in a priority-setting, and proposed criteria and guidelines to direct the fair allocation of the scarce medical resources (9–14). Questions targeting the allocation of ventilators and ICU beds are examples that have been reiterated in literature (15–18). Nine ethical principles are often used to stratify patients in order of priority; sickest first, waiting list, prognosis, youngest first, instrumental values, lottery, monetary contribution, reciprocity, and individual behavior (14, 15). A few presented the perception of healthcare workers and the general public on this topic, and whether individual characteristics should be taken into consideration as part of the decision-making process (19–24).

In a study of 1,267 participants responding to an online questionnaire in which they were asked to prioritize patients in 3 limited-resource settings: scarce donor organs, hospital beds during an epidemic, and joint replacements (19); lay people believed that the "sickest-first" (95% CI 81.2–86.2%) and "first-come, first served" (95% CI 66.2–72.4%) were of top priority. On the other hand, both general practitioners and medical students believed that patients should be ranked based on prognosis (95% CI 74.2–84.9%), or a combination of criteria (95% CI 66.4–78.5%) leaving the degree of sickness as their third priority option. Interestingly, "lottery," "reciprocity," "instrumental value," and "monetary contribution" were considered unfair principles by both groups.

In another study, the opinions of Jewish religious scholars were inconsistent. They varied between leaving the decision to chance—based on the belief that only God decides people's fate, lottery, or first come, first served, and delegating the decision to ethical committees (25). When ∼500 Canadian participants were surveyed, over 90% of respondents agreed that the most important goal of pandemic preparations was saving lives. Individuals of older age (OR = 8.51, $p < 0.05$) and employment (OR = 9.48, $p < 0.05$) were agreed to be of highest priority (26). Furthermore, an article comparing the public community and local authorities in Australia reported similar views in both groups; healthcare workers should be prioritized, followed by viral and vaccine researchers and developers (27) in support of the "instrumental-value" principle. Treating the young was considered more ethical, but the elderly believed that patients' overall well-being should affect prioritization, rather than age (28). Scarcity of organs for donation serves as another example where ethical dilemma might ensue. Priority should be given to maximize benefit which respondents believed meant targeting younger patients or those who have a worse prognosis. Waiting list was considered of lower priority, as were individuals who engaged in socially undesirable behaviors, especially if they were liable for their illness (29–31).

Jordan is a lower-middle income country (32) with a population of 9.9 million (33) most of whom reside in the capital, Amman. More than 94% of Jordanians are Muslims and approximately 6% are Christians (34). In 2019, the Gross Domestic Product (GDP) in Jordan was worth 43.74 billion US dollars (35). Unemployment rate in 2019 was 14.7% (36), and 31.9% of Jordanians were not covered by health insurance (37). The health care system in Jordan is divided between the private and public sector. With a total of 106 hospitals and 12,081 beds, the public sector accounts for 67% of beds. Up until 2017, Jordan had 2.3 physicians and 2.8 nurses per 1,000 people (38). Even though Jordan is known for its high-quality healthcare services, both the escalating population growth rate and the recent increase in refugee numbers render the current bed availability in Jordan deficient (39).

The objective of our study is to explore the moral intuitions held by the different members of the Jordanian society (religion scholars, physicians, medical students, allied health practitioners, and lay people) on several topics that have arisen in light of limited medical resources. It also aims to explore whether or not different participant groups of the same society will have different perceptions on the way resources should be allocated and the way their results will compared to that of international literature.

METHODOLOGY

An online survey containing three hypothetical scenarios of scarcity of medical resources including organ donation, hospital beds amid flu epidemics, and novel therapeutics for lung cancer patients was distributed. The first two scenarios along with the allocation criteria were developed in a previous study by Krütli et al. (19), permission was sought from the corresponding authors. The third scenario, however, was new and addressed the allocation of expensive and novel therapeutic drugs for cancer patients. All scenarios were initially written in English and then translated to Arabic, validated then piloted and modified accordingly. Identical English and Arabic versions of the scenarios were shared with participants allowing them to choose their preferred language. The survey asked participants to rank the allocation criteria for fair distribution of certain limited resources from the most important (score-1) to the least

important (score-9) prioritizing principle. In addition, a free-comment text option was allowed at the end of the survey.

The following principles and their definitions were used,

- Behavior: priority to those who have not become ill by own fault.
- Instrumental value: priority to those who have essential roles for keeping society operational (e.g., hospital staff).
- Monetary: substantial contribution to the costs of the treatment.
- Order: according to the order of registration.
- Random: random selection, e.g., via a lottery.
- Service: contribution in the past to the common good (e.g., by volunteering).
- Sickest first: the sickest individuals to be given priority.
- Survival: the likelihood to survive the longest.
- Youngest: prioritizing young individuals.
- Combination: a combination of criteria including age (youngest first), and prognosis (longest survival with intervention).

In the first scenario: a team of medical consultants was responsible for allocating 100 kidneys from eligible donors. However, 500 individuals needed a kidney transplant. For convenience, we assumed that all 500 individuals were eligible for the transplant. The following allocation principles were used in this order: sickest, order, survival, behavior, young, random, combined, service, and money. In the second scenario: a very severe flu epidemic hit a mid-sized town of ∼50,000 inhabitants. There were, however, only 500 hospital beds available and 2,500 individuals who needed hospital care. The following allocation principles were used in this order: sickest, order, survival, instrumental value, combined, young, random, service, and money. In the third scenario: One hundred lung cancer patients were tested for a novel targeted treatment that will cost 10,000 JDs (14,000 USD) per patient. The financial coverage was available for ten patients. For convenience, all 100 patients were assumed eligible for the treatment. The following allocation principles were used in this order: sickest, order, survival, behavior, young, random, combined, service, and money

The research protocol was approved by the Institutional Review Board (IRB) at King Hussein Cancer Center (KHCC). Informed consent documentation was waived, and a cover page that informed all participants about the purpose of this study was used. Data collection took place between the 27th of April 2020 and the 18th of May 2020. The research team aimed to target five groups of individuals: religion scholars, physicians, medical students, allied health practitioners and lay people. The objective was to enable a comparison between the various groups. This was achieved through sending an email with the questionnaire's link to the staff at several healthcare facilities in order to reach to professionals (physicians, allied health professionals including nurses, and pharmacists). Medical students were targeted through many of the co-authors, as well as contacting deans of the medical schools in Jordan to share the link with the students. Lay people were targeted through social media channels and through the snowball effect where those who completed the questionnaire were asked to share the link with friends and relatives. Religion scholars were identified and communicated with by one of the authors (AM). Of those, participants 18 years and above were then selected.

Descriptive analyses including the mean, median, frequency, and percentages were used to describe the numerical and categorical demographic data of the participants, as well as their preferred prioritization principle. Odds ratio extracted out of the logistic regression was reported with the corresponding 95% confidence interval (CI), and was used to compare opinions amongst all groups in comparison to the lay people group, which served as a reference. Additionally, gender was taken into consideration, where male vs. female was tested among the whole sample with a specific comparison among physicians. A significant $p \leq 0.05$ was used as the cut-off.

RESULTS

The Whole Group

A total of 1,286 survey responses were gathered, out of which 58.6% ($n = 754$) of the respondents completed at least one scenario. There were no significant gender-based or age-based differences between those who completed the survey and those who did not ($p = 0.328$, and 0.860, respectively). The mean and median age for all participants was 35.5 and 33 years, respectively, with an age range of 18–78 years. There were 372 males (49.3%), and 382 females (50.7%). The majority had an undergraduate degree ($n = 469$, 62.2%). **Table 1** details the demographics of the participating groups.

Detailed Data on Subgroups

Religion Scholars: There were 30 (3.9%) participants, with predominance of males ($n = 24$, 80.0%) and a mean age of 48 years. The majority ($n = 18$, 60.0%) completed postgraduate studies.

Physicians: There were 166 (22.0%) participants, with predominance of males ($n = 99$, 59.6%) and a mean age of 43 years. The majority of physicians completed postgraduate studies ($n = 118$, 71.1%) and practiced medicine in Jordan ($n = 115$, 70.1%), followed by Arab countries ($n = 32$, 19.5%), and 17 (10.4%) practiced in Western countries.

Medical Students: There were 162 (21.5%) participants, with a slight predominance of females ($n = 89$, 54.9%) and a mean age of 21.5 years. The vast majority had undergraduate education ($n = 158$, 97.5%).

Allied Health Practitioners: There were 122 (16.2%) participants, with a predominance of females ($n = 86$, 70.5%) and a mean age of 32.6 years. The majority ($n = 84$, 68.9%) with undergraduate studies.

Lay People: This constituted the largest group, with a total of 274 (36.3%) respondents. There was an almost equal representation of both genders (males $n = 140$, 51.1%, and females $n = 134$, 49.9%). The mean age of the group was 38.7 years. Most had undergraduate studies ($n = 199$, 72.6%).

Prioritization Principle Allocation

Overall, the most commonly prioritized principle was "sickest first" in all 3 scenarios, except for physicians in the first scenario where "sickest first" and "combination" were of

TABLE 1 | Demographics of the study group ($N = 754$).

	n (%)	Total 754 (100)	Religion scholars 30 (3.9)	Physicians 166 (22)	Medical students 162 (21.5)	Allied health 122 (16.2)	Lay people 274 (36.3)
Gender	Male	372 (49.3)	24 (80)	99 (59.6)	73 (45.1)	36 (29.5)	140 (51.1)
	Female	382 (50.7)	6 (20)	67 (40.4)	89 (54.9)	86 (70.5)	134 (48.9)
Educational level	Primary	47 (6.2)	3 (10)	0 (0)	0 (0)	2 (1.6)	13 (4.7)
	Undergraduate education	469 (62.2)	9 (30)	48 (28.9)	158 (97.5)	84 (68.9)	199 (72.6)
	Higher Education	238 (31.6)	18 (60)	118 (71.1)	4 (2.5)	36 (29.5)	62 (22.6)
Age (years)	Min	18	29	22	18	20	19
	Max	78	70	78	26	62	75
	Mean	35.5	48	43.1	21.5	32.6	38.7
	Median	32	46.5	45	22	29.5	37

equal importance. In the first scenario, the second most common prioritization principle chosen by all groups was the "combination." For the second scenario the second most chosen principle was "survival" in all groups. For the third scenario the second most chosen allocation principle was "survival" in all groups except for physicians and medical students who chose "combination" as their second prioritization principle. Interestingly, "monetary," and "service" were the least favored principles in all scenarios among all groups (**Table 2** demonstrates the 3 scenarios with scoring of the priority principles among all groups).

Scenario One

This was answered by 754 participants (100.0%). In general, all groups concurred with "sickest first" as the main allocation principle chosen by 48.5%, apart from physicians. In second place, the "combination" principle was chosen by all groups. In detail, 60% of religion scholars chose the "sickest first" as the mainstay principle to allocate resources, followed by lay people where 55% chose it as the priority principle. The allied health practitioners chose sickest first in 51.6% of responses, physicians, however, chose "sickest first "and "combination" principle as equal priority principles. Medical students' first option was "sickest first" in 48.8% of responses. It is worth noting that the contribution to financial cost "monetary," and voluntary contribution "services" were the least selected principles among all groups.

Scenario Two

This was answered by 614 participants (81.0%). The overall most commonly chosen principle was "sickest first" (54.1%). This was chosen by 59.0% of allied health practioners, followed by 58.3% of lay people, 54.2% of religion scholars, 53.3% of medical students, and 44.5% of physicians. The second most common choice for all groups was "survival." The least commonly chosen principle was the contribution to cost of treatment "monetary" and "services." It is worth noting that the "instrumental value" was favored twice as much by religion scholars in comparison to other groups.

Scenario Three

This was answered by 588 participants (78.0%). This scenario was especially designed to address the special needs of cancer patients in the era of personalized medicine and the cost of novel medication. Overall, the most commonly chosen principle was "sickest first" (52.4%). This was chosen by 60.9% of religion scholars, 56.8% of the allied health professionals, 55.2% of medical students, 55.0% of lay people, and lastly, 41.2% of physicians. The "combination" principle was chosen by 27.2% of the physicians. An interesting finding unique to this scenario is that in comparison to other scenarios, the contribution to cost "monetary" principle was chosen by a larger percentage of participants. The least commonly chosen principle remained to be "service."

Comparison Between all Groups With Reference to Lay People

Overall, no differences were noted when comparing religion scholars and allied health practitioners to lay people in the preference of options for all scenarios. However, differences between physicians' and lay people's prioritization principles were noted (**Supplementary Table 1**). When compared to lay people, physicians were less likely to choose "sickest first" as their top priority (OR 0.46; 95% CI 0.31–0.69; $p < 0.01$) in the first scenario. Physicians ranked "sickest first" and "combination" as equally important in priority to allocate scarce medical resources (OR 2.52; 95% CI 1.60–3.97; $p < 0.01$). In the second scenario, physicians tended to choose the "survival" as the principle to allocate the scarce medical resources (OR 1.72; 95% CI 0.97–3.06; $p = 0.06$). Physicians were more likely to choose "combination" in the second and third scenarios (OR 3.70, 95% CI 1.62–8.44, and 2.62, 95% CI 1.48–4.59; $p < 0.01$). Physicians were less likely to choose the "sickest first" option as the single most important priority principle (OR 0.57, CI 0.37–0.88, and 0.57; 95% CI 0.36–0.88; $p = 0.01$), in comparison to lay people.

Medical students were more likely to choose the "combination" as their top priority in the first and second

TABLE 2 | Percentages of respondents who chose each allocation principle as the most important one among the study group.

Percentage (%)	Sickest First	Order	Survival	Behavior	Young first	Random	Combination	Service	Monetary	*N*
Scenario 1. Organ donation for transplant										
Religion scholars	60.0	10.0	6.7	3.3	3.3	3.3	13.3	0	0	30
Physicians	33.1	11.4	14.5	3.0	3.6	0.6	33.1	0.6	0	166
Medical Students	48.8	7.4	14.2	1.9	1.2	1.2	24.7	0.6	0	162
Allied Health	51.6	7.4	11.5	4.9	2.5	0	22.1	0	0	122
Lay people	55.1	9.5	12.0	1.8	2.2	2.2	16.4	0.4	0.4	274
Total	48.5	9.2	12.7	2.7	2.4	1.3	22.7	0.4	0.1	754
Scenario 2. Flu epidemic										
Religious Leaders	54.2	0	25.0	20.8	0	0	0	0	0	24
Physician	44.5	3.6	20.4	8.8	13.9	0	7.3	0.7	0.7	137
Medical Students	53.3	6.6	16.7	4.4	12.4	1.5	4.4	0.7	0	137
Allied Health	59.0	2.0	12.0	9.0	7.0	1.0	10.0	0	0	100
Lay people	58.3	6.9	12.9	9.3	4.2	1.4	6.9	0.0	0	216
Total	54.1	5.0	15.8	8.5	8.5	1.0	6.7	0.3	0.2	614
Scenario 3. Expensive cancer medication										
Religious Leaders	60.9	13	13.0	0	4.3	0	4.3	0	4.3	23
Physician	41.2	5.1	21.3	3.7	0.7	0	27.2	0	0.7	136
Medical Students	55.2	7.5	16.4	1.5	0	1.5	17.2	0	0.7	134
Allied Health	56.8	6.3	15.8	4.2	1.1	1.1	12.6	0	2.1	95
Lay people	55.0	8.0	17.5	2.0	1.5	2.0	12.5	0.0	1.5	200
Total	52.4	7.1	17.7	2.6	1.0	1.2	16.7	0. 5	1.4	588

scenarios when compared to lay people (OR 1.67, 3.26; 95% CI 1.03–2.69, and 1.40–7.53; $p = 0.04$, and 0.01, respectively).

Comparisons Based on Gender Among the Different Scenarios

Males were more likely to choose "random" (OR 1.97; 95% CI = 1.02–3.80, $p = 0.04$) in the second scenario, and "combination" (OR 1.57; 95% CI = 1.01–2.43, $p = 0.04$) in the third scenario, in comparison to females. However, gender was not a significant factor to stratify the preferences among physicians.

The Free Text Comments Analysis

One hundred (13.3%) participants added free comments that addressed their opinion. Each comment was then stratified based on one of the three principles of ethics: autonomy ($n = 8$), beneficence ($n = 30$) and justice ($n = 60$). In two comments, the link to any of the principles could not be determined. Among the comments, 27 (27.0%) thought that the "social-value" of patients, i.e., being the principle care- and food providers to the family, should be considered.

DISCUSSION

Overall, our results clearly indicate that "sickest first" is the prioritization principle that should be considered when encountering scarce medical resources in all three scenarios. In general, there was an overall concordance between participants from the five different groups.

Throughout history, physicians have been faced with the difficult decision of prioritizing patients amid scarcity of essential medical resources. Currently, physicians are forced to decide on the allocation of intensive care unit beds and ventilators in overwhelmed facilities dealing with SARS-CoV-2 infection (18, 40). In countries where the economy is poor, this scenario tends to recur often (41, 42).

We carefully chose to discuss three particular scarce resources. The first scenario, organ donation for transplantation, was chosen as a universal dilemma; there will always be less organs available than there are patients on the waiting lists for the foreseeable future. In Jordan and other countries in the region, this is a particularly scarce resource, not only due to limitations in facilities and trained personnel, but also because there is still concern regarding organ donation (43). The second scenario addresses the shortage of hospital beds during a flu epidemic. This is analogous to the current situation in light of the COVID-19 pandemic (44), which has resulted in a plethora of publications and discussions on this particular issue (15–18, 25). The third scenario aimed to address the limitation to the availability of expensive novel therapeutics to cancer patients, including targeted therapies and immunotherapy. The costs of the novel drugs are exhausting the medical sector in countries with limited resources, further widening the gap between cancer patients worldwide. Other examples of resources that could become at some point scarce are ventilators, medical staff, and vaccines (45).

There are nine common ethical principles, and a multitude of varying opinions on how to rank them according to priority (14, 45). It would be a huge relief to decision-makers, however, if there was a clear consensus regarding how to allocate scarce medical resources. The criteria for patient selection and the allocation of resources should be transparent, yet a clear-cut approach to the

development of such guidelines might not be easily attained. The trend across various studies regarding the allocation of organs to those on waiting lists is to prioritize maximizing benefit while attempting to achieve equity (46, 47). In light of the COVID-19 pandemic, many articles aimed to set guidelines regarding the rationing of scarce healthcare resources during this crisis (40).

The quality-adjusted life-year (QALY) is a measure of the years of life remaining for a patient following a particular treatment or intervention. By including both the quality and the quantity of life lived, QALY became a favored tool in healthcare priority settings (48). Patients with the lowest cost per QALY are usually prioritized in scarce medical resource allocation, therefore increasing health benefit and social welfare (49). One popular study argues that the value of maximizing benefits is the most fundamental in prioritizing patients, including saving the most lives as well as saving the most life-years—thus maximize prognosis (15). However, QALY and health-benefit maximization are so often criticized for having the potential to be "ageist" because life expectancy is part of QALY calculation. Elderly, with a shorter life expectancy will be given the lowest cost per QALY and are therefore the least prioritized (50).

Another way of prioritization is explored by Golan et al study (51), which demonstrated a conjoint analysis method (also known as discrete choice experiments) which aimed to derive weights for a set of criteria related primarily to "benefits from technologies." Weights for criteria were measured by an internet-based software as respondents were asked 40 questions about choosing between two hypothetical technologies which were defined in terms of just two criteria, whereby one of the technologies had a higher performance rating on one criterion and a lower rating on the other criterion than the other technology. So when answering, respondents had to make a tradeoff and a choice. The advantage authors saw in this method relative to alternative scaling methods used in our survey, was that choice is natural and people, knowingly or unknowingly, experience similar situations daily. Our study results showed that among the three scenarios, "the-sickest" was the most important priority principle, where in this study the most important criterion was "lives-saved and statistical lives" with similar weight to "quality-of-life gains" and "life-prolongation benefits," all of which were related to the principle of "need," defined as the extent to which a technology is expected to achieve any of the ultimate health goals of saving and prolonging life and or improving health-related quality of life (HRQoL).

Multicriteria decision analysis (MCDA) is yet another frequently used method in literature to make decisions for prioritizing alternatives that are ranked based on a variety of criteria (52, 53). In a pilot study conducted in New Zeeland (54), the authors conducted a discrete choice experiment. The survey was conducted using 1000 Minds software (55), which asks participants to choose between hypothetical patients who could be treated by the healthcare technologies. It used the potentially all pairwise rankings of all possible alternatives (PAPRIKA) method (56), which identifies all pairs of hypothetical patients defined on two criteria at a time that involve a trade-off. Each participant was asked to rank pairs of patients and eliminated pairs that can be identified by transitivity. For example, if a participant prioritizes patient A over patient B, and then patient B over patient C, then patient A is prioritized over patient C by transitivity and the software will not ask the participant to rank the third pair of patients. At the end, six benefit-related criteria were created.

An ongoing question is who gets to decide these guidelines? In other words, who gets to decide who lives? (57) Many people may intuitively say that this burden falls in the hands of physicians; while others believe that all members of society should be involved (58, 59). We decided to explore the opinions of five groups, with the goal of determining the collective-group opinions and comparing the results to explore any significant differences. We included lay people, since their values might diverge with those of physicians (59). Our findings clearly indicate that there are no major differences in opinion regarding the allocation of scarce resources in the three scenarios. All groups in our study considered the "sickest-first" principle as the most important allocation principle in the 3 hypothetical scenarios, while "monetary contribution" and "reciprocity" were found to be the least important. This is similar to the study by Krütli et al. (19), in which the most important allocation priorities for lay people were "sickest-first" and "waiting-list," whereas "lottery," "monetary contribution" and "reciprocity" received the lowest rank and were considered unfair. Physicians were more likely to choose "prognosis," "combined criteria," and "youngest first" in all 3 hypothetical scenarios but were less likely to choose "waiting-list" and "sickest-first" except in the allocation of joint replacement surgery.

An ethicist's perception on how scarce medical resources should be allocated might provide a reasonable source of prioritization. In two studies conducted by Persad et al. (14) and Emanuel et al. (15), ethicists prioritized maximizing the total benefit which includes "saving more lives" and "life-years saved" or prognosis. All other principles were used to facilitate decision making when two patients have an equal prognoses. They considered "sickest-first" and "waiting list" as morally unacceptable. In Jordan, the ethicist's role is still emerging. However, similar to other countries in the region, religion scholars play a major role in contemplating issues of everyday life and are viewed by many to hold the most ethical and just decisions based on the creed. For example, during the recent COVID-19 outbreak, the Jordanian government recommended the closure of mosques and churches as part of their social-distancing measures. This unfavorable decision was frowned upon by a large number of the lay people who refused to comply until Muslim and Christian scholars alike publicly stated their support of the decision as it represents what is best for society (60).

We do not presume our findings are the solution to the aforementioned ethical dilemmas, albeit we believe that empirical research into these attitudes can be useful in many ways. By showing which beliefs are most adopted by the public, and which are commonly regarded as frank, physicians can make their informed decisions when faced with scenarios of limited resources. Persad wrote "even though popularity does not

constitute correctness, the unpopularity of a normative position can justify placing it under scrutiny." (45).

We have attempted to address participants' concerns, comments, and other ideas that could have evaded inclusion among the nine ethical principles. The "social-value" of individuals was presented as an additional ethical principle that was not previously included. This is defined as the presence of social- and financial-liability on the patients, such as children, elderly parents, or siblings, so that his/ her loss cannot be compensated. In the absence of well-developed national security system in countries like Jordan to support dependent individuals, especially elderly parents and young offspring, those individuals might find themselves in jeopardy if their primary caregiver is lost.

Interestingly, voice messages were sent from some of participants to the corresponding author on the overwhelming feelings they experienced while completing the survey. They found it "morally draining" once they imagined themselves in a position to take decisions to prioritize the scarce resources or as patients awaiting the decision to be made by others on whether or not they will be prioritized (Personal communication)

LIMITATIONS

We acknowledge limitations in our study. Some participants completed only one or two of the scenarios, but their responses were still included in the study. This could be attributed to the emotional burden that comes with being faced with choices that all seem rational to allocate scarce medical resources. This is especially critical in times of the COVID-19 pandemic. Moreover, the choices in each of the three scenarios were put in the same order without randomization, possibly creating a raw-effect bias which might have contributed to participants selecting the "sickest-first" option more often. However, this is the first attempt to delve into this repressing exercise of trying to allocate the scarce medical resources within our population.

CONCLUSION

In conclusion, our findings are at large consistent with international literature in terms of prioritizing patients under conditions of scarce medical resources. In addition, "social-value" appeared to be an important priority principle, most likely unique to the region, where social security systems are under-developed. We recommend considering the findings in our study by policymakers when allocation of scarce medical resources is an issue, such as with the COVID-19 pandemic. Repeating the study after the pandemic should be considered, the results might vary given that the participants would have been subjected to a real-life example.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB ethics committee at King Hussein Cancer Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AMas and MA-H inception of the idea, critical review of the first draft, critical review, and final approval. MY and YA-S collection of data, writing the first draft, review, and final approval. RM literature review, reviewing and editing the first draft, final review, and approval. HS, AMan, YA, NA, and RS collection of data, reviewing and editing the first draft, final review, and approval. All authors are accountable for the content of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.603406/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

MINI REVIEW
published: 14 January 2021
doi: 10.3389/fmed.2020.616277

Allocation of the "Already" Limited Medical Resources Amid the COVID-19 Pandemic, an Iterative Ethical Encounter Including Suggested Solutions From a Real Life Encounter

Yazan Nedal Alhalaseh[1], *Hatem A. Elshabrawy*[2], *Madiha Erashdi*[3], *Mohammed Shahait*[4], *Abdulrahman Mohammad Abu-Humdan*[5] *and Maysa Al-Hussaini*[3,6]*

[1] Department of Internal Medicine, King Hussein Cancer Center, Amman, Jordan, [2] Department of Molecular and Cellular Biology, College of Osteopathic Medicine, Sam Houston State University, Conroe, TX, United States, [3] Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, Amman, Jordan, [4] Department of Surgery, King Hussein Cancer Center, Amman, Jordan, [5] Independent Researcher, Amman, Jordan, [6] Human Research Protection Program Office, King Hussein Cancer Center, Amman, Jordan

OPEN ACCESS

Edited by:
Hilde Stevens,
Université Libre de Bruxelles, Belgium

Reviewed by:
Domenico Criscuolo,
Italian Society of Pharmaceutical Medicine, Italy
Frits Lekkerkerker,
Consultant, Amsterdam, Netherlands

***Correspondence:**
Maysa Al-Hussaini
mhussaini@khcc.jo

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: 11 October 2020
Accepted: 11 December 2020
Published: 14 January 2021

Citation:
Alhalaseh YN, Elshabrawy HA, Erashdi M, Shahait M, Abu-Humdan AM and Al-Hussaini M (2021) Allocation of the "Already" Limited Medical Resources Amid the COVID-19 Pandemic, an Iterative Ethical Encounter Including Suggested Solutions From a Real Life Encounter. Front. Med. 7:616277. doi: 10.3389/fmed.2020.616277

The shortage of healthcare providers is well-documented in low-income countries (LIC) prior to COVID-19, due to various causes including the migration to developed countries, scarcity of supplies, poor healthcare infrastructure, limited ICU facilities, and lack of access to guidelines and protocols. One of the important hitches in LIC is the insufficient testing capacity that precluded accurate assessment of disease burden and subsequently resource allocations. Trying to adhere to the principles of bioethics including respect to others, beneficence, and justice should be applied on the ground in the particular setting of the LIC. Solutions should be tailored to the tangible needs and possibility of implementation in real life in the face of the "already" limited resources by making use of simple, yet plausible, measures. Implementing guidelines and frameworks that were set to work in the better-resourced nations is a call for futility. The adoption of novel solutions to overcome the unique challenges in the LIC is exigent. These include the use of automated screening algorithms and virtual video clinics. Moreover, integrating electronic intensive care unit (e-ICU) software may allow for remote monitoring of multiple patients simultaneously. Telemedicine could help in getting consultations worldwide. It can also enhance healthcare workers' knowledge and introduce new skills through teleconferences, e-workshops, and free webinars. Healthcare workers can be remotely trained to enhance their skills. Agencies, such as the WHO, should develop comprehensive programs to tackle different health issues in LIC in collaboration with major institutions and experts around the world.

Keywords: COVID-19, resources, low-income countries, challenges, solutions

INTRODUCTION

Coronaviruses (CoVs) are a family of positive single-stranded RNA ($_{+}$ssRNA) viruses that belong to family *Coronaviridae* (1). Three out of seven human coronaviruses (HCoVs) cause severe respiratory diseases of high fatality rates (2, 3). The first is Severe Acute Respiratory Syndrome-CoV (SARS-CoV) that emerged in 2002 followed by Middle East Respiratory Syndrome-CoV (MERS-CoV) in 2012 (2). In December 2019, SARS-CoV-2 was identified as the third HCoV that causes acute respiratory distress syndrome (ARD) with viral pneumonia (3). This disease was later named COVID-19 (4). The first cases of SARS-CoV-2 infections originated in the city of Wuhan, China and soon the disease spread to 177 countries causing a global outbreak (4). Millions of COVID-19 cases and more than a million deaths have been reported worldwide. The World Health Organization (WHO) had declared a public health emergency and characterized COVID-19 as a global pandemic on March 11, 2020 (5). SARS-CoV-2 positive cases with varying disease severity have flooded hospitals and healthcare facilities. The number of cases and deaths varied per country depending on the protective measures and resources to deal with such a highly transmissible and infectious virus.

The main concern in COVID-19 pandemic is that the disease burden may exceed healthcare resources that are available for treating patients (6). Even in developed countries, there was a concern that healthcare systems would be overwhelmed if COVID-19 cases increase dramatically (6). For example, in USA, there were not enough N95 masks which necessitated the reuse of such single use masks (7, 8). In Italy, ventilators and ICU beds were made available only for critically ill patients during the peak of the disease (9, 10). South Korea faced a shortage in hospital beds which lead to many deaths (10, 11).

Healthcare systems in developing countries face major problems during this time and are unlikely to offer the care needed. The scarcity in healthcare resources, training, and low number of healthcare workers are the most important reasons (10). Developing countries lack the testing capacities and the technologies to trace the infected individuals. Moreover, the cost of the COVID-19 screening test in developing countries mostly exceeds the total sum that healthcare systems spend per individual. N95 masks are in short supply in many developing countries. According to the United Nations, there are only an average of 113 hospital beds per 100,000 in developing countries which is 80% lower than the number in developed countries (12). Moreover, developing countries have a scarcity of ICU beds (0.1–2.5 per 100,000) when compared to developed countries (5–30 beds per 100,000) (13).

The scarcity of healthcare resources, particularly in developing countries, may create ethical dilemmas. This may include the need to provide care and treatment for more severely ill patients while delaying treatment for others who are in a better condition (14). The need to take such decisions may cause some healthcare workers to experience moral injury or mental health problems (15). It becomes very challenging when such decisions have to be made at the expense of ethical values.

In this article, we will discuss the deleterious impacts of the COVID-19 pandemic on healthcare workers and availability of resources, particularly in countries with limited resources, and will provide possible solutions to cope with the current emergency.

METHODOLOGY

We did a literature search to identify challenges facing healthcare workers in countries with limited resources during COVID-19 pandemic. We discuss the number of physician per capita, the number of hospital beds, ICU and ventilators in limited settings, the allocation of limited budget to the healthcare system and its impact on other services and more prevalent health conditions. Finally, we provide insight into possible solutions that may help alleviate the stress and demand on healthcare system, resources, and personnel.

Challenges Faced by the Healthcare Systems in LIC

Healthcare Workers Shortage and Burnout

A disparity between different countries' response to COVID 19 pandemic is evident. According to the World Bank data (**Table 1**), high and high-intermediate income countries have a higher number of physicians and nurses per capita as compared to low and low-intermediate income countries. Shortage of physicians in countries with insufficient resources could be attributed to slow economic growth that leads to limited healthcare annual budget and exodus of physicians to work in higher income countries. A study conducted by Astor et al. investigated the factors that contributed to physician migration from developing to developed countries. The desire for increased income, greater access to enhanced technology, need for safer, more stable, and better future for the family were the main listed causes (24). Another study discussed the insufficient numbers of surgeons, obstetricians and anesthesiologists in low- and intermediate income countries which was in part due to lack of training and educational opportunities for surgeons and other healthcare workers (25–27). The shortage of healthcare workers and scarcity of resources in low- and intermediate-income countries have led to increased work hours and burnout of healthcare personnel in these countries and more severe economic deterioration.

In the 2013–2016 Ebola outbreak, studies showed that stress and anxiety, due to tremendous pressure on healthcare workers, could lead to faster spread of the disease and the probability of healthcare workers quitting their job (28). This could result in a healthcare system collapse.

The healthcare systems worldwide are dealing with pandemic-related challenges and stressors that could eventually lead to healthcare workers' burnout (14). These include the fear of spreading infection to family members, and others, due to the close interaction with COVID-19 patients, increased workload, and requirement to provide care and treatment for all critically ill patients in the setting of inadequate PPE and other resources (14). This may require treatment of more severely

TABLE 1 | The medical resources available in low income countries, low-intermediate, high-intermediate countries in comparison with high-income countries.

	Low	Low-intermediate	High-intermediate	High
Income (July 2019/ $)[+]	<1,026	1,026–3,995	3,996–12,375	>12,375
Number of countries (2020) [+]	29	50	56	82
Physicians/10,000 population (2017)[+]	3	8	20	31
Nurses and midwifery/10,000 population (2018)[+]	9	18	35	109
Hospital beds/ 1,000 population [+] Examples: *	0.8 (2006) 0.87 (2017) (Bangladesh)	1 (2011) 1.38 (2017) (Mexico)	3.5 (2012) 8.05 (2017) (Russia)	4.2 (2013) 8.00 (2017) (Germany)
ICU beds/100,000 population *	0.72 (Bangladesh) (16)	1.2 (Mexico) (17)	8.3 (Russia) (18)	38.7 (Germany) (19)
Ventilators*	No data (Bangladesh)	2,050 (Mexico) (20)	40,000 (Russia) (21)	25,000 (Germany) (22)
Total expenditure on health Per capita (PPP int. $) (2017)[+]	44.8	80.5	459.9	5284.1
Gross national income per capita g (PPP int. $)/(2019)[+]	791.8	2189.4	9074	45307.3
Cellular phone subscriber (per 100 population) (2018)[+]	60.8	94.3	117.3	127.6

[+]*The data in these rows were referenced from world bank data (23).*
**The data in these rows were taken from different references (16–22).*

ill patients while delaying treatment for others who are in a better condition; decisions which may cause some healthcare workers to experience moral injury or mental health problems. This may potentially progress to mental health problems such as depression, post-traumatic stress disorder, and even suicide (15). Furthermore, reduced social support, lack of self-care and family time, and lack of information about the COVID-19 transmission and disease prognosis are all factors that add up to the stressors that healthcare workers have to face (29). During the last SARS-CoV outbreak in Guangdong, China, there were reports of stress, anxiety, depression, and general psychological stress among health professionals (30). In addition, 21% of SARS cases were reported among healthcare providers (30).

Exhausted Healthcare Systems and Limited Testing Capacity

LIC have long been challenged by the limited healthcare resources including the availability of ICU and mechanical ventilators, even before the pandemic. The high cost of mechanical ventilators, the need for proper training and education, and the unavailability of ventilator protocols are factors that contributed to the challenges facing healthcare systems in developing countries (31). Unfortunately, the militarization of healthcare in some of the LIC, particularly in areas of conflicts and wars, adds to the limitation. The ongoing wars in some of LICs have put these countries in a more compromised situation (32). Patients suffering from chronic diseases have also suffered from decreased follow up to their conditions with others not even getting diagnosed due to the overwhelming of the health sector. For example, Skeete et al. found that patients with hypertension have suffered worse outcomes (higher mortality and morbidity) during the ongoing pandemic (33).

In addition, the shortage of testing capacity in LIC has left most people untested, thus precluding the accurate estimation of disease burden (**Figure 1**). Consequently, low testing capacity has led to inadequate planning to maximize the use of the available healthcare resources (35–37). Without enough data, countries would not be able to estimate the disease burden leading to poor allocation of resources toward combating the pandemic. In Jordan, for example, the government opted for a complete and strict lockdown at the beginning of the pandemic. Then gradually these measures were loosened causing a delay in the first major wave till mid to late October. During this time the government was able to ramp up its testing capabilities and have testing be wildly available and immediately act when the number of COVID-19 cases started increasing in October (**Figure 2**).

The Scarcity of Personal Protective Equipment (PPE)

Disposable filtering face piece respirators (FFRs) including N95 respirator and surgical masks are designed for one-time use. LICs have always struggled with a deficient supply of Personal Protective Equipment (PPE). In view of the increased demand and shortage of supply, even with donations, stocks remained insufficient (35, 38, 39). Accordingly healthcare workers are wearing these masks for an extended period of time or they consider reusing them (40).

Humanitarian Aid Challenges

The withdrawal of humanitarian organizations' personnel, and travel constraints that interfere with international aids all add to the challenges that LICs have to face (35, 41, 42). During a crisis, the need for humanitarian aid spikes in LIC. This spike is normally dealt with by providing quick response, from logistical hubs, to supply the countries in need with the necessary provisions. However, during the lock downs and travel restrictions, aimed to suppress the spread of the virus, imposed by the countries that contain these hubs has left the countries dependent on aid in a dire need (43).

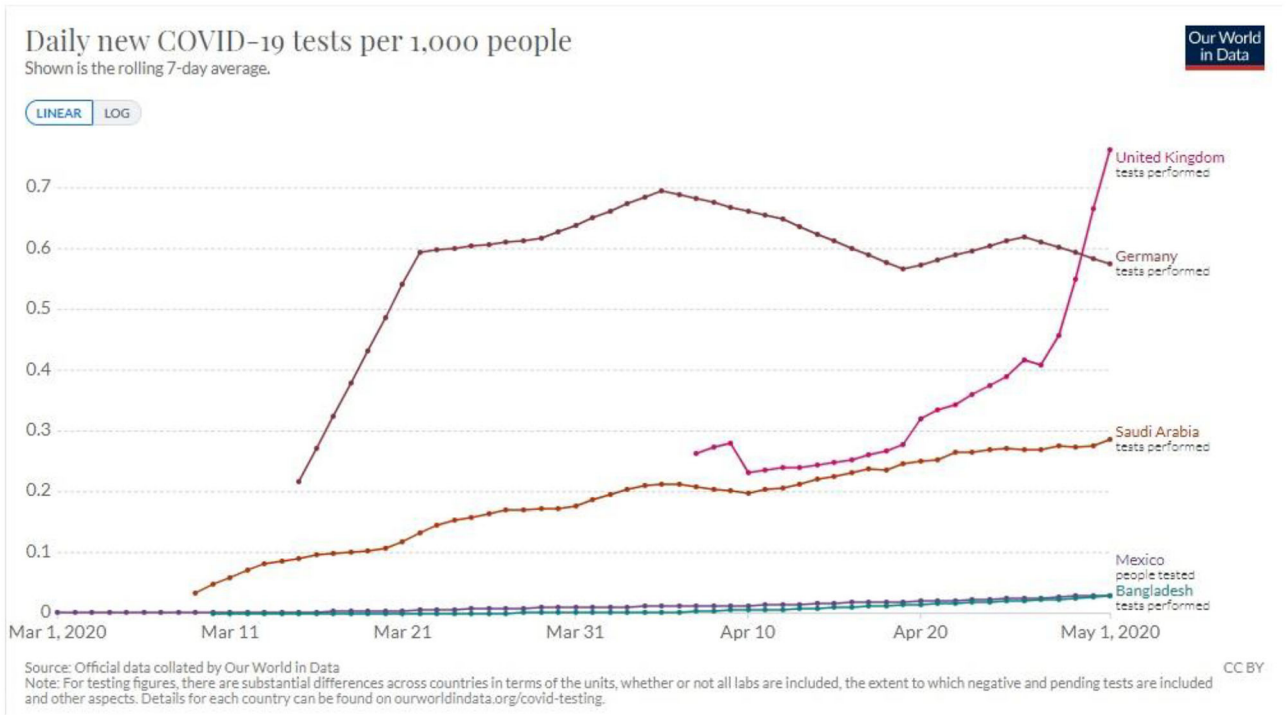

FIGURE 1 | Testing capacity variations among countries of different incomes during the beginning of the pandemic (34).

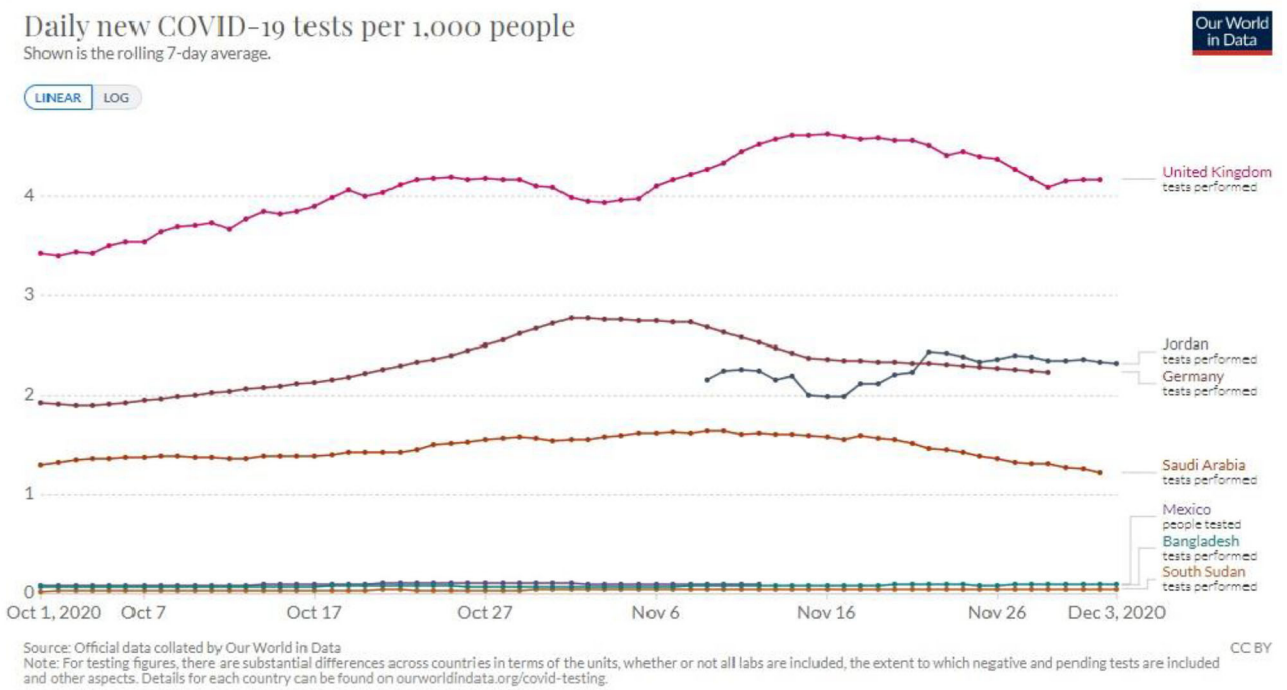

FIGURE 2 | Testing capacity variations among countries of different incomes during the period of October–December, with a focus on Jordan's testing capacity in comparison to higher income countries (34).

Suggested Solutions Tailored to the Actual Needs and Applicability to the LIC

Increasing Healthcare Systems' Work Force

Asking retired health care professionals to join the workforce to fight COVID-19, is an option adopted by some health authorities. Waiver of medical licensing fees and expediting the renewal of licenses for healthcare professionals, while providing extensions for the licenses that are expiring soon, could assist in promoting the accruing of this group of physicians. This might help in reducing the load on the practicing doctors. Retired healthcare workers are experienced, knowledgeable, and emotionally stable. However, asking retired healthcare professionals who are in their 60s and beyond to provide direct patient care could pose risk of infections for such individuals. We believe that it is better for this particular group of healthcare professionals to provide telemedicine or support services. Additinally, physicians who are specialized in other clinical areas may be trained to work in intensive care units. Medical assistants and nurses may be asked to help in patients' treatments under physicians' supervision.

Asking medical students of different institutions to help according to the level of seniority might also alleviate some of the workload. Medical students are usually young individuals who might be better suited to support the medical teams. We believe that these stratigies may increase the number of physicians at emergency care eventually leading to a reduced workload on individual physicions.

Social Support of the Healthcare Frontline Workers

In LIC, the extended families play a pivotal role in supporting working familiy members. However, practicing healthcare workers might be living away from their families. It is important that healthcare system leadership take measures to ensure that the healthcare workers are fully supported and cared for. Physicians who are placed on quarantine or are working over extended hours should be offered care for their children. Alternatively they could be asked to do office work for those who are in clinics and hospitals, and provide remote care and consultation for patients. Additional institutional policies that may help in alleviating healthcare workers stress and burnout may include paid time off and sick days in addition to coverage of expenses for employees with COVID-19-related illnesses.

Telemedicine

The application of telemedicine can be a sustainable solution to many of our challenges during the COVID 19 pandemic. According to the European commission, it can be defined as the provision of healthcare by using electronic information and communication technology to securely transmit information in text, sound, images and other forms to prevent, diagnose, or treat patients (44). Given the novelty of the COVID 19 virus, telemedicine can offer the community with a trusted medical opinion and avoid the chaos created by unreliable information on social media (45). It can help with the spread of experiences and medical knowledge form different parts of the world to reach remote areas and underserved communities by conducting frequent conferences and meetings between healthcare professionals and improving the response to this healthcare emergency (45). With the large increase in smartphone and internet users in developing countries, programs, and phone applications that allow for remote patient-doctor interaction are widely available (46). This can be very quickly utilized by training healthcare professionals to conduct online consults, as these applications don't require much training for use (46, 47).

Between October 5 and October 26, an online virtual workshop, organized by the WHO, took place. In this workshop, medical health professionals from the Jordanian public health sector were given lectures on various topics pertinent to COVID-19 screening and patient management protocols. This online workshop facilitated the sharing of medical knowledge and protocols while at the same time setting the trend of online lecturing and data sharing. These methods were then implemented in various hospitals in the public sector, thus facilitating a better quality of health care while limiting the need for large gatherings (48).

Another major benefit is the provision of direct interaction between patients and healthcare professionals. This helps maintain follow-up on chronic diseases from a distance, which might be interrupted due to fear from acquiring the infection (45). Moreover, it can maximize the granted benefit from limited resources and physicians by enhancing the efficacy of critical care services and making it possible to expand ICUs with the same number of physicians by allowing off site intensivist to monitor patients in multiple locations simultaneously (49). Consultations from worldwide experts through many freely available applications on the readily available personal mobile phones can enhance healthcare workers knowledge and introduce new skills by teleconferences, e-workshops, and free webinars. Healthcare workers can be remotely trained to enhance their skills.

In King Hussein Cancer Center in Jordan various methods of limiting unnecessary exposure were implemented. Patients were contacted, by phone, by nurse coordinators from the center before scheduled appointments. In these phone calls, patients were asked if they suffered from any symptoms that would suggest a COVID-19 infection. They were also asked if they had been in contact with a confirmed COVID-19 case. Screening tests and vital signs were taken for patient with a high degree of suspicion before being admitted for scheduled procedures. Upgrades were also made to an existing call center to facilitate remote clinics (50).

Mobile Applications in Tracking Possible COVID-19 Patients

LIC have limited resources to allocate to testing a large number of people, so it is important to develop ways to maximize the efficiency of the testing process (**Figures 1**, **2**). Mobile applications that use location to determine the proximity of a person to an affected individual can help in contact tracing, ultimately maximizing the efficiency of testing. These applications, if used by a large enough number of people, along with social distancing

measures, could be sufficient in slowing the progress of the pandemic to a manageable rate. Similar measures have been deployed in Mainland China and South Korea with great success (51).

The Use of 3D Printing as a Possible Solution for Limited Equipment Due to Lack of Resources

The shortage in the medical supply chain has triggered us to search for bright solutions that can reshape our future response to persistent challenges. The technology of 3D printing is evolving and has a wide variety of applications. It has the ability to produce anything anywhere and can adapt complex manufacturing instruction in a short time and at a lower cost. During the current pandemic, it was used to manufacture PPE including facemasks, face shields, and goggles. Some universities used 3D printing to create diagnostic tools such as microscopes. In china, 3D printers were used to create quarantine booths (52). Moreover, 3D printing firms are volunteering their expertise and skills to respond to the current crises. Many 3D printing companies such as Stratasys, Carbon, and Shape ways are working rapidly to produce ventilator components, face masks, and medical test equipment. To globally materialize 3D printing service, they have shared free files for a 3D printed add-on hands-free door handles (52). These add-ons allows users to open most modern doors using their elbows to avoid touching door handles (hotspot for microbes) that are subjected to a lot of physical contact, especially in public places such as offices and hospitals (52).

CONCLUSION

This pandemic has presented a unique challenge to developed and developing countries alike. LIC countries have faced a harder toll due to preexisting challenges in their healthcare systems. Despite this there are many ways to utilize existing infrastructure to help combat the pandemic by utilizing retired healthcare workers, using telemedicine, or taking advantage of cheaper technologies (such as 3D printing) to decrease the burden of the pandemic. Raising public awareness remains of pivotal importance to decrease the pressure of the pandemic on the health care system. Public health measures known to limit viral spread are highly encouraged, these include hand hygiene, cough etiquette and social distancing; as they will reduce the need for limited supplies (10). We also believe that the WHO, as a global health oversight board, should develop comprehensive programs to tackle the different issue facing healthcare systems in LIC. Emergency health funding should be offered to enable health authorities in LIC to purchase appropriate consumables for healthcare workers.

AUTHOR CONTRIBUTIONS

MA-H: the conception of the idea. YA, HE, ME, MS, and AA-H: literature review. YA, HE, and AA-H: writing the first draft. ME, MS, AA-H, and MA-H: critical review. All authors: final approval. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

OPINION
published: 12 February 2021
doi: 10.3389/fpsyt.2021.619296

A Reflection on the Main Ethical Obstacles Related to the Strategic Action "*O Brasil Conta Comigo*"

Jucycler Ferreira Freitas[1], *Jucier Gonçalves Júnior*[2]* *and Estelita Lima Cândido*[1]

[1] *Programa de Pós-Graduação em Desenvolvimento Regional Sustentável – PRODER, Universidade Federal Do Cariri (UFCA), Juazeiro Do Norte, Brazil,* [2] *Department of Internal Medicine, Santa Casa de Misericórdia, Fortaleza, Brazil*

Keywords: bioethics, coronavirus infection, public health, education, medical, government program

INTRODUCTION

The COVID-19 pandemic began in China in December 2019 and quickly spread to the rest of the world, forcing countries to develop strategies to fight the disease. By January 16, 2021, the virus had infected 91,816,091 people and caused 1,986,871 deaths (1).

Countries have adopted policies requiring individuals to practice social isolation, enforced through administrative and criminal sanctions. Additionally, it was necessary to create measures that would increase the number of professionals available to serve the population in medical and hospital units (2–5).

Countries such as the United Kingdom (2), Denmark (3), and Brazil (4, 5) adopted measures capable of having a direct impact on academic training and subsequently on the professional lives of students in the health field, such as accelerating medical graduation and the recruitment of students from other disciplines, such as nursing and pharmacy to act on the front lines of the pandemic response. To attract volunteer students from other areas of health, the government proposals offer benefits ranging from financial resources to advantages over other students in public tenders. These questions and others that will be raised in this paper represent ethical conflicts that need to be discussed from an academic, occupational, and human perspective.

This paper aims to promote a reflection on the main ethical obstacles related to the Strategic Action "*O Brasil Conta Comigo*" ("Brazil counts on me"), which is focused on employing students of health courses to face the coronavirus pandemic (COVID-19). To this end, our arguments are based on the strategy itself, on Notice 4/2020, on Brazillian laws, and on ordinances issued by official bodies, including the Ministry of Health of Brazil (DH), the Ministry of Education (ME), and the Open University of the Brazilian Unified Health System (UNA/SUS).

DISCUSSION

A Brief Presentation of the Program "O Brasil Conta Comigo" (Brazil Counts on Me)

The Strategic Action "*O Brasil Conta Comigo*" ("Brazil counts on me") consists of an emergency measure implemented by the Brazilian government, in the form of a program with national coverage, whose objective is to optimize the availability of health services within the scope of SUS in order to contain the COVID-19 pandemic. The aforementioned strategic action was instituted by Ordinance numbers 356, of March 20, 2020 (4) and 492, of March 23, 2020 (5), which originated respectively from the MH and the DH. This program will be achieved through the participation of undergraduate students in healthcare delivery, while the state of public health emergency resulting from the worldwide pandemic persists (5).

OPEN ACCESS

Edited by:
Ma'n H. Zawati,
McGill University, Canada

Reviewed by:
Alexander Bernier,
McGill University, Canada
Michael Lang,
McGill University, Canada

***Correspondence:**
Jucier Gonçalves Júnior
juciergjunior@hotmail.com

Specialty section:
This article was submitted to Public Mental Health, a section of the journal Frontiers in Psychiatry

Received: *20 October 2020*
Accepted: *20 January 2021*
Published: *12 February 2021*

Citation:
Freitas JF, Gonçalves Júnior J and Cândido EL (2021) A Reflection on the Main Ethical Obstacles Related to the Strategic Action "O Brasil Conta Comigo." Front. Psychiatry 12:619296. doi: 10.3389/fpsyt.2021.619296

The strategic action is aimed at students regularly enrolled in the last 2 years of the medical course, and in the last year of the nursing, pharmacy and physiotherapy courses of the federal education system (4). Normally, these health courses have, prior to graduation, an internship regulated and supervised by qualified teachers who belong to the higher education institutions to which the students belong. In the "O Brasil Conta Comigo" program these students act in care, that is, face-to-face activities for patients with or without suspected COVID-19 in health units during the pandemic (5) under the supervision of local professionals. During the participation of students, they will be involved in activities including (a) screening patients; (b) outpatient care; (c) hospital care; and (d) care in the home care system in internal medicine, primary health care, and pediatrics. There is a pre-established workload (20–40 h) and the proposal provides for professor / preceptor supervision accredited by UNA/SUS (5–7) for theoretical activities. Thus, the program fits into an internship modality.

The participation of students can be done in two ways: computing the workload in the program as the workload of the supervised internship; or through voluntary work. There are three compensations provided for in the Public Notice: (I) an additional 10% in the public selection process for Health Residency Programs promoted by the Ministry of Health; (II) obtaining a discount on the monthly fee, to be defined and granted by Higher Education Institutions; or (III) receiving a scholarship to work in SUS (4, 5).

It is up to the managers and personnel responsible for the health units of the municipalities, states, and the Federal District, to adhere to the strategic action, to select the advisors for the students and to determine the number of places destined for the students.

Thus, medical, nursing, pharmacy, and physical therapy students, in supplementing the health service, will face the coronavirus and guarantee additional healthcare to the population (6, 7). The strategic action serves as a mechanism for optimizing the availability of services in the Unified Health System.

Ethical Implications of the "O Brasil Conta Comigo" Program (Brazil Counts on Me)

First, the educational system and society need to reflect on the risks and benefits of exposing students to the attempt at trial and error in the face of ethical situations distanced from controlled teaching environments (8). It is necessary to remember that in extreme situations and when there is a lack of adequate information such as the pandemic, decision making involves and requires much more from the professional. In this way, ethical decision-making becomes quite challenging for young professionals who have not yet completed their undergraduate studies. In this context, good teacher preceptorship / assistance is essential (8). Although the "O Brasil Conta Comigo" Program provides for the supervision of students by local professionals linked to UNSA / SUS, it cannot guarantee their supervision by professionals who are qualified to teach or who are linked to educational institutions. Also, it does not establish assessment instruments to verify the teaching-learning process (5). Further, the workload is excessive, based on the assumption that the program constitutes an internship (6).

These aspects differ from Law number 11,788, of September 25, 2008—Internship Law (7) in several points, such as student supervision, monitoring criteria, workload requirements, and security measures. The aforementioned law requires the guidance of a professor in the area indicated by the educational institution. This implies closer monitoring of students through the registration of attendance, and evaluation according to the rules of the student's home institution. It also provides for the internship to be carried out with a maximum workload of 30 h per week and a personal accident insurance agreement in favor of the students.

Secondly, it is noteworthy that this proposal to insert students in the fight against COVID-19 in health services arose while universities suspended face-to-face classes and the internship fields suspended their activities, no longer receiving students. The reasons for this suspension included the risk of infection, and the logistical difficulties inherent in ensuring the supervision of students. Given the pandemic period and its severity, the Brazilian Medical Association (9), before October 2, 2020, received 3,931 complaints about the absence of PPE, which affects 782 municipalities and mainly concerns the absence of masks, goggles, and waterproof covers. In this sense, according to the normative acts that govern the Strategic Action "O Brasil Conta Comigo" ("Brazil counts on me"), it is up to the federated entities to provide PPE to their students. Thus, there must be an increase in PPE transfers, given that several municipalities do not even have sufficient materials for their employees.

In this context, it is important to remember that in Brazil, SUS has an important shortage throughout the national territory of personal protective equipment (PPE) (9), of qualified professionals, and services prepared for teaching-learning activities (10). An example of this is that, according to Gonçalves Júnior et al. the shortage of professionals with an adequate profile for integral care, coupled with insufficiency and maldistribution, are some of the main barriers to the universalization of access to health in Brazil, where the number of physicians per inhabitant (2.11 doctors/1,000 inhabitants) is small compared to other countries such as France (3.0 physicians/1,000 inhabitants), the United Kingdom (2.7 physicians/1,000 inhabitants), and Sweden (4.0 physicians/1,000 inhabitants) (11). The "O Brasil Conta Comigo" program does not take this perspective into account. Thus, there is a concern that these students are being placed in extreme situations, without sufficient scientific knowledge, with inadequate preceptorship, and lacking the minimum necessary PPE.

Thirdly, it can be seen that the aforementioned strategic action, through the notice 4/2020, does not include insurance against accidents and recess, as required in the internship law. According to the Pan American Health Organization (9), almost 570 thousand health professionals were infected and more than 2,500 succumbed to the virus. Of these, 258,200 infected health professionals are from Brazil, accounting for 226 deaths prior to August of 2020 (12).

Fourth, another perspective to be explored is the impact that these experiences can have on students' mental health. O'Byrne et al. (13) emphasize that those who engage in such work without sufficient preparation are subject to moral trauma and adverse health outcomes. Brazilian medical school interns were asked about whether they felt prepared to act in the fight against the pandemic, and 57.5% stated that they did not (14). Among Spanish students in Nursing and Medicine courses, a survey revealed a lack of knowledge regarding virus transmission and basic preventive measures, and further revealed that a low percentage of students had received training specific thereto (15). According to Rolim Neto et al. (16), Work-related stress is a potential cause of concern for health professionals. It has been associated with anxiety including multiple clinical cases thereof, depression in the face of the coexistence with countless deaths, and long work shifts that incorporate the most diverse unknowns and heightened demands in the treatment of patients with COVID-19. Therefore, it is an important indicator of psychic exhaustion. Besides that, situations of extreme vulnerability such as the pandemic resonate with health professionals who suffer or have suffered from anxiety and obsessive-compulsive disorder (OCD) in the treatment of patients in hospitals. Panic attacks can also be a response to the stress load linked to the demands imposed by the coronavirus outbreak (16). Considering that experienced professionals become sick psychically in unhealthy environments such as the pandemic, it can be expected that the impact of the pandemic on students' mental health will be even more severe.

Fifthly, we want to discuss the tempting benefits or advantages offered to recruits, such as the receipt of a scholarship and of a certificate that guarantee such students an additional score of 10% in the public admission process for residency programs promoted by the DH, which is valid for 2 years, counting from the date of certificate issue (5, 6). This benefit violates the principle of isonomy, since many students who are prevented from participating in the process because they form part of an at-risk group, for instance, will be penalized in the aforementioned process. The Brazilian Medical Education Association (17) also disagrees with this point and warns that interns who have already completed the rotations in the areas highlighted in Ordinance No. 492 and Request for Proposal No. 4 will not have the opportunity to participate. In the competitive health market, offering bonuses in public tenders, such as the residency program, would encourage young professionals to participate. However, this in combination with a lack of experience and the great impetus for work could expose them to greater risks. So, could this conduct by society and the government be seen as ethical? (8).

Furthermore, students who are not selected through a scholarship, and volunteer when summoned by a specific municipality, may lack the financial resources required to participate (5). It is not clear which institution will provide such students with the resources needed to ensure their meaningful participation in the initiative. This violates the equality provided for in the 1988 Brazilian Federal constitution (18).

Finally, we point out that the measure "Brazil Counts on Me" was prepared without prior consultation with the competent bodies such as CNS - National Health Council, Federal Nursing Council (COFEN) and The Brazilian Medical Education Association (17, 19, 20). In fact, the CNS itself points out that the use of health students in training on the frontline of care should be a last resort, to be relied on only after all calls for professionals through other mechanisms have been issued. The hierarchy of intervention scenarios is devised according to the potential risk to the health of students, protecting them from "cognitive, psychic, and occupational stress and working hours" (20).

FINAL CONSIDERATIONS

We pointed out and discussed some ethical obstacles contained in the Strategic Action "*O Brasil Conta Comigo*" and envisioned an environment of risk and insecurity for students, not only related to their learning, but also in personal, physical, and emotional aspects. Future health professionals must be prepared to face similar situations, given the characteristics of their academic backgrounds. However, it is prudent to assess the urgency of the situation, and to determine if there is a real need to introduce these students to the front lines of the pandemic response effort, despite their lack of adequate experience. It is necessary to ensure that the Higher Education Institutions from which the participating students originate effectively participate in the supervision thereof. Further, the principle of isonomy should be respected regarding students' participation in the "Brazil Counts on Me" initiative.

In order to reformulate the "*O Brasil Conta Comigo"* Program, there is a need to: (1) map the most fragile areas of SUS - which services are most precarious? Which need more manpower? Which have a larger population for analysis? (2) Define goals for the occupation of sectors with an interval of 3 or 6 months, depending on the logistics available (resources, work team, mobility); (3) invest in formal training for professionals already working; (4) only once all of these efforts have been made should the recruitment of students be considered. Such initiatives should be implemented under the strict supervision of Brazilian public higher education institutions, as was done in the case of another federal program, the "Mais Médicos para o Brasil" program. In the latter initiative, higher education institutions were made responsible for doctors who work in primary care, designating competent professionals to provide face-to-face tutoring, guide face-to-face educational activities and provide classes to improve teaching and learning outcomes. In addition, there must be agreement terms which address all of the particularities inherent in the curricular internship, such as the identification of the advisor, the supervisor, and the activities that will be practiced.

Thus, we see the need to develop new studies that assess the impact of the program on the lives of students who participate in this action, especially regarding psychological and professional

aspects, as well as situations triggered by the unequal treatment of applicants entering into residency programs.

AUTHOR CONTRIBUTIONS

All authors prepared the review, developed the inclusion criteria, selected titles and abstracts, evaluated the quality of the articles included, and wrote the manuscript.

ACKNOWLEDGMENTS

The authors would like to thank the Núcleo de desenvolvimento e aplicação de estratégias para o combate a doenças e agravos das coletividades humanas of the Faculty of Medicine of the Federal University of Cariri (UFCA), Programa de Desenvolvimento Regional Sustentável - PRODER/UFCA, and the National Council for Scientific and Technological Development (CNPq).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 16 February 2021
doi: 10.3389/fpsyt.2021.605676

Effect of COVID-19 Quarantine on the Sleep Quality and the Depressive Symptom Levels of University Students in Jordan During the Spring of 2020

Heba Saadeh[1†], Maha Saadeh[2†], Wesam Almobaideen[1,3], Assem Al Refaei[4], Nour Shewaikani[4], Reem Qadan Al Fayez[5], Hamzah Khawaldah[6], Sobuh Abu-Shanab[7] and Maysa Al-Hussaini[8,9]*

[1] Computer Science Department, King Abdullah II School of Information Technology Faculty, The University of Jordan, Amman, Jordan, [2] Computer Engineering and Informatics, Middlesex University Dubai, Dubai, United Arab Emirates, [3] Electrical Engineering and Computing Sciences, Rochester Institute of Technology, Dubai, United Arab Emirates, [4] School of Medicine, The University of Jordan, Amman, Jordan, [5] Computer Information System Department, King Abdullah II School of Information Technology Faculty, The University of Jordan, Amman, Jordan, [6] Geography Department, School of Arts, The University of Jordan, Amman, Jordan, [7] Psychosocial Program, King Hussein Cancer Center, Amman, Jordan, [8] Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, Amman, Jordan, [9] Human Research Protection Program Office, King Hussein Cancer Center, Amman, Jordan

OPEN ACCESS

Edited by:
Maria Francesca Moro,
University of Cagliari, Italy

Reviewed by:
Franco Mascayano,
New York State Psychiatric Institute (NYSPI), United States
Michele Fornaro,
New York State Psychiatric Institute (NYSPI), United States

***Correspondence:**
Heba Saadeh
Heba.saadeh@ju.edu.jo

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Public Mental Health, a section of the journal Frontiers in Psychiatry

Received: 18 September 2020
Accepted: 25 January 2021
Published: 16 February 2021

Citation:
Saadeh H, Saadeh M, Almobaideen W, Al Refaei A, Shewaikani N, Al Fayez RQ, Khawaldah H, Abu-Shanab S and Al-Hussaini M (2021) Effect of COVID-19 Quarantine on the Sleep Quality and the Depressive Symptom Levels of University Students in Jordan During the Spring of 2020. Front. Psychiatry 12:605676. doi: 10.3389/fpsyt.2021.605676

Objectives: This study was designed to assess the effect of COVID-19 home quarantine and its lifestyle challenges on the sleep quality and mental health of a large sample of undergraduate University students in Jordan. It is the first study applied to the Jordanian population. The aim was to investigate how quarantine for several weeks changed the students' habits and affected their mental health.

Methods: A cross-sectional study was conducted using a random representative sample of 6,157 undergraduate students (mean age 19.79 ± 1.67 years, males 28.7%) from the University of Jordan through voluntarily filling an online questionnaire. The Pittsburgh Sleep Quality Index (PSQI) and the Center for Epidemiologic Studies-Depression Scale (CES-D) were used to assess sleep quality and depressive symptoms, respectively.

Results: The PSQI mean score for the study participants was 8.1 ± 3.6. The sleep quality of three-quarters of the participants was negatively affected by the extended quarantine. Nearly half of the participants reported poor sleep quality. The prevalence of poor sleep quality among participants was 76% (males: 71.5% and females: 77.8%). Similarly, the prevalence of the depressive symptoms was 71% (34% for moderate and 37% for high depressive symptoms), with females showing higher prevalence than males. The overall mean CES-D score for the group with low depressive symptoms is 9.3, for the moderate group is 19.8, while it is 34.3 for the high depressive symptoms group. More than half of the students (62.5%) reported that the quarantine had a negative effect on their mental health. Finally, females, smokers, and students with decreased income levels during the extended quarantine were the common exposures

that are significantly associated with a higher risk of developing sleep disturbances and depressive symptoms.

Conclusions: Mass and extended quarantine succeeded in controlling the spread of the COVID-19 virus; however, it comes with a high cost of potential psychological impacts. Most of the students reported that they suffer from sleeping disorders and had a degree of depressive symptoms. Officials should provide psychological support and clear guidance to help the general public to reduce these potential effects and overcome the quarantine period with minimum negative impacts.

Keywords: University students, mental health, COVID-19 quarantine, PSQI, CES-D

INTRODUCTION

In early December of 2019, the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), known later as COVID-19, emerged in Wuhan city of China (1). As of 20th of December 2020, COVID-19 affected more than 200 countries, with more than 77 million cases and a death toll that is nearly two million globally (2). This respiratory pandemic is highly contagious, and containment strategies include quarantine, lockdown, isolation, travel bans, country-wide closure, social distancing, personal hygiene, and face-mask mandating were applied by many countries (3). These stringent measures helped in controlling the virus spread. Many countries had applied quarantine or stay at home procedures from the detection of early cases; it aims to restrict people's movement and reduce their social mixing (4). Even though quarantine limits the spread of COVID-19 and other infectious diseases (5–9), its psychological effect, along with its social, economic, and physiological impacts, should not be neglected (10–14).

Having sufficient sleep at night plays an essential role in the efficiency of accomplishing everyday tasks and having good mental abilities (15). Globally, inadequate sleep is considered a public health epidemic, being linked to 7 of the 15 leading causes of death in the U.S. (16). A study among Canadians reported that poor sleep quality with short sleep duration was prevalent, as 43% of men and 55% of women had a disturbance in sleeping or staying asleep (17). Another study in Ethiopia reported poor sleep quality among 65.4% of the participants (18). Furthermore, in Saudi Arabia, a study conducted on a sample of health care workers revealed that 42.3% suffer from poor sleep quality (19).

Several studies assess the sleep quality amid the COVID-19 pandemic. In France, deteriorated sleep quality during the current quarantine was reported by 47% of the study sample (20). 57.1% of Italians who participated in an online questionnaire suffered from decreased sleep quality (21). Moreover, during the 2 weeks of quarantine in February in China, the sleeping disorders were significantly increased in the age group of 18–24 years (22). Likewise, a study in Greece showed that although the quantity of sleeping hours increased in 66.3% of the study participants, the sleep quality decreases to 43% (23). Furthermore, more than half of the Spanish participants in a study reported a change in their sleeping habits due to quarantine (24).

Depression is a widespread mental disorder that affects millions of people worldwide, and it is the leading cause of disability (25). Persistent negative thoughts, feeling down, lack of energy, losing interest in joyful activities, sleep disturbance, and many more are among the common symptoms of depression (25). This long-lasting pessimistic mood may lead to suicidal thoughts (26, 27). Many people suffering from depressive symptoms tend to escape real-life and dealing with surrounding family, friends, and colleagues into social media looking for comforts and relief in positive comments and news, which is reflected in their high usage of their smart devices; like smartphones, tablets, iPad, and other devices (28–32). Globally, 40.5% (31.7–49.2%) of the disability-adjusted years of life caused by depressive disorders, with a 4.7% (4.4–5.0%) global prevalence of major depressive disorders and an annual incidence of 3.0% (2.4–3.8%) (33, 34). Regionally, researchers in the Middle East and North Africa regions had evaluated depressive symptoms rates ranging from around 13 to 29%, with women and University students having higher rates, among others (35). Another study reported depressive symptoms among University students in Oman and Egypt as 27.7 and 60.8%, respectively (36, 37). In Jordan, around 74% showed a degree of depressive symptoms among school and University students (38, 39).

The fear of the current pandemic and its consequences, especially on the economy, caused a depression that sometimes leads to suicidal incidents (40–42). The extended quarantine and disturbance of everyday life routine increase the anxiety and depression levels. In Southwestern China, Lei et al. reported significant differences in the prevalence of anxiety and depressive symptoms among the public affected by quarantine (12.9 and 22.4%, respectively) and those unaffected (6.7 and 11.9%, respectively) during the COVID-19 pandemic (43). Similarly, after the stay-at-home order was issued, Spanish researchers identified higher levels of depressive symptoms in northern Spain, specifically among younger individuals with chronic diseases (44). These results are in line with the 2003 SARS outbreak findings in which the sample group that showed the highest levels of depression symptoms were quarantined during the outbreak (45).

Treating and taking care of COVID-19 infected patients, in addition to protecting others from catching the virus, are the priority for most countries worldwide. However, COVID-19 has psychological stress impact on non-infected members, which

may last longer than the pandemic's actual time. Understanding the level and prevalence of these impacts on the current situation can improve the population's health and reduce its consequences during COVID-19 and future similar pandemics. Therefore, this is the first study that aims to assess the impact of the extended COVID-19 quarantine on the mental health, especially depressive symptom levels, and the sleep quality of a large sample of undergraduate University students in Jordan. This is assessed by collecting many exposures to cover the demographic, economic, and quarantine-related factors that might worsen the effect of quarantine on both the students' sleep quality and mental health.

METHOD

Participants

The online questionnaire participants were undergraduate students at the University of Jordan (UJ, located in Amman) who voluntarily completed its questions. The total number of collected responses had reached 7,146. Six thousand one hundred fifty-seven unique participants remained after cleaning the data by removing all the duplicated submissions. All the questions were obligatory; hence there was no missing data. At any time, any participant could have ignored answering any of the questions to withdraw from the study. The Institutional Review Board / the Research Ethics Committee at UJ had approved the study objectives and procedures. The age of the participants ranged between 17 and 30, with a mean of 19.79 $\pm$ 1.67. Nearly half of the students were in their first year. 28.7% of participants were males (1,769), and 71.3% were females (4,388), with a male to female ratio of 1:2.48. Half of the students were studying humanities-related majors, and 36.2% were studying scientific majors, while 13.6% were from the medical schools (medicine, dentistry, nursing, pharmacy, and rehabilitation sciences).

Measurements of Clinical Symptoms

The questionnaire collects an extensive list of general socio-demographic, socio-economic, and quarantine-related information (as a measure of exposures) in addition to the questions in the PSQI and CES-D measures to assess the primary outcomes: sleep quality and depressive symptom levels. The reason for collecting this extensive list of exposures was to cover the main confounding factors and assess how these many different exposures may affect/associate with the two primary outcomes.

Socio-Economic and Socio-Demographic Factors

Socio-economic factors regarding the household income, parents' education levels ranging from "did not reach high school" to "postgraduate," and parents' employment status during the quarantine were collected. Furthermore, gender, age, year level, academic major/performance, and students' smoking practices were measured.

TABLE 1 | Items of Pittsburgh Sleep Quality Index (PSQI).

	Component	Description
1	Sleep quality	Perceived overall sleep quality
2	Sleep latency	Measures how long it took to fall asleep
3	Sleep duration	The actual length of sleep
4	Sleep efficiency	The total number of hours slept divided by and the number of hours spent in bed
5	Sleep disturbances	Behaviors that negatively affect sleep, such as waking up at late night or early in the morning, getting up at night to use the bathroom, uncomfortable breathing, coughing or snoring loudly, feeling too hot or too cold, having nightmares, or pain
6	Sleep medication	Whether there is a need to use them to go to sleep
7	Daytime dysfunction	Troubles staying awake while driving, eating meals or engaging in social activity, or keep enough enthusiasm to get thing done

This scale was proposed by Buysse et al. (46).

Quarantine Variables

To assess the effect of home quarantine on student's mental health, more information related to the stay at home period, including the number of members (and children) quarantined with each student, place of quarantine (rural or urban), house specifications (apartment/independent house with/without a garden), household income during the quarantine, communication with family members, and practiced hobbies were gathered.

Clinical Assessment of Sleep Quality

The sleep quality of the undergraduate University students during the several weeks of COVID-19 home quarantine was assessed using Pittsburgh's Sleep Quality Index (PSQI) (46). This index is a validated self-reported questionnaire that measures the quality of sleep subjectively from different perspectives. It contains 19 items grouped into seven components, each measures one aspect (**Table 1**). The components are subjective sleep quality (very good, fairly good, fairly bad, and very bad), sleep latency (time between lying down in bed and falling asleep), duration (<5 h, 5–6 h, 6–7 h, >7 h), efficiency (<65%, 65–74%, 75–84%, >85%), disturbance, the need to use sleep medication (yes, no), and daytime dysfunction. Each component is scored on a four-point scale from 0 (no difficulty) to 3 (severe difficulty). The global score is calculated by adding each component's score and can range from 0 to 21, with higher scores indicating lower sleep quality (46).

Clinical Assessment of Depressive Symptoms

Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression Scale (CES-D) (47). It is a validated self-reporting scale that contains 20 items, each ranged between 0 and 3 (**Table 2**). The global score is calculated by

TABLE 2 | Items of Center for Epidemiologic Studies-Depression Scale (CES-D).

Items		Items	
1	I was bothered by things that usually don't bother me	11	My sleep was restless
2	I did not feel like eating; my appetite was poor	12	I was happy
3	I felt that I could not shake off the blues even with help from my family or friends	13	I talked less than usual
4	I felt I was just as good as other people	14	I felt lonely
5	I had trouble keeping my mind on what I was doing	15	People were unfriendly
6	I felt depressed	16	I enjoyed life
7	I felt that everything I did was an effort	17	I had crying spells
8	I felt hopeful about the future	18	I felt sad
9	I thought my life had been a failure	19	I felt that people dislike me
10	I felt fearful	20	I could not get "going"

This scale was proposed by Radloff et al. (47).

adding all items' scores, which ranged from 0 to 60. The four-point scale is: rarely or less than once a day (scores 0 points), some of the time or 1-2 days (scores one point), occasionally or moderate amount of time or 3-4 days (scores two points), and most of the time or 5–7 days (scores three points). The higher the global score is, the higher levels of depressive symptoms there are (47).

Statistical Analysis

Frequencies and percentages were used to analyze the categorical demographic, economic, and quarantine variables, while mean and standard deviation were used for continuous variables. A two-sample *t*-test was used to test for significance for the binary variables, while multi-values variables were tested using a one-way analysis of variance (ANOVA). As a *post-hoc* analysis, Tukey Honestly Significance Difference (TukeyHSD) was used to follow up on the significant factors that resulted from the ANOVA to identify the pair of values that had a significant mean difference. The significant factors were further investigated using logistic regression, and the significant associations between the exposures and the primary outcomes were identified using the Backward selection method. While binary logistic regression was used for the sleep quality state (1: poor, 0: normal), the multinomial logistic regression was used for the depressive symptoms state (1: low, 2: moderate, and 3: high). A p-value of ≤ 0.05 was considered to be statistically significant. All statistical analyses were performed using R version 4.0.0 and RStudio version 1.2.5042.

RESULTS

Demographic and Economic Characteristics of the Study Participants

Nearly half of the participants ($n = 3{,}003$) were fresh students, with most ($n = 3{,}092$) studying humanities-related majors. Around three-quarters were females ($n = 4{,}388$), and only 16.3% were smokers ($n = 1{,}006$). The average mean age was 19.79, and the standard deviation was 1.67. Only 3.5% of the students are about to graduate ($n = 217$) (**Table 3**; the first two columns).

Furthermore, around 45% ($n = 2{,}798$) and 34% ($n = 2{,}087$) of the students' fathers and mothers had a University degree (bachelor or postgraduate). The household income level ranged from <200 JD ($ 282) to more than 1,500 JD ($ 2,115), which mainly fall into three categories; very low to low income (<600 JD: 45%, $n = 2{,}807$), medium income (600–1,000 JD: 30%, $n = 1{,}906$), and high income (more than a 1,000 JD: 25%, $n = 1{,}444$) (**Table 3**; the first two columns).

Quarantine Characteristics of the Study Participants

Only 4.5% ($n = 275$) of the students had their household income increased during the quarantine, whereas nearly 50% had either a decreased or a completely stopped income ($n = 2{,}467$ and $n = 775$, respectively). A low proportion of 13.7% ($n = 842$) of the students were quarantined in rural areas. 55% ($n = 3{,}350$) lived in an apartment; one-third of these apartments had a garden. The majority (∼80%, $n = 2{,}210$) of the students who lived in an independent house had a garden (**Table 4**; the first two columns). Watching movies and/or TV series in addition to sleeping were the most common activities (70%, $n = 4{,}310$) among the students during the quarantine, and then eating or cooking with a percentage of nearly 50% ($n = 3{,}079$). More than half of the students (68%, $n = 4{,}187$) start practicing new hobbies like board games (25%, $n = 1{,}539$), drawing (11%, $n = 677$), cooking (42%, $n = 2{,}586$), meditation (16%, $n = 985$) and watching movies/series (51%, $n = 3{,}140$). Despite the different demographics for the students, the majority of them (89.7%, $n = 5{,}523$) communicated more with their families and reported that they are spending more time with their families during the quarantine, and around 70% ($n = 4{,}310$) increased their communication with the members living apart. Furthermore, students were asked about the health of the family members and friends that they were quarantined with; more than half of the students reported that they were quarantined with a smoker ($n = 3{,}386$), around 20% ($n = 1{,}416$) with a diabetic patient, about 8% ($n = 493$) with a cardiac patient, and 17% ($n = 1{,}047$) with an elderly member (>65 years). Finally, during the quarantine, 77% ($n = 4{,}741$) of the students lived with 3–7 family members, and 43% ($n = 2{,}648$) were not quarantined with children.

Psychological Findings of the Study Participants (Sleep Quality)

Students' sleeping behaviors were assessed through the PSQI. It revealed an evident abnormal and unhealthy sleeping habits, which might affect sleep quality. For instance, more than three-quarters of the students (77%, $n = 4{,}764$) went to bed after midnight during the quarantine, more than half of them ($n = 2{,}711$) went to bed after 3 a.m. About half of the students ($n = 3{,}003$) needed more than 30 min to fall asleep after going to bed, and 30% ($n = 1{,}847$) needed more than 40 min. Sixty percentage of the students ($n = 3{,}669$) woke up after midday and 33% ($n =$

TABLE 3 | Socio-demographic and socio-economic characteristics, PSQI and CES-D scores of study participants.

Variable	Mean ± SD or *N* (N%)	PSQI Score Mean ± SD or (*p*-value)	CES-D Score Mean ± SD or (*p*-value)
Age	19.79 ± 1.67	8.1 ± 3.6	22.2 ± 11.7
Gender		(8.34e-04[a]*)	(4.02e-07[a]*)
Male	1,769 (28.7%)	7.9 ± 3.7	21.0 ± 11.7
Female	4,388 (71.3%)	8.2 ± 3.5	22.6 ± 11.7
Major		(6.28e-06[b]*)	(0.941[b])
Humanities	3,092 (50.2%)	8.4 ± 3.6	22.1 ± 11.9
Medical	840 (13.6%)	7.9 ± 3.6	22.3 ± 11.7
Scientific	2,235 (36.2%)	7.9 ± 3.5	22.2 ± 11.6
Class		(2.69e-05[b]*)	(0.472[b])
Year 1	3,003 (48.8%)	7.9 ± 3.5	21.9 ± 11.7
Year 2	1,757 (28.5%)	8.2 ± 3.6	22.6 ± 11.5
Year 3	793 (12.9%)	8.4 ± 3.7	21.9 ± 12.3
Year 4	481 (7.8%)	8.5 ± 3.7	22.3 ± 11.5
> Year 4 (Year 5, Year 6, and more)	123 (2.0%)	9.1 ± 4.0	22.0 ± 12.4
About to graduate		(8.09e-04[a]*)	(0.168[a])
Yes	217 (3.5%)	9.0 ± 3.8	23.3 ± 12.0
No	5,940 (96.5%)	8.1 ± 3.6	22.1 ± 11.7
Smoking		(3.85-03[a]*)	(0.285[a])
Yes	1,006 (16.3%)	8.4 ± 3.6	22.5 ± 11.9
No	5,151 (83.7%)	8.1 ± 3.6	22.1 ± 11.7
Household Income Level (1 JD = ∼1.4 USD)		(8.30e-13[b]*)	(0.181[b])
Less than 200 JD	375 (6.2%)	9.1 ± 3.7	22.7 ± 13.9
200–400 JD	1,225 (19.9%)	8.5 ± 3.6	22.5 ± 12.1
400–600 JD	1,207 (19.6%)	8.2 ± 3.6	22.4 ± 11.6
600–800 JD	951 (15.4%)	8.1 ±3.4	22.2 ± 11.7
800–1,000 JD	955 (15.5%)	7.9 ± 3.4	22.2 ± 11.3
1,000–1,200 JD	493 (8.0%)	7.8 ± 3.5	22.2 ± 11.2
1,200–1,500 JD	341 (5.5%)	7.5 ± 3.6	20.9 ± 11.1
More than 1,500 JD	610 (9.9%)	7.7 ± 3.8	21.2 ± 11.2
Education level (Father)		(0.011[b]*)	(0.031[b]*)
Post graduates	732 (11.9%)	8.0 ± 3.6	21.5 ± 11.8
Bachelor	2,066 (33.6%)	8.0 ± 3.6	21.7 ± 11.4
Diploma	1,126 (18.3%)	8.2 ± 3.5	22.8 ± 11.6
High School	1,485 (24.1%)	8.3 ± 3.5	22.5 ± 12.0
Others (did not reach high school)	748 (12.1)	8.4 ± 3.6	22.4 ± 12.1
Education level (Mother)		(6.72e-03[b]*)	(0.502[b])
Post graduates	308 (5.0%)	7.9 ± 3.8	21.3 ± 12.0
Bachelor	1,779 (28.8%)	8.0 ± 3.7	22.0 ± 11.5
Diploma	1,543 (25.1%)	8.2 ± 3.5	22.4 ± 11.9
High school	1,900 (30.9%)	8.2 ± 3.5	22.1 ± 11.7
others (did not reach high school)	627 (10.2%)	8.5 ± 3.7	22.6 ± 12.2

Total number of participants: 6,157 students,—SD, Standard Deviation.
Numerical variables were summarized as mean and standard deviation, while the categorical variables were summarized using percentages.
PSOI, Pittsburgh's Sleep Quality Index (46).
CES-D, Center for Epidemiologic Studies Depression Scale (47).
[a]p-value is obtained using t-test; [b]p-value is obtained using one-way-ANOVA.
**Statistically significant p-value (≤ 0.05).*

2,031) woke up after 2 p.m. Forty percentage of the students (n = 2,463) slept for more than 9 h and around 8% (n = 493) slept more than 12 h a day.

More than one-fifth (n = 1,416) of the students had to take medications to help them sleep during the quarantine. Around half of the students (n = 3,196) experienced difficulties staying

TABLE 4 | Study participants statistics of quarantine factors, and their corresponding PSQI and CES-D scores.

Variable	*N* (N%)	PSQI Score Mean ± SD	CES-D Score Mean ± SD
Location of house during quarantine		(0.205[a])	(0.806[a])
Urban areas	5,315 (86.3%)	8.1 ± 3.5	22.2 ± 11.6
Rural areas	842 (13.7%)	8.3 ± 3.7	22.1 ± 12.4
Home specification		(1.36e-07[b]*)	(0.572 [b])
Apartment with garden	1,176 (19.1%)	8.0 ± 3.5	22.0 ± 11.3
Apartment without a garden	2,174 (35.3%)	8.0 ± 3.5	22.4 ± 11.6
House with garden	2,210 (35.9%)	8.1 ± 3.6	22.0 ± 11.9
House without a garden	597 (9.7%)	9.0 ± 3.7	22.2 ± 12.3
Household income during quarantine		(4.37e-10[b]*)	(2.21e-07[b]*)
Increased	275 (4.5%)	8.6 ± 3.9	21.2 ± 11.2
Stay the same	2,640 (42.9%)	7.8 ± 3.5	21.2 ± 11.4
Decreased	2,467 (40.1%)	8.3 ± 3.5	23.0 ± 11.8
Stopped completely	775 (12.5%)	8.6 ± 3.7	23.0 ± 12.3
Number of people quarantined with		(1.49e-03[b]*)	(0.093[b])
Less than 4	941 (15.3%)	8.1 ± 3.7	21.6 ± 11.2
4–7	4,248 (69.0%)	8.1 ± 3.5	22.1 ± 11.7
8–10	845 (13.7%)	8.5 ± 3.6	22.7 ± 12.4
More than 10	123 (2.0%)	8.7 ± 3.8	23.8 ± 13.4
Number of children quarantined with		(5.58e-15[b]*)	(2.26e-06[b]*)
None	2,624 (42.6%)	7.9 ± 3.6	21.5 ± 11.4
1	1,447 (23.5%)	8.1 ± 3.4	22.0 ± 11.1
2	1,120 (18.2%)	8.3 ± 3.5	22.3 ± 12.2
3	513 (8.3%)	8.3 ± 3.5	23.9 ± 12.0
4–6	395 (6.4%)	9.1 ± 4.1	24.4 ± 12.9
More than 6	58 (1.0%)	10.8 ± 4.4	22.6 ± 16.7

Total number of participants: 6,157 students.
SD, Standard Deviation.
Numerical variables were summarized as mean and standard deviation, while the categorical variables were summarized using percentages.
PSOI, Pittsburgh's Sleep Quality Index (46).
CES-D, Center for Epidemiologic Studies Depression Scale (47).
[a]*p-value is obtained using t-test.*
[b]*p-value is obtained using one-way-ANOVA.*
**Statistically significant p-value (≤ 0.05).*

awake while doing a daytime activity. Furthermore, around 80% (n = 4,870) of the students found it challenging to stay enthusiastic in order to complete tasks during the quarantine (30%; n = 1,866, reported that this had been a minor problem, another 30%; n = 1,865, found this somewhat of a problem, and about 20%; n = 1,139, stated that this was a big problem they suffer from). According to self-reporting, nearly half of the students (n = 3,060) had poor sleep quality (12.1%; n = 745 very good, 38.2%; n = 2,352 good, 27%; n = 1,662 bad, and 22.7%; n = 1,398 very bad).

Other than the PSQI 19 items, the students were asked a few more questions regarding their sleeping habits during the quarantine. Almost all students (94.9%, n = 5,843) reported that the quarantine affected their sleeping times (greatly: 72.5%; n = 4,464, slightly: 22.5%; n = 1,380), only 5.1% (n = 316) were not affected. Around 65% (n = 4,002) reverse their sleeping habits as they used to sleep most of the day and woke up most of the night during the quarantine. About 40% (n = 2,421) of the students slept 3 h or less, around 10% (n = 584) slept more than 10 h, and around 30% (n = 1,803) slept more than 7 h during the day (**Figure 1**). Finally, only 10% (n = 611) reported that quarantine affected their sleeping habits positively, whereas 74% (n = 4,539) were negatively affected, while the rest (n = 1,010) were not affected.

The PSQI mean scores for the different socio-demographic, socio-economic, and quarantine variables are presented in **Tables 3**, **4**, with an overall mean score of 8.1 ± 3.6. The lowest PSQI score was 7.5 ± 3.6 reported by the students with a household income level of 1,200–1,500 JD (**Table 3**), while the highest score was 10.8 ± 4.4 reported by the students who were quarantined with more than six children (**Table 4**). A global PSQI score higher than 5 points indicates poor sleep quality (46). Thus, the prevalence of poor sleep quality among participants was 76% (n = 4,680), with a mean PSQI score of 9.5 and a standard deviation of 2.9. The prevalence of poor sleep quality in male students was 71.5% (n = 1,264) and in females was 77.8% (n = 3,416) with very close PSQI scores of 9.6 ± 3.0 and 9.5 ± 2.9 for males and females, respectively (**Table 5**).

The only non-significant binary exposure was the quarantine's house location (t-test p-value: 0.2: **Table 4**). Other binary exposures, like gender, graduation status, and smoking habit, were significant (t-test p-value < 0.05). Females, students in their final University semester, and smokers had a significant association with poor sleep quality than their inverse (**Table 3**). Students' field of study was also significantly associated with poor sleep quality (ANOVA p-value: 6.28e-06), where the mean difference between the humanities and each of the scientific and medical majors were significant (TukeyHSD p-values: 2.9e-05 and 2.5e-3, respectively). The humanities-related majors had a larger PSQI mean score than the scientific and medical majors (**Table 3**).

Besides, students' year of study was significantly associated with poor sleep quality (ANOVA p-value: 2.69e-05: **Table 3**), with the most significant difference between fresh students and those in their third, fourth, and fifth years. The economic status was significantly negatively associated with poor sleep quality (ANOVA p-value: 8.30e-13: **Table 3**), where the most significant mean difference was between lower and higher incomes. Similarly, the parents' education level was inversely associated with the PSQI scores (**Table 3**), with the significant difference between University degrees and school degrees. Furthermore, house specifications were found significantly associated with sleep quality (ANOVA p-value: 1.36e-07: **Table 4**); the highest PSQI scores were for those living in a house without a garden (9.0 ± 3.7). The income status during the quarantine had a significant association with the PSQI (ANOVA p-value: 4.37e-10: **Table 4**); when income stayed the same, the PSQI was the lowest (7.8 ± 3.5). Finally, the number of people and children quarantined with the student affected the poor sleep quality directly, such that the larger the number of the quarantined members, the higher the PSQI scores and thus the lower sleep quality (**Table 4**).

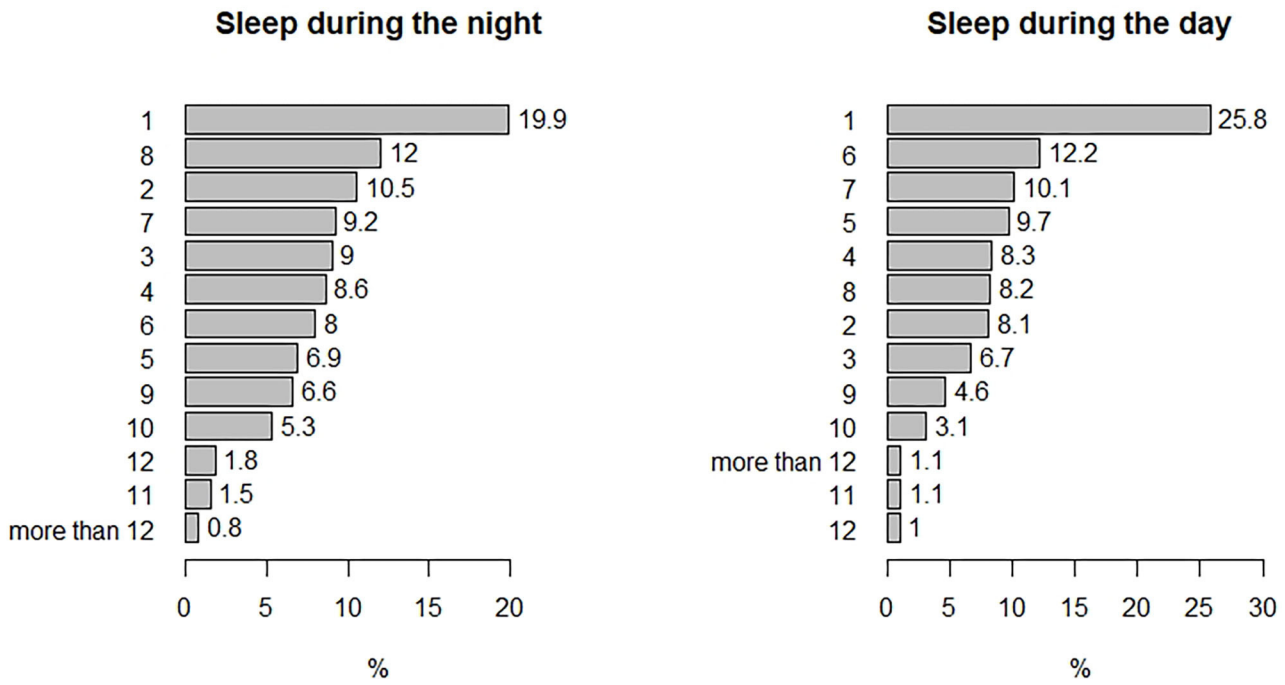

FIGURE 1 | Percentages of the number of sleeping hours reported by the students during the nights and during the days of the quarantine.

All significant exposures (resulting from the pair-wise *t*-test/ANOVA) were combined into one model and analyzed using logistic regression (**Table 6**) to assess each factor's association with the poor sleep quality after controlling other factors. Females, students in their final semester, smokers, lower household income, living in a house without a garden, decreased income during the quarantine, and being quarantined with more than four children all have a significant association and a potentially higher risk of suffering from poor sleep quality (**Table 6**). The model was evaluated using the Backward selection method with an Akaike Information Criterion (AIC) of 6692.8 and a difference of 127.6 between residual and null deviance with 17 degrees of freedom.

Psychological Findings of the Study Participants (Depressive Symptoms)

The CES-D mean scores for the different socio-demographic, socio-economic, and quarantine variables are presented in **Tables 3**, **4**, with an overall mean score of 22.2 ± 11.7. However, students were divided into three groups based on their CES-D scores as suggested by a study on depression levels for hospital employees after the 2003 SARS epidemic (45); low level of depressive symptoms group with a CES-D score of <16, moderate level of depressive symptoms group with CES-D score between 16 and 24, and high level of depressive symptoms group with a CES-D score of >24. The prevalence of moderate and high depressive symptoms was higher in female students (34.3 and 38.4%, respectively) than the male students. Similarly, the CES-D mean scores were higher in females in all groups than their male colleagues (**Table 5**). The overall mean CES-D score for the low depressive symptoms group is 9.3, for the moderate group is 19.8, while it is 34.3 for the high symptoms group (**Table 5**).

More than half of the students (62.5%, $n = 3{,}851$) reported that the quarantine had a negative effect on their mental health, and only 10.4% ($n = 640$) reported the opposite, whereas the rest (27.1%, $n = 1{,}666$) were not affected. Around one-fifth ($n = 1{,}285$) of the students reported a change in their attitude by becoming more anxious with hard-tempered than they used to be, while about one-tenth ($n = 596$) reported a change in the opposite direction.

Using pair-wise *t*-test/ANOVA, only four factors were significantly associated with high depressive symptom levels; the gender (*t*-test *p*-value: 4.02e-07: **Table 3**), father's education level (ANOVA *p*-value: 0.031: **Table 3**), household income during quarantine, and number of children quarantined with (ANOVA *p*-values: 2.21e-07 and 2.26e-06, respectively: **Table 4**). However, the multinomial logistic regression results used to control for confounding factors and study the combined effect of the different exposures on the depressive symptoms state show a different pattern. Female students are more likely to suffer from moderate (Wald test *p*-value: 6.08e-03) and high (Wald test *p*-value: 4.55e-07) depressive symptoms than male students. Furthermore, smokers and students with decreased income during quarantine have higher risks for developing high depressive symptoms than their counterparts with Wald test *p*-values of 7.78e-04 and 5.58e-07, respectively.

TABLE 5 | Sleep quality and depressive symptoms prevalence among the study participants based on PSQI and CES-D scores, respectively.

Participant groups	Factor	Prevalence as *N* (N%)	PSQI or CES-D Score as mean ± SD
Poor sleep quality	Male	1,264 (71.5%)	9.6 ± 3.0
	Female	3,416 (77.8%)	9.5 ± 2.9
	Total	4,680 (76.0%)	9.5 ± 2.9
Good sleep quality	Male	505 (28.5%)	3.7 ± 1.3
	Female	972 (22.2%)	3.8 ± 1.1
	Total	1,477 (24.0%)	3.8 ±1.2
Low depressive symptoms (CES-D score < 16)	Male	569 (32.2%)	8.9 ± 5.3
	Female	1,201 (27.3%)	9.5 ± 5.2
	Total	1,770 (28.7%)	9.3 ± 5.2
Moderate depressive symptoms (16 ≤ CES-D score ≤ 24)	Male	597 (33.7%)	19.6 ± 2.5
	Female	1,503 (34.3%)	19.9 ± 2.4
	Total	2,100 (34.1%)	19.8 ± 2.5
High depressive symptoms (CES-D score > 24)	Male	603 (34.1%)	33.7 ± 8.1
	Female	1,684 (38.4%)	34.5 ± 7.9
	Total	2,287 (37.2%)	34.3 ± 8.0

Total number of participants: 6,157 students: 1,769 males, and 4,388 females.
SD, Standard Deviation.
PSOI, Pittsburgh's Sleep Quality Index (46).
Sleep quality cut-off value (poor quality: PSQI score > 5) is based on what was reported in Buysse et al. (46).
CES-D, Center for Epidemiologic Studies Depression Scale in Radloff (47).
Participant groups division is based on what was reported in Liu et al. (45).

DISCUSSION

This study's participants were students from the University of Jordan, the largest public University in Jordan, Amman. UJ hosts about 35,000 students studying undergraduate and postgraduate degrees in humanities, science, and health disciplines. Seventy-six percent of the UJ students are females, and about half of the students (50.3%) study humanities-related majors. The total number of participants in this study was 6,157 students (represent 18% of the whole University students) who filled the online questionnaire. The questionnaire link was uploaded as part of several University compulsory courses which are mainly covered during the first 2 years of the majors, thus, explaining why around 77% of the participants were in year 1 and year 2, with a mean age of 20 years, whereas only 3.5% of the students were in their final semester (**Table 3**). This sample of participants is a good representative of the University demographics as 71.3% of the study participants are females, and 50.2% are studying humanities.

Moreover, this sample is representative of the Jordanian population. According to the national survey conducted by the National Council for Family Affairs (NCFA) in 2017 (48), about 78% of the families that participated had 3–7 members, which is comparable to sample study demographics (**Table 4**). Furthermore, according to the NCFA survey, about 57 and 42% of the families that participated lived in apartments and separate houses. This is consistent with the current study in which the students reported percentages of 54.4 and 45.6% correspondingly (**Table 4**). Regarding chronic diseases, non-communicable chronic diseases (NCCD) prevail in the society, as 14.5 and 7.2% suffer from diabetes and cardiovascular diseases, respectively. In this sample, 23 and 8% of the students were quarantined with a family member suffering from diabetes and cardiovascular diseases, respectively. Additionally, as reported by WHO (49), tobacco smoking is more prevalent in Jordanian males, where 70% of males aged more than 14 years are smokers (50). This explains the high percentage of nearly half of the students who were quarantined with a smoker. The preponderance of females who participated might account for the 16.3% reported smoker status (**Table 3**). Nevertheless, around 70% of the student participants were females. Although this represents the UJ community (public universities tend to admit students with high grades, which is more achievable by females than males in Jordan), it is not representative of the University student population in Jordan. This potential selection bias was controlled by logistic regression.

The impact of the extended quarantine on students' sleeping behavior is tremendously apparent. 94.9% of the students reported that their sleeping habits were affected; 74% in a negative way, especially in reversing the day-night activities (65%) and highly increasing or decreasing the quantity of sleeping hours, which resulted in reducing the quality of their sleep (∼50%). These results can be explained by the staying-at-home order, distance-learning/working, banning outdoor activities, COVID-19 updates news all over the media, the broad and unprecedented closure, and many more different forced lifestyles, which affected the well-being of most if not all the Jordanians. All these factors contributed to the high prevalence of sleeping disorders among the participants, reaching 76% of the sample. The gender was significantly associated with lower sleep quality (**Table 6**; logistic regression coefficient *p*-value: 2.33e-09) and had significantly higher PSQI scores (**Table 3**; *t*-test *p*-value: 8.34e-04), with a clear difference in the prevalence between male (71.5%) and female (77.8%) students, which is aligned with the reported literature (51–54). However, a few studies reported the opposite (55, 56).

Furthermore, this study revealed that smokers had significantly lower sleep quality than non-smokers (**Table 6**; logistic regression coefficient *p*-value: 8.01e-05). A cross-sectional study from central China's general population reported that smokers demonstrated lower sleep quality and more sleeping disturbances, a finding supported by a plethora of other studies (57–60). One plausible explanation would be tobacco's effect and the changes it induces to the core circadian clock gene expression, which affects sleeping habits (61, 62). Likewise, the significant correlation between lower incomes and poor sleep quality (**Table 6**) is consistent with previous studies (53, 63, 64).

The parameters related to the University-study variables, including the effect of the study major, and year of study, impacted the sleep quality. The pair-wise significant association between studying in humanities and poor sleep quality when compared to medical and scientific students (**Table 3**; ANOVA *p*-value: 6.28e-06) as reported in this study contradicts what

TABLE 6 | Association between poor sleep quality state and each of the identified significant exposures, as assessed by logistic regression[+].

Coefficients	Estimate	*p*-value	Odd ratio	CI lower	CI upper
(Intercept)	0.827	5.41e−15*	2.287	0.621	1.036
Sex (Male)	−0.426	2.22e−09*	0.653	−0.565	−0.286
Graduation semester (yes)	0.404	0.027*	1.498	0.057	0.776
Smoking (yes)	0.360	8.01e−05*	1.434	0.183	0.541
Household income (0–200 JD)	0.726	2.74e−05*	2.068	0.392	1.072
Household income (200–400 JD)	0.371	0.002*	1.449	0.141	0.600
Household income (400–600 JD)	0.267	0.019*	1.307	0.043	0.491
Household income (600–800 JD)	0.237	0.045*	1.268	0.004	0.469
Household income (800–1,000 JD)	0.299	0.012*	1.348	0.066	0.530
Household income (1,000–1,200 JD)	0.134	0.328	1.143	−0.133	0.402
Household income (1,200–1,500 JD)	−0.180	0.218	0.835	−0.467	0.108
Home specification (Apart. without a garden)	−0.054	0.449	0.947	−0.194	0.086
Home specification (Apart. with a garden)	−0.001	0.989	0.999	−0.168	0.167
Home specification (House without a garden)	0.325	0.007*	1.383	0.092	0.564
Income during quarantine (Stopped)	0.097	0.341	1.101	−0.101	0.297
Income during quarantine (Increased)	0.175	0.253	1.191	−0.118	0.481
Income during quarantine (Decreased)	0.255	0.0001*	1.290	0.124	0.386
Quarantine with more than four children	0.516	0.009*	1.675	0.145	0.917

CI: Confidence Interval.

**Statistically significant p-value (≤ 0.05).*

[+]Dependent variable: poor sleep quality state; calculated based on the suggested PSQI scores threshold of > 5, reported in Buysse et al. (46).

Baseline for Household Income is "more than 1,500 JD".

Baseline for Home specification is "House with a garden".

Baseline for Income during quarantine is "Stayed the same".

was reported in an abstract presented in SLEEP 2007; the 21st Annual Meeting of the Associated Professional Sleep Societies (APSS). It revealed that medical students suffer more from poor sleep quality than their peers in humanities majors (65). More-so, the pair-wise significant difference in respect to students' year of study (with the most significant difference between fresh students who had relatively better sleep and those in their third, fourth, and fifth years) is also consistent with a study of 860 medical students from 49 medical colleges in the United States, which revealed higher rates of sleeping disorders in first- and third-year students relative to second- and fourth-year students (66). It is not surprising that students in their final semester, or with low household income or decreased income during the unprecedented closure, significantly suffer from sleeping disturbances more than their peers (**Table 6**). Likewise, when the number of children the student quarantined with increase, their sleep quality decrease (**Tables 4**, **6**). Interestingly, living in a house without a garden resulted in lower sleep quality (**Table 6**: logistic regression coefficient *p*-value: 0.009).

The assessment of the depressive symptoms among the Jordanian students is alarming as the prevalence of the high/and potentially-high risk group that showed high/and moderate depressive symptoms was 37.2 and 34.1%, respectively, with a total risk percentage of 71.3%. This is comparable to the 74.3% prevalence reported in Greece (23). Uncertainty and unclear plans for the academic semester and the grades probably left the students anxious and stressed. Besides, social distancing and lack of social communication may have affected the students with loneliness and isolation, ultimately leading to more depressive symptoms and sad feelings. The female gender is considered a significant risk factor for high depressive symptoms (logistic regression coefficient *p*-value: 4.55e-07). The susceptibility of females to develop depressive symptoms was also reported in previous studies (67, 68). Female sensitivity to stress might be explained by the role sex steroids play in mood regulation (69). Depressive symptoms in low-income families were prevalent, regardless of quarantine (70, 71). During the quarantine, the effect of the sudden closure and losing the source of income with a lack of savings can lead to an unstable and stressful financial state. So, decreased income during quarantine is also significantly linked with higher depressive symptoms (logistic regression coefficient *p*-value: 5.58e-07). In addition, two previous studies conducted in Southwestern China and Canada showed similar findings; high levels of anxiety and depressive symptoms were correlated with low average household income (43, 72). Students in their final semester did not show significantly higher depressive symptoms than their colleagues (both categories had high CES-D scores; **Table 3**), albeit a study of home-quarantined students in China reported the opposite (73).

Finally, poor sleep quality is a risk factor for many chronic diseases' incidence and progression and psychological problems, including depression, anxiety, and suicidal behavior (64, 74–80). According to Celik et al. the risk of depressive symptoms in students with poor sleep quality was 3.28 times higher (81). This is consistent with this study's finding, as there

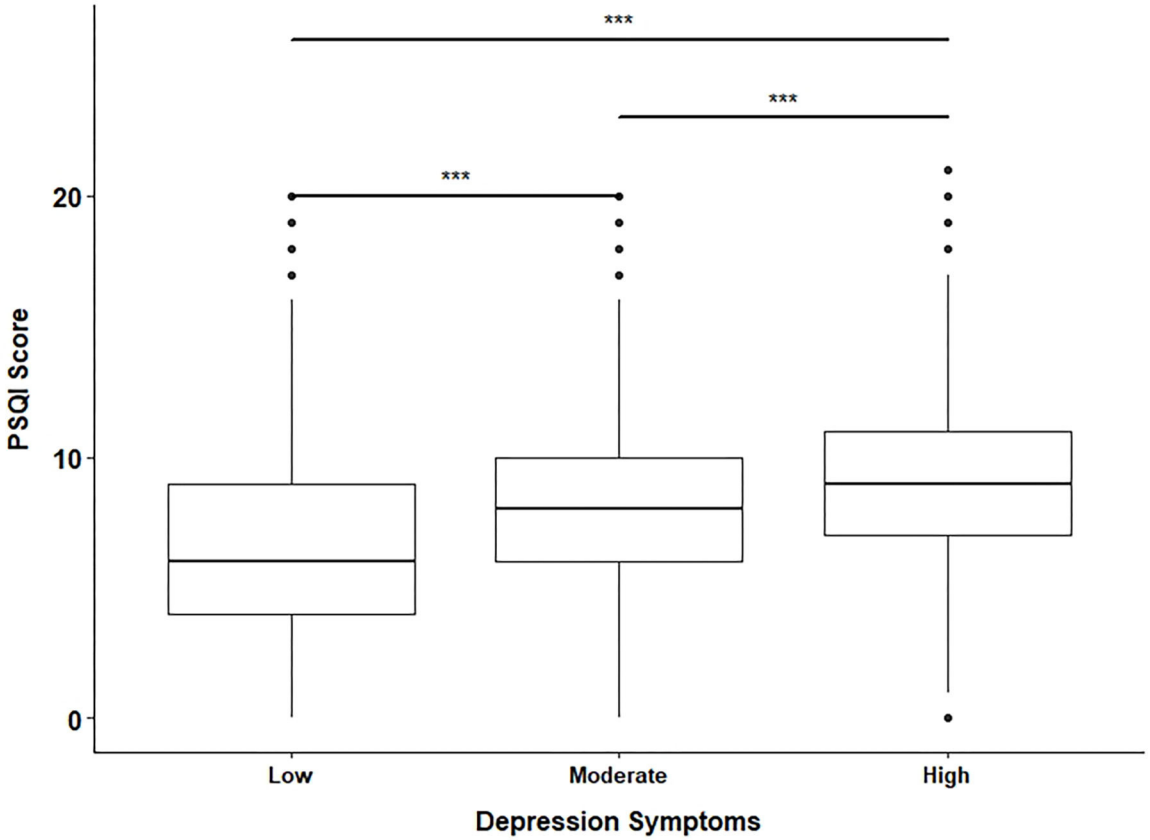

FIGURE 2 | Box plot for PSQI scores of the three groups of depressive symptoms levels. The low depressive symptoms group was determined by a CES-D score <16, the moderate had a CES-D score between 16 and 24, while the high group had a score >24. The pair-wise comparisons between the three groups were significant. The *p*-values from the *t*-test were all < 0.001 (***).

was a positive correlation between the PSQI scores and the severity of the depressive symptoms (**Figure 2**). In addition, non-pharmacological sleep interventions were found to be effective in reducing the severity of clinical depressive symptoms (82). Thus, engagement in healthy life patterns, including exercise, might help tackle these serious issues.

We acknowledge the limitations of this study. The sample was drawn from one University in the capital city of Amman. The quarantine effects, including sleep quality and depressive symptoms, could differ in other cities in Jordan. Also, the preponderance of earlier University year's students could have skewed the results. One significant limitation is the potential selection bias resulted from having around 70% of female participants. More balanced selection criteria would be better to apply. However, this factor was controlled in the logistic regression model. Another significant limitation is related to the deficiency of literature on the sleep quality and depressive symptoms scales before the quarantine on the Jordanian population, thus hindering any comparison outside the quarantine period. We recommend that this study be repeated outside the quarantine period, in other areas outside Amman, and to target older University students. Nevertheless, a recent pre-quarantine study reported moderate depressive symptom levels for 600 University students in Jordan using the Depression, Anxiety, and Stress Scale (DASS-21) (83).

CONCLUSION

In conclusion, this is the first study that evaluated the effect of the COVID-19 pandemic and the resultant quarantine among University students in Jordan. Poor sleep quality and depressive symptoms were prevalent among this group of participants. The results of this study should be taken seriously to address and guide policy-makers and authorities when planning for extended closures and lock-down. Repeating the study outside the COVID-19 pandemic might help to quantify these issues among University students better. The COVID-19 pandemic has infringed on many aspects of our lives. This has gone beyond the economic into the mental and psychological reverberation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board and the Research Ethics Committee at UJ. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

HS and MS conceived the idea, performed the analysis, and wrote the manuscript. MA-H co-wrote the manuscript and helped in design the study. WA, AA, NS, RA, HK, and SA-S contributed to collect the data and to the literature search. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 23 February 2021
doi: 10.3389/fmed.2021.608959

Factors Influencing Participation in COVID-19 Clinical Trials: A Multi-National Study

*Ahmed Samir Abdelhafiz[1], Samar Abd ElHafeez[2], Mohammad Adnan Khalil[3], Manal Shahrouri[4], Bandar Alosaim[5], Raneem O. Salem[3], Mohamed Alorabi[5,6], Fatma Abdelgawad[7] and Mamoun Ahram[8]**

[1] Department of Clinical Pathology, National Cancer Institute, Cairo University, Cairo, Egypt, [2] Epidemiology Department, High Institute of Public Health, Alexandria University, Alexandria, Egypt, [3] Department of Basic Medical Sciences, Faculty of Medicine, King Fahad Medical City, Riyadh, Saudi Arabia, [4] Office of Monitoring, Research, Learning and Evaluation, Tetra Tech DPK, Amman, Jordan, [5] Department of Research Labs, Research Center, King Fahad Medical City, Riyadh, Saudi Arabia, [6] Department of Clinical Oncology, Faculty of Medicine, Ain Shams University, Cairo, Egypt, [7] Department of Pediatric Dentistry and Dental Public Health, Faculty of Dentistry, Cairo University, Cairo, Egypt, [8] Department of Physiology and Biochemistry, The University of Jordan, Amman, Jordan

OPEN ACCESS

Edited by:
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***Correspondence:**
Mamoun Ahram
m.ahram@ju.edu.jo; dr.ahram@gmail.com

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *22 September 2020*
Accepted: *29 January 2021*
Published: *23 February 2021*

Citation:
Abdelhafiz AS, Abd ElHafeez S, Khalil MA, Shahrouri M, Alosaim B, Salem RO, Alorabi M, Abdelgawad F and Ahram M (2021) Factors Influencing Participation in COVID-19 Clinical Trials: A Multi-National Study. Front. Med. 8:608959. doi: 10.3389/fmed.2021.608959

In 2020, the World Health Organization has characterized COVID-19, a disease caused by infection with the SARS-CoV-2 virus, as a pandemic. Although a few vaccines and drugs have been approved to, respectively, prevent or treat the disease, several clinical trials are still ongoing to test new vaccines or drugs to mitigate the burden of the pandemic. Few studies have shown the role of host genetics in disease prognosis and drug response highlighting the importance of diverse participation in COVID-19 clinical trials. The goal of this study is to assess public attitudes in Egypt, Saudi Arabia, and Jordan toward participating in COVID-19 clinical trials and to identify the factors that may influence their attitude. An online questionnaire was developed and distributed among the target group through social media platforms. The number of responses was 1,576. Three quarters (74.9%) of participants heard about clinical trials before, 57.6% of them had a positive attitude toward participation in COVID-19 clinical trials. The conduct of clinical trials in accordance with the scientific, research, and ethical guidelines was a strong predictor of willingness to participate in clinical trials. Other positive factors also included protection of family from COVID-19 and contributing to the return to normal community life as well as receiving additional healthcare benefit was the fourth significant predictor. On the other hand, the thought that clinical trials can have a negative impact on the health of participants strongly predicted the unwillingness of individuals to participate in such trials. This was followed by having limited information about the novel coronavirus and COVID-19 and the lack of trust in physicians and hospitals. In general, Arab citizens are accepting the concept and have a positive attitude toward COVID-19 clinical trials. Increasing awareness of COVID-19 and clinical trials, enforcing the concept of altruism, and placing clear policies in conducting clinical trials are needed to increase participation in clinical trials among Arabs.

Keywords: COVID-19, clinical trials, Arabs, bioethics, attitude

INTRODUCTION

In December 2019, the coronavirus disease-19 (COVID-19) was first identified during an outbreak of respiratory illness in Wuhan, China (1). On the 11th of March 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic (2). The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is associated with a variety of symptoms ranging from mild, self-limiting respiratory symptoms, to severe, debilitating illness leading to progressive pneumonia, development of cytokine storm, multi-organ failure, or even death (3, 4). Older age, male gender, and the presence of comorbidities were the main risk factors leading to severe complications and death (5, 6). The disease has spread rapidly affecting millions of people around the world, including Arab countries.

COVID-19 is considered a health crisis to individuals. It has impacted and overburdened healthcare systems. Countries have been racing to slow the spread of the virus by testing and treating patients, carrying out contact tracing, limiting travel, quarantining citizens, and canceling large gatherings such as sporting events, concerts, and schools. By stressing every one of the countries it inflicts, it has created devastating social, economic, and political crises that are expected to persist (7). Although some vaccines and drugs have been approved to prevent or treat the disease (8–10), clinical trials are still ongoing to test newer ones that can mitigate the burden of the pandemic. This is particularly important in the case of vaccines considering the insufficient supplies to achieve global immunization against COVID-19. Prevention and treatment of COVID-19 have emerged as critical needs and challenges to find new approaches, which may help in controlling the spread of the pandemic, treating the disease, or alleviate its symptoms. Ethnic variation in the distribution of COVID-19 has been thought to be genetically influenced (11, 12), particularly that certain genetic variants are associated with the clinical outcome of COVID-19 (13, 14). Similarly, the role of genetics in treatment efficacy is also proposed (15). Thus, the participation of various ethnic groups in COVID-19 clinical trials is critical in order to assess the efficacy of treatments.

Willingness to participate in clinical trials could be influenced by several factors including anticipated benefits, patients' understanding of trials, and the level of trust patients place in investigators. In addition, the majority of participants in clinical trials are reluctant to do additional monitoring tests, particularly invasive ones, since they can be associated with potential morbidity or may be inconvenient for the participant (16).

Up to January 2nd of 2021, more than 4,000 clinical trials have been registered for COVID-19. Of them, 154 studies are held in Egypt, 25 studies are conducted in KSA, and nine studies are registered in Jordan (17). While there are structural and demographic challenges for the successful conduct of clinical trials in the Arab region, little is known about perceptions of the public toward participation in clinical trials to prevent or manage COVID-19. Therefore, the current study is conducted to assess the knowledge, attitudes, and perceptions of the general population in, Egypt, KSA, and Jordan toward participation in clinical trials, and to determine the associated factors that may influence their attitude toward participation in COVID-19 clinical trials. The three countries represent different regions of the Arab countries with Egypt representing countries of Northern Africa and Sudan, KSA representing Gulf countries, and Jordan representing the Levant.

SUBJECTS AND METHODS

Study Design and Populations

This is a cross-sectional study that was conducted through an online survey using Google Forms between July 27 and August 4, 2020, in Egypt, KSA, and Jordan. The survey was distributed using different social media platforms according to what is commonly used in each country. Whereas, Twitter was used in Saudi Arabia, Facebook, LinkedIn, and WhatsApp were used in Egypt and Jordan. The authors posted the survey links on their own social media profiles, sent messages to different groups, and asked their contacts to circulate them. Advertisements were also purchased to recruit participants in Egypt reaching over 100,000 individuals. The target audience was adults 18 years and older of both gender, educational background, and economic status. Participants completed the survey after reading a well-developed informed consent that explained the following: purpose and nature of the study, the difference between a drug and a vaccine, the definitions of COVID-19 and clinical trials, and how clinical trials are reviewed and conducted including ethical considerations. The informed consent assured participants of protecting their privacy and confidentiality as anonymity was mentioned explicitly and confirming that collected responses would be analyzed collectively. In addition, participants were assured that the only purpose of their participation was to examine their perceptions and attitudes toward COVID-19 clinical trials, and not to register them for an actual clinical trial. Finally, participants were informed that their participation was voluntary and no financial compensation would be provided. The study protocol was approved by three independent ethics committees: Institutional Review Board, National Cancer Institute, Cairo University, Institutional Review Board, King Fahad Medical City, and Institutional Review Board, Jordan University Hospital, The University of Jordan.

Measurement

A pre-designed data collection questionnaire was prepared in Arabic and divided into seven sections: basic socio-demographic background (section 1), health status including if they were diagnosed with COVID-19, had suspected to have had COVID-19, or had been in contact with a COVID-19 patient, in addition to a question regarding their diagnosis of a chronic disease(s) and nature of the chronic diseases (section 2), knowledge of clinical trials (yes/no) and, if knowledgeable, sources of this knowledge (section 3), perceptions toward COVID-19 (13 statements with three options of "agree," "disagree," and "unsure") (section 4), motivating factors toward participation in COVID-19 clinical trials (seven statements with three choices: "yes," "no," or "unsure") (section 5), deterring factors of participation in a

COVID-19 clinical trial of (14 statements with three choices: "yes," "no," or "unsure") (section 6), and, finally, attitude toward self-participation or participation of a family member in COVID-19 vaccine or drug clinical trials measured by four questions with responses based on a five-point Likert scale of "definitely yes," "probably yes," "unsure," "probably no," and "definitely no" (section 7). All "unsure" responses were grouped with "no" responses (sections 3–6), and "disagree" responses (section 4). The attitude questions in section 7 were scored as one point for: "definitely yes," two points for "probably yes" three points for "unsure," four points for "probably no," and five points for "definitely no." Participants who had a sum of 10 or less were considered as having a positive attitude and those with scores of more than 10 were considered to have a negative attitude.

Psychometric Properties of the Questionnaire

Questionnaire items were formulated in Arabic and verified by all authors who are native Arabic speakers. English translation was put forth for the manuscript purposes only and verified by three of the authors (ASA, MAK, and MA2).

Pilot Study and Validation

Questionnaire validity was tested using the two-tier verification model. First, 100 participants were recruited (60 from Egypt, 30 from KSA, and 10 from Jordan) and feedback was collected from respondents and discussed by the authors. Unclear or conflicting items were modified to eliminate ambiguity. The questionnaire was re-distributed to 50% of original respondents from the three countries, respectively, at least a week later.

Content Validity

Content validity was assessed by an expert panel of five investigators with knowledge and expertise in instrument development. The content clarity was determined for all items. Convergent validity was assessed by calculating item-total correlations for each construct of the questionnaire. Divergent validity was assessed by testing the correlation between total scores for each construct (18).

Reliability

The intra-class correlation coefficient (ICC) was used for the assessment of the test-retest reliability, while Cronbach's α coefficient was used to assess the internal consistency of the questionnaire (19).

Statistical Analysis

Psychometric evaluation of the pilot questionnaire was done by assessment of intra-class correlation coefficient (ICC). Cronbach's α coefficient was also used to assess the internal consistency of the questionnaire. Pearson's correlation analysis was used to calculate item-total and correlation between total scores. Data of the final version of the questionnaire were summarized as frequencies and percentages. Attitudes were classified as either positive or negative as described earlier. Cross-tabulation of categorical data by attitude (positive vs. negative) was done by testing the association using Chi-square. Spearman's correlation coefficient was calculated between the total attitude scores, which were calculated as described earlier, and all variables. Multiple logistic regression model using stepwise approach was constructed for identifying the independent predictors of attitudes toward participation in clinical trials of vaccine or drug treatment of COVID-19. All variables with $P < 0.05$ in the bivariate analysis were included in the model. The final model included gender, the conduct of clinical trials will be in accordance with the scientific research and ethical guidelines, contributing to the protection of my family from COVID-19, receiving additional healthcare benefits, contributing to the protection of my community from COVID-19, the possibility of getting ill prevents me from participating in such trials, limited knowledge about the coronavirus or COVID-19 disease, and lack of trust in physicians and hospitals variables. The Odds Ratio (OR) and 95% confidence interval (CI) were reported for all variables. Receiver operating characteristic (ROC) curve was used to evaluate the risk prediction of the model (19). The Statistical Package for the Social Sciences (SPSS), version 20.0, for Windows and STATA, version 11 were used for the analyses. The tests were two-tailed and $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Piloting and Validation

The initial survey was distributed to 100 individuals. At least a week later, the same survey was distributed to 50 individuals from the same group in order to examine the validity and reproducibility of the survey. Analyses of convergent validity revealed that all items in all sections significantly correlated with the total score ($P < 0.001$) except for one statement in the "perceptions toward COVID-19" section. The statement was "if a vaccine is made available, it should be mandatory for all to take it." This statement was deleted in the final version of the questionnaire.

Analyses of divergent validity revealed that the total scores of "knowledge of clinical trials" significantly correlated with "motivating factors toward participation in COVID-19 clinical trials" ($r = 0.31$, $P = 0.004$), the total scores of "perceptions toward COVID-19" section correlated with "attitude toward self-participation or participation of a family member in COVID-19 vaccine or drug clinical trials" ($r = 0.30$, $P = 0.005$), and there was an inverse correlation between "motivating factors toward participation in COVID-19 clinical trials" and "deterring factors of participation in a COVID-19 clinical trial" ($r = -0.29$, $P = 0.007$).

Reliability analyses revealed acceptable Cronbach's α scores and ICC for all sections. The score for the "knowledge of clinical trials" section had a Cronbach's α of 0.70 and ICC ranged between 0.62 and 0.75, the "perceptions toward COVID-19" section had a Cronbach's α score of 0.72 and ICC ranged between 0.65 and 0.70, the "motivating factors toward participation in COVID-19 clinical trials" section had a Cronbach's α of 0.83 and ICC ranged between 0.60 and 0.80, the "deterring factors of participation in

a COVID-19 clinical trial" had a Cronbach's α of 0.85 and ICC ranged between 0.63 and 0.88, and, finally, the "attitude toward self-participation or participation of a family member in COVID-19 vaccine or drug clinical trials" had a Cronbach's α of 0.89 and ICC ranged between 0.64 and 0.86.

Characteristics of Participants

Fifteen hundred and seventy-six individuals participated in the study. **Table 1** summarizes the demographic characteristics of the study population. More than half of them were from KSA (53.5%), followed by Egypt (28.4%), then Jordan (18.1%). About two-thirds (64.4%) of the study population aged <40 years, and 58% of them were males. The majority (82.1%) resided in urban areas and 61.4% had a diploma or a bachelor's degree, whereas, a quarter held a higher degree. Almost half of them (49.6%) thought they were infected with the coronavirus, but only 6.3% of them were, and 16.7% were in contact with an actual COVID-19 patient. The majority of the study population (80.3%) indicated that they did not suffer from chronic diseases. Interestingly, three quarters (74.9%) of respondents were knowledgeable of the term "clinical trials" prior to the survey. The main source of information of clinical trials was obtained from social media (82.5%) and internet search (81.8%), followed by TV/radio, a medical institute, or from family or friends (**Figure 1**).

Willingness to Participate in COVID-19 Clinical Trials

Respondents were asked about their willingness to participate in COVID-19 clinical trials involving either a vaccine or a drug and their attitude if a family member expressed willingness to participate in such trials. Over half of them (57.6%) had an overall positive attitude. More specifically, ∼60% of respondents indicated they would either definitely or probably participate in a drug clinical trial (**Figure 2**). This positive attitude dropped by 16% toward participating in a vaccine trial whereby about 43.9% either definitely or probably participate in a clinical trial for a vaccine. The decrease in willingness came specifically from those who were "definite" participants who were 33% of respondents for a drug trial vs. 15.5% for a vaccine trial. The difference in supporting the participation of a family member in a vaccine trial vs. a drug trial (52.7 vs. 62.2%, respectively) was also observed. Interestingly, more respondents were hesitant toward vaccine trials compared with drug trials.

Attitudes of participants were divided into either positive or negative based on the scoring system (see Methodology) and were associated with sociodemographic characteristics (**Table 1**). Participants with negative attitudes were females, living in urban areas and from Jordan compared to those with positive attitudes. Those from KSA appeared to have a more positive attitude. However, it is important to mention that two-thirds of respondents from Jordan were females, whereas females were one-third of KSA respondents (data not shown). The total attitude score positively correlated with the country and residence and negatively correlated with age and gender (**Table 1**).

Perceptions of COVID-19 and Its Association With Willingness to Participate in COVID-19 Clinical Trials

Respondents were asked whether they agree with several statements related to COVID-19 (**Table 2**). Respondents had very good knowledge that clinical trials are conducted to ensure vaccine or drug safety (93.4%) and that they are initially conducted on animals (86.3%). However, ∼60% indicated that they would not take the vaccine or drug unless they are sure of their efficacy. Interestingly, 28.5% of respondents thought that participation in a vaccine clinical trial might cause them to be affected by COVID-19. More respondents were concerned that a family member would be affected by COVID-19 than themselves (85.6 vs. 62.3%, respectively). In addition, more than half of the respondents indicated that any new vaccine or drug for COVID-19 will be exploited either commercially (65%) or politically (62.8%), and thought that price of a vaccine or a drug would not be reasonable to the public (60 and 58.7%, respectively). Nearly, one-third of the respondents believed that there was exaggerated attention to this virus. Only a small portion (9.2%) of respondents thought that COVID-19 is linked to death.

We tested the association between their perceptions and attitudes toward clinical trials. Several perceptions were found to influence participants' willingness to participate in COVID-19 clinical trials. Fear of an increased risk of infection with the virus, potential commercial exploitation through excessive pricing, and issues related to drug or vaccine efficacy were all found to significantly associate with negative attitudes toward participation in COVID-19 clinical trials.

Factors Influencing the Respondents' Willingness to Participate in COVID-19 Clinical Trials

Respondents were given statements that had either positive or negative connotations to examine their decision to participate in clinical trials (**Table 3**). Contribution to protecting family was the most selected motivating statement (80.5%). This was followed by conducting trials in accordance with scientific and ethical guidelines (77.1%). In addition, three-quarters of the respondents believed that participation could protect the community, restore life to normal, and save humankind. More than half of the respondents (54.3%) indicated that receiving additional healthcare would motivate them to participate in COVID-19 clinical trials, and only 21% would participate if granted financial compensation. All of the motivating factors significantly and directionally correlated with the positive attitude score toward participation in COVID-19 clinical trials with correlation coefficients of 0.40 and higher except for gaining benefits having correlation coefficients of 0.31 and of 0.13 for receiving healthcare benefits and financial compensation, respectively. All positive statements showed significant associations with the attitude toward participation in COVID-19 clinical trials ($P < 0.001$).

Similarly, several negative statements were provided to respondents, and association with attitude to participate in COVID-19 clinical trials was assessed. Fear of negative health

TABLE 1 | Baseline data of participants and association with knowledge of clinical trials.

Variables	No. of respondents (%) (*N* = 1,576)	Attitude toward participating in a clinical trial		Rho (*P*-value)	*P*-value*
		Positive (*n* = 909)	Negative (*n* = 667)		
Country					
Egypt	448 (28.4)	256 (28.2)	192 (28.8)	**0.11 (<0.001)****	**0.001**
KSA	843 (53.5)	516 (56.8)	327 (49.0)		
Jordan	285 (18.1)	137 (15.1)	148 (22.2)		
Gender					
Male	907 (58)	568 (63)	339 (51.1)	**0.16 (<0.001)**	**0.001**
Female	658 (42)	334 (37)	324 (48.9)		
Age categories					
18–29	403 (25.6)	245 (27.0)	158 (23.7)	**−0.07 (0.004)**	0.46
30–39	611 (38.8)	351 (38.6)	260 (39.0)		
40–49	353 (22.4)	190 (20.9)	163 (24.4)		
50–59	155 (9.8)	92 (10.1)	63 (9.4)		
60–69	45 (2.9)	27 (3.0)	18 (2.7)		
> =70	9 (0.6)	4 (0.4)	5 (0.7)		
Residence					
Urban	1,287 (82.1)	727 (80.3)	560 (84.5)	**0.08 (0.001)**	**0.04**
Rural	281 (17.9)	178 (19.7)	103 (15.5)		
Education					
Elementary	4 (0.3)	2 (0.2)	2 (0.3)	−0.04 (0.21)	0.63
Preparatory	22 (1.4)	16 (1.8)	6 (0.9)		
High school	183 (11.7)	107 (11.8)	76 (11.5)		
Diploma/Bachelor degree	962 (61.4)	557 (61.5)	405 (61.1)		
High diploma/Master/PhD	397 (25.3)	223 (24.6)	174 (26.2)		
Monthly income					
<500 USD	189 (13.3)	108 (12.9)	81 (13.9)	**−0.08 (0.002)**	0.07
500–1,000 USD	428 (30.2)	265 (31.8)	163 (27.9)		
1,000–1,500 USD	319 (22.5)	200 (24.0)	119 (20.4)		
1,500–2,000 USD	188 (13.3)	99 (11.9)	89 (15.2)		
>2,000 USD	294 (20.7)	162 (19.4)	132 (22.6)		
Ever diagnosed with COVID-19					
Yes	99 (6.3)	59 (6.5)	40 (6.0)	−0.02 (0.35)	0.79
No	1,289 (82.0)	748 (82.3)	541 (81.7)		
Not sure	183 (11.6)	102 (11.2)	81 (12.2)		
Contact with a COVID-19 case					
Yes	262 (16.7)	161 (17.7)	101 (15.2)	−0.03 (0.21)	0.25
No	1,153 (73.4)	664 (73.1)	489 (73.8)		
Not sure	156 (9.9)	83 (9.1)	73 (11.0)		
Suspected of having COVID-19					
Yes	779 (49.6)	460 (50.7)	319 (48.0)	−0.02 (0.39)	0.59
No	661 (42.0)	373 (41.1)	288 (43.4)		
Not sure	132 (8.4)	75 (8.3)	57 (8.6)		
History of chronic disease(s)					
Yes	309 (19.7)	182 (20.0)	127 (19.0)	0.004 (0.87)	0.25
No	1,276 (80.3)	727(80.0)	540 (81.0)		
Heard about clinical trial s before					
Yes	1,174 (74.9)	680 (75.1)	494 (74.5)	0.002 (0.98)	0.78
No	402 (25.1)	229 (24.9)	173 (25.5)		

*This P-value is based on Chi-square test.

** Bold values indicate significant P values (<0.05).

consequences was found to be the main hindering factor to participate in clinical trials. The latter was indicated by 67.4% of respondents and had the most negative correlation ($r = -0.33$, $P < 0.001$) with a significance of <0.001 between those with positive vs. negative attitudes. Interestingly, lack of knowledge of clinical trials was the second highest factor that negatively influenced participation in COVID-19 clinical trials. It was selected by 56.5% of the respondents and significantly correlated with the negative attitude toward participation in clinical trials ($r = -0.13$, $P < 0.001$). Violating research ethics or fear of turning into experimental animals were also considered significant hindering factors with correlation to negative attitudes for almost half of the respondents. Lack of trust in pharmaceutical companies (45.5%), a healthcare system in the form of physicians and hospitals (27.2%) as well as scientists/researchers (20.7%) could prevent respondents from participating in clinical trials. All three statements related to trust significantly correlated with the negative attitudes toward participation in COVID-19 clinical trials. The least factors that might prevent respondents from participating in clinical trials were religious beliefs (10%) and community customs and traditions (9.7%). The latter factors, in addition to having limited time, did not correlate to the attitude toward participation in COVID-19 clinical trials. All negative statements were significantly associated with the attitude toward participation in COVID-19 clinical trials ($P < 0.05$), except for "having limited time prevents me from participation in such studies" and "my religious beliefs toward participation in these studies prevent me from participation in such studies."

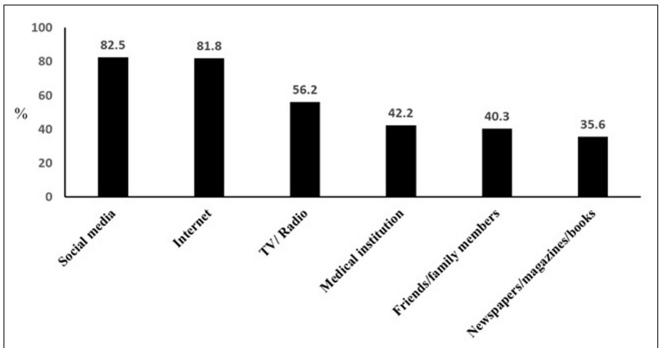

FIGURE 1 | Sources of knowledge regarding clinical trials.

Predictors of Attitudes Toward Participation in COVID-19 Clinical Trials

A regression analysis of all the statements revealed that, in addition to gender, seven statements were found to predict willingness to participate in COVID-19 clinical trials, four positive predictors, and three negative ones (**Table 4**). The conduct of clinical trials in accordance with the scientific research and ethical guidelines strongly decreased the risk of not participating in clinical trials ($P < 0.001$). Other factors with positive influence included protection of family from COVID-19 ($P = 0.007$), contribution to return to normal community life ($P = 0.04$), and receiving additional healthcare benefits ($P < 0.001$). On the other hand, the thought that clinical trials can have a negative impact on the health of participants increased the risk of having a negative attitude toward participation in such trials ($P < 0.001$). This was followed by having limited information about the novel coronavirus and COVID-19 ($P < 0.001$) and a lack of trust in physicians and hospitals ($P = 0.006$). Being a female also significantly increased the risk of not participating in COVID-19 clinical trials ($P = 0.005$). It is notable that the country of origin, which correlated with a negative attitude toward participating in COVID-19 clinical trials, was not a predictor as displayed in **Table 1**. **Figure 3** showed that the area under the curve (AUC) was 0.77 which reflects that the model was capable of predicting the attitude of participants toward self-participation or participation of a family member in COVID-19 vaccine or drug clinical trials by 77% (AUC = 0.77, $P < 0.001$).

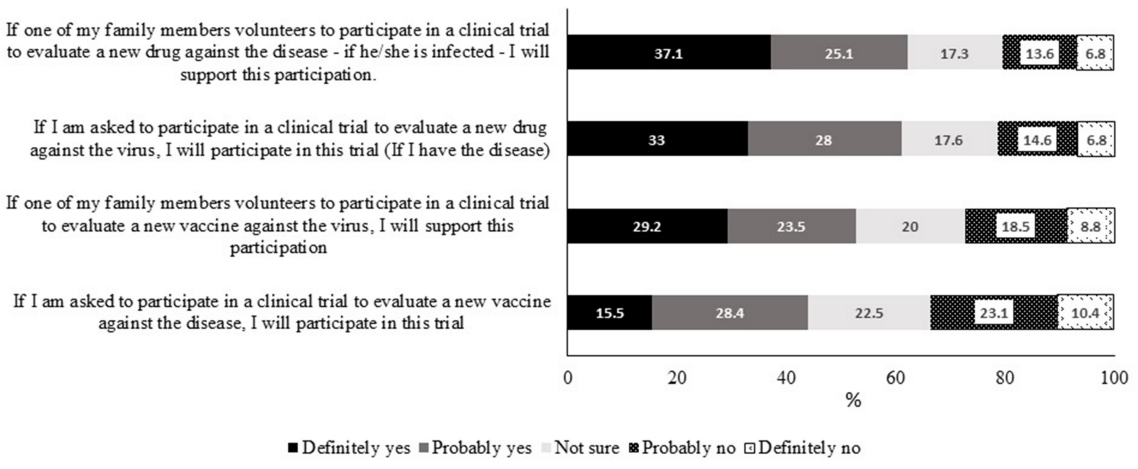

FIGURE 2 | Attitudes of participants toward self-participation or participation of a family member in COVID-19 vaccine or drug clinical trials.

TABLE 2 | Perceptions of respondents on COVID-19 and correlation with attitude toward participation in COVID-19 clinical trials.

Do you agree with the following statements? (Yes/no)	No. of "yes" respondents of the total sample (%) (*N* = 1,576)	Attitude toward participating in a clinical trial		Rho (*P*-value)	*P*-value*
		Positive (%) (*n* = 909)	Negative (%) (*n* = 667)		
The goal of conducting a clinical trial on a vaccine or drug against COVID-19 is to determine its safety and efficacy in humans.	1,464 (93.4)	859 (94.8)	605 (91.4)	**0.06 (0.02)****	**0.01**
Before conducting a clinical trial on either a drug or a vaccine for COVID-19, its safety and effectiveness should first be tested in animals to ensure their safety in humans.	1,352 (86.3)	784 (86.8)	568 (85.7)	−0.01 (0.71)	0.51
When a vaccine for COVID-19 becomes available, I will not take it unless I am sure it is effective.	969 (61.9)	524 (57.8)	445 (67.5)	**0.16 (<0.001)**	**<0.001**
When a drug for COVID-19 becomes available, I will not take it unless I am sure it is effective.	925 (59.1)	493 (54.5)	432 (65.5)	**–0.15 (<0.001)**	**<0.001**
Participating in a clinical trial on a vaccine for COVID-19 will increase my risk of contracting it.	447 (28.5)	217 (24.0)	230 (34.7)	**–0.14 (<0.001)**	**<0.001**
I am worried that I will contract COVID-19.	978 (62.3)	564 (62.2)	414 (62.4)	−0.003 (0.31)	0.92
I am worried a family member (s) would contract COVID-19.	1,340 (85.6)	779 (86.0)	561 (85.0)	−0.02 (0.43)	0.59
A newly developed vaccine or drug for COVID-19 will be exploited commercially.	1,017 (65.0)	567 (62.7)	450 (68.2)	**–0.08 (0.001)**	**0.02**
A newly developed vaccine or drug for COVID-19 will be exploited politically.	983 (62.8)	559 (61.6)	424 (64.4)	**–0.05 (0.04)**	0.26
Once a treatment for COVID-19 is made available, it will be affordable for most.	647 (41.3)	409 (45.1)	238 (36.1)	**0.08 (0.002)**	**<0.001**
Once a vaccine for COVID-19 is made available, it will be affordable for most.	627 (40.0)	392 (43.2)	235 (35.7)	**0.08 (0.001)**	**0.003**
Interest in COVID-19 is exaggerated in general.	563 (35.9)	318 (35.1)	245 (37.1)	−0.01 (0.60)	0.40
Contracting COVID-19 is closely linked to death.	144 (9.2)	90 (9.9)	54 (8.2)	**0.05 (0.03)**	0.23

**P-value is based on Chi-square test.*
*** Bold values indicate significant P values (<0.05).*

DISCUSSION

During the first two decades of the twenty-first century, the human race witnessed the emergence of three previously unknown coronaviruses: severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and, recently, SARS-CoV-2. Although SARS-CoV-2 is genetically related to SARS-CoV, the new virus has unique features that contributed to its rapid spread globally (20). Although some vaccines and drugs have been approved for COVID-19, significant efforts are still ongoing to support the development of more vaccines and therapeutic drugs. The success of these studies depends on the active engagement of potential participants. In our study, we report that participants from the three countries had a positive attitude toward participation in COVID-19 clinical trials, and this attitude was significantly associated with altruism, personal and community benefits, and conducting the trials according to ethical guidelines. On the other hand, the female gender, lack of trust in physicians and hospitals, and potential negative health consequences were associated with negative attitudes toward participation in these trials.

About three-quarters of the respondents had previous knowledge of clinical trials. This percentage is much higher than previous results reported in Jordan (21.8%) (21) and in Oman (31.3%) (22). On the other hand, they are comparable to the results reported in the United States, where 66% of the participants reported that they had previous information about clinical trials (23). This can be interpreted to the higher knowledge among our participants compared to previous studies in Arab countries as the vast majority of our respondents had, at least, a university degree. In fact, knowledge about clinical trials was associated with higher education in the studies conducted in Jordan and the United States (21, 23). Another reason is the unprecedented media coverage of this pandemic and the news covering clinical trials launched to test new vaccines or treatments for the virus. This has increased public knowledge of clinical trials.

Several platforms represented the sources of information about clinical trials for our participants. Social media and the internet ranked first followed by other platforms. The internet and social media were also the main sources of general information about COVID-19 among the public in Egypt (24). These results are in accordance with a previous population-based survey conducted in Jordan where the internet was the most searched source of health-related information (25). Social media have also been effectively used to communicate research concepts with specific target groups (26). Although the internet and social media provide easy and quick access to information, they can be a source of misinformation, and the public should be educated about their use.

When investigating the attitude toward participation in COVID-19 clinical trials, notable and interesting differences could be observed in regards to two items: first, participation in

TABLE 3 | Factors influencing decision to participate in COVID-19 clinical trials.

Would the following statements influence your decision to participate in a COVID-19 clinical trial?	No. of "yes" respondents of the total sample (%) (*N* = 1,576)	Attitude toward participating in a clinical trial		Rho (*P*-value)	*P*-value*
		Positive (%) (*n* = 909)	Negative (%) (*n* = 667)		
A. Positive factors					
Contributing to the protection of my family from COVID-19 encourages me to participate.	1,259 (80.5)	836 (92.4)	423 (64.2)	**0.40 (<0.001)****	**<0.001**
The conduct of clinical trials will be in accordance with the scientific research, and ethical guidelines encourages me to participate.	1,202 (77.1)	825 (91.0)	377 (57.6)	**0.45 (<0.001)**	**<0.001**
Contributing to the return of normal life encourages me to participate.	1,187 (76.2)	810 (89.6)	377 (57.7)	**0.43 (<0.001)**	**<0.001**
Contributing to the salvation of humankind from COVID-19 encourages me to participate.	1,169 (74.9)	803 (88.5)	366 (56.0)	**0.43 (<0.001)**	**<0.001**
Contributing to the protection of my community from COVID-19 encourages me to participate.	1,151 (73.6)	794 (87.7	357 (54.2)	**0.44 (<0.001)**	**<0.001**
Receiving additional health care benefits encourages me to participate.	850 (54.3)	599 (66.1)	251 (38.1)	**0.31 (<0.001)**	**<0.001**
Receiving a financial reward encourages me to participate.	323 (20.6)	216 (23.9)	107 (16.2)	**0.13 (<0.001)**	**<0.001**
B. Negative factors					
The probability of occurrence of negative consequences to my health prevents me from participating in such studies.	1,054 (67.4)	528 (58.2)	526 (80.1)	**−0.33 (<0.001)**	**<0.001**
Having limited information about clinical trials, in general, prevents me from participating in such studies.	876 (56.5)	481 (53.3)	395 (61.0)	**−0.13 (<0.001)**	**0.003**
The possibility that these studies will not be conducted in an ethical manner that follows the required scientific and research methods prevents me from participating in such studies.	849 (54.5)	462 (51.2)	387 (59.1)	**−0.11 (<0.001)**	**0.002**
The possibility of exploiting me and turning into a "lab rat" prevents me from participating in such studies.	842 (53.9)	416 (45.9)	426 (65.0)	**−0.24 (<0.001)**	**<0.001**
Lack of trust in pharmaceutical companies, in general, prevents me from participating in such studies.	709 (45.5)	364 (40.3)	345 (52.8)	**−0.17 (<0.001)**	**<0.001**
Having limited information about the novel coronavirus and COVID-19 prevents me from participating in such studies.	684 (44.0)	343 (38.0)	341 (52.4)	**−0.15 (<0.001)**	**<0.001**
The possibility of violating my privacy (such as if my samples and health data are sent to other centers and countries) prevents me from participating in such studies.	558 (35.7)	288 (31.8)	270 (41.1)	**−0.13 (<0.001)**	**<0.001**
Having limited time prevents me from participating in such studies.	525 (34.0)	295 (32.9)	230 (35.5)	−0.05 (0.06)	0.28
My family's attitude toward participation in these studies prevents me from participating in such studies.	523 (33.7)	277 (30.7)	246 (37.8)	**−0.09 (<0.001)**	**0.003**
My current medical problems prevent me from participating in such studies.	425 (27.5)	224 (24.9)	201 (30.9)	**−0.07 (0.008)**	**0.009**
Lack of trust in physicians and hospitals, in general, prevents me from participating in such studies.	424 (27.2)	186 (20.6)	238 (36.4)	**−0.19 (<0.001)**	**<0.001**
Lack of trust in researchers and scientists, in general, prevents me from participating in such studies.	321 (20.7)	142 (15.7)	179 (27.5)	**−0.15 (<0.001)**	**<0.001**
Lack of conviction about the value and benefits of these trials prevents me from participating in such studies.	283 (18.3)	135 (15.0)	148 (22.9)	**−0.10 (<0.001)**	**<0.001**
My religious beliefs toward participation in these studies prevent me from participating in such studies.	156 (10.0)	86 (9.5)	70 (10.7)	−0.01 (0.58)	0.46
Customs and traditions in my community prevent me from participating in such studies	151 (9.7)	75 (8.3)	76 (11.7)	−0.04 (0.09)	**0.03**

*This P-value is based on Chi-square test.

** Bold values indicate significant P values (<0.05).

a vaccine trial vs. a drug trial and, second, personal participation vs. supporting the participation of a family member in a clinical trial. The difference in enthusiasm was more apparent in the percentage of individuals responding with the "very likely" option. This is expected since participation in a COVID-19 drug trial is conditioned by being affected by the virus as stated in the questionnaire and lack of the therapeutic drug. These results may suggest that there are issues associated with vaccines

TABLE 4 | Predictors of attitude toward participation in COVID-19 clinical trials.

Statement	Unit of increase	OR (95% CI)	*P*-value
The conduct of clinical trials will be in accordance with scientific research and ethical guidelines.	No = 0, Yes = 1	0.35 (0.24–0.51)	<0.001
Contributing to the protection of my family from COVID-19.	No = 0, Yes = 1	0.53 (0.33–0.84)	0.007
Receiving additional healthcare benefits.	No = 0, Yes = 1	0.61 (0.47–0.79)	<0.001
Contributing to the protection of my community from COVID-19.	No = 0, Yes = 1	0.65 (0.43–0.98)	0.04
The possibility of getting ill prevents me from participating in such trials.	No = 0, Yes = 1	1.68 (1.26–2.24)	<0.001
Limited knowledge about the coronavirus or COVID-19 disease.	No = 0, Yes = 1	1.58 (1.22–2.04)	<0.001
Lack of trust in physicians and hospitals	No = 0, Yes = 1	1.49 (1.12–1.97)	0.006
Gender	Male = 0, Female = 1	1.42 (1.11–1.81)	0.005

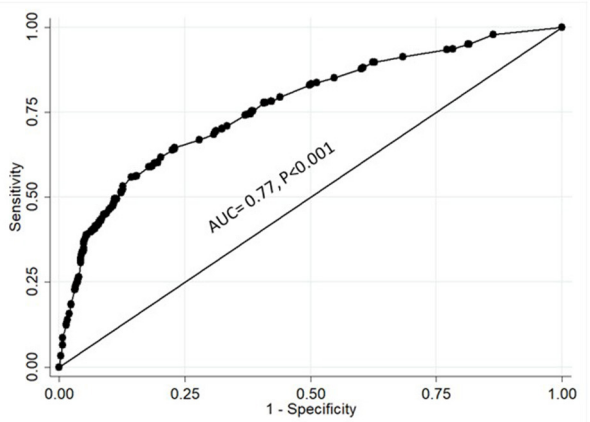

FIGURE 3 | ROC curve analysis for evaluating the prediction of logistic regression model.

including the concern about the potential association between known vaccines and the development of disease conditions such as autism (27). The overall positive attitudes toward participation in clinical trials and the lack of difference between personal participation in a drug trial or supporting a family member to participate in such trials positively reflect the importance of clinical trials among Arabs.

Our results are comparable to previous reports. In Oman, 50% of participants showed interest in participating in clinical trials related to their medical condition (22). In addition, 58% of KSA respondents in an independent study were willing to participate in a clinical trial if they were healthy (28). However, this was more than twice the percentage of respondents who indicated their willingness to participate in clinical trials in Jordan (21).

Several factors were considered as the predictors of likeliness to participate in COVID-19 clinical trials. Altruism appears to be one factor where respondents indicated that they would participate in clinical trials to protect their families and to return their communities to normal conditions. This is similar to previous studies in three Arab countries, KSA, Egypt, and Qatar, where participation in clinical trials and research is considered a form of charity and means to help society, advance medical knowledge, and help others (28–30). Altruism and hope for a better treatment were the main factors that motivated most cancer patients to participate in oncology clinical trials (6, 31). In general, altruism improves self-image and the sense of fulfillment and usefulness of participants (32).

Previously, a review of factors affecting patients' participation in clinical trials identified personal gain in the form of better healthcare and extra medical attention as the primary reasons for participating in this type of studies (33). Herein, receiving additional healthcare, but not financial reward, was a significant predictor of participation. The same was reported in Qatar where additional medical care was among the factors that encouraged individuals to participate in different types of medical research (30). It seems that both personal and community benefits represent two important motives for participation in clinical trials. These benefits should be clarified to potential participants and can be used to encourage them to share in these studies.

In the introductory section of our questionnaire, the main ethical issues linked to clinical trials were briefly explained in the informed consent. Interestingly, our respondents were aware of the importance of this issue where the conduct of research under ethical guidelines was associated with a positive attitude toward participation and a predictor of participation. Moreover, they had concerns regarding their potential exploitation, being used as "lab rats," and the potential violation of privacy, all of which were associated with negative attitudes toward participation. A recent study highlighted the presence of racial disparity in COVID-19 clinical trials in the United States and called for justice and equitable selection of participants together with a presentation of demographic data and outcomes of these studies (34). In a previous study in KSA, <50% of participants believed that clinical trials are conducted ethically (28). On the other hand, positive outcomes for self and others, and ethical conduct of different types of research in Qatar encouraged them to join future research initiatives (30). We believe that transparency and assurances to adherence to Good Clinical Practice (GCP) are important factors to encourage participation in clinical trials in Arab countries (35).

Questions arise with the development of vaccines and drugs for COVID-19. One important question is what if a vaccine and or drug is exploited commercially or politically. Recently, the Russian president announced that a locally developed vaccine has been given regulatory approval and could be available to the

public soon. As soon as the news spread about the approved vaccine, a debate started about its safety, efficacy, cost, and economics, as well as political implications of this announcement (36–38). It should be noted that the contradictory information in the media may affect public trust in clinical trials and medical research in general. About two-thirds of our respondents were concerned about the commercial and political exploitation of newly developed vaccines or drugs once developed.

The possibility of commercial exploitation has a significant association with the refusal to participate in COVID-19 clinical trials. If participants are convinced that a medical intervention to treat COVID-19 is available at an affordable price; this could encourage them to participate in clinical trials. We call for global collaboration among nations, organizations, and commercial entities to overcome this unprecedented pandemic. Technology transfer is one way to ensure sufficient supplies of vaccines in developing countries. To reach this goal, WHO recommends the achievement of a win-win situation through a commitment from governments to support this kind of technology transfer or the presence of a large local or regional market (39). During the current pandemic, WHO launched the Access to COVID-19 Tools (ACT) Accelerator, which brings together governments and organizations to support the development and fair distribution of diagnostics, treatments, and vaccines needed by different countries in the world (40). Lack of knowledge of two issues is associated with less enthusiasm to participate in clinical trials. One issue is related to the perception that participation in clinical trials can pose a threat to participants' health. The same perception was also reported as the major reason for unwillingness to participate in clinical trials in Jordan (21). Fear of negative consequences on health was emphasized among African Americans in two independent studies (41, 42), and among Danish participants (43). Fear from negative consequences of participation may explain the general negative attitude toward participation among females in our study where they may tend to be more concerned about their families during such pandemic. In fact, Jordanian participants had a negative attitude toward participation in COVID-19 clinical trials compared to KSA participants as most Jordanian respondents were females. This was corrected in the prediction analysis where the country was not a predictor of participation. We believe that this is an appropriate time to increase public awareness of clinical trials and enforce the introduction of this concept into education curricula.

The other knowledge-based issue is the lack of information regarding coronavirus and COVID-19. However, it is not clear what information our respondents exactly need. The media was flooded with news of the virus and the disease. The problem may be due to the contradictory information that the media transmit regarding the virus, the mechanisms of transmission, and the consequence of infection. These could result in building doubts about the disease and its severity and, hence, make people hesitant about participating in a trial. Conflicting information can also create mistrust in the healthcare system including physicians and pharmaceutical companies. What is interesting is the association of low trust in physicians and hospitals in discouraging participation in clinical trials. About three-quarters of KSA respondents in a previous study were willing to participate in clinical trials after discussing this issue with their family physician (28). The intentions of physicians, when offering the public the opportunity to participate in a clinical trial, can be sensed and can affect their decisions (33). The sense of trust can be divided into four dimensions: general trustworthiness, perceptions of discrimination, deception, and exploitation (44). A scale to measure trust was developed (45) and it would be interesting to modify it, taking into consideration the different cultural backgrounds in the Arab world, and apply it in an independent study.

It is promising that although several negative statements were found to correlate with the unwillingness to participate in clinical trials, they were not predictors. One example is the thought that a vaccine or drug will be exploited commercially. Another is the possibility of turning those enrolled in clinical trials into "lab rats."

CONCLUSIONS AND RECOMMENDATIONS

In general, Arab citizens have good knowledge of and a positive attitude toward COVID-19 clinical trials. It is recommended to increase public awareness of clinical trials and the significance of diversifying participation using various means. We recommend further studies to understand the factors that may affect trust among citizens in the Arab region, and how these factors influence participation in research in general and, specifically, clinical trials. The role of physicians in increasing awareness and trust is critical and should be emphasized in any educational initiative. Fair distribution of benefits between high- and low-income countries, especially when it comes to the COVID-19 vaccine or treatment, is an important strategy to overcome this pandemic. Clear international policies about these issues should be discussed and communicated with the public to encourage their participation in research regarding this global problem.

Limitations of the Study

In light of the limited studies related to the topic, the results of our study add to the global evidence about the perception and attitudes of Arab citizens in participating in clinical trials and, particularly, those that target COVID-19. Using multiple country sampling and settings and the large sample size contribute to the validity as well as the generalizability of the study findings. A major strength of this study is the inclusion of three countries that represent a diverse group of Arab peoples thus providing credibility to the data. However, there are also some limitations of the study that must be considered. First, data are based on a self-reporting, electronic questionnaire; this is a method that could jeopardize participants' understanding of some items or may allow them to answer the questionnaire hastily. Additionally, using online data collection platforms could have prevented us from reaching a certain segment of populations of the three societies, i.e., those with lower education or lower income. We tried to overcome this limitation by using multiple platforms.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, Jordan University Hospital, The University of Jordan, Institutional Review Board, King Fahad Medical City, and Institutional Review Board, National Cancer Institute, Cairo University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AA proposed the idea, participated in data collection, and wrote the manuscript. SA analyzed data, participated in data collection, and manuscript writing. MK led data collection from KSA and revised the manuscript. MS, BA, RS, MAl, and FA participated in data collection and revised the manuscript. MAh supervised and led the study, participated in data collection, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

ORIGINAL RESEARCH
published: 01 March 2021
doi: 10.3389/fpubh.2021.580561

Anxiety and Depression Among Health Sciences Students in Home Quarantine During the COVID-19 Pandemic in Selected Provinces of Nepal

Rajesh Kumar Yadav[1,2,3], *Sushila Baral*[4], *Elina Khatri*[5], *Sony Pandey*[4], *Pawan Pandeya*[4], *Roshan Neupane*[6], *Dipendra Kumar Yadav*[1]*, *Sujan Babu Marahatta*[2,4,7], *Hari Prasad Kaphle*[1], *Jiwan Kumar Poudyal*[8] and *Chiranjivi Adhikari*[1]

[1] School of Health and Allied Sciences, Pokhara University, Pokhara, Nepal, [2] Health Research Together Initiative-Nepal (HeaRT: Initiative), Kathmandu, Nepal, [3] Monitoring and Evaluation Officer (WHP-V), Aasaman Nepal, Janakpurdham, Nepal, [4] Department of Public Health, Manmohan Memorial Institute of Health Sciences, Kathmandu, Nepal, [5] School of Public Health, Patan Academy of Health Sciences, Lalitpur, Nepal, [6] Faculty of Social Sciences, Oslo Metropolitan University, Oslo, Norway, [7] Faculty of Health Science and Technology, Nepal Open University, Lalitpur, Nepal, [8] Department of Public Health, Shree Medical and Technical College, Chitwan, Nepal

OPEN ACCESS

Edited by:
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***Correspondence:**
Dipendra Kumar Yadav
dipendrayadavph@gmail.com

Specialty section:
This article was submitted to Public Mental Health, a section of the journal Frontiers in Public Health

Received: 06 July 2020
Accepted: 03 February 2021
Published: 01 March 2021

Citation:
Yadav RK, Baral S, Khatri E, Pandey S, Pandeya P, Neupane R, Yadav DK, Marahatta SB, Kaphle HP, Poudyal JK and Adhikari C (2021) Anxiety and Depression Among Health Sciences Students in Home Quarantine During the COVID-19 Pandemic in Selected Provinces of Nepal. Front. Public Health 9:580561. doi: 10.3389/fpubh.2021.580561

Aim: This study aimed to assess anxiety and depression among health sciences students at home quarantine during the COVID-19 pandemic in selected provinces of Nepal.

Methods: A web-based cross-sectional study was conducted among 409 health science students enrolled at graduate and post-graduate levels in selected universities and their affiliated colleges. Students from selected colleges were asked to fill out a survey, that was made available through email and social media outlets such as Facebook and Viber. The data were downloaded in Excel and imported to SPSS version 16 for analysis.

Results : The prevalence of anxiety and depression was 15.7 and 10.7%, respectively. The study showed significant associations between (i) place of province and anxiety; (ii) sleep per day and depression; (iii) hours spent on the internet per day for education and depression; (iv) postponement of final exams and depression. There were no significant associations with the socio-demographic variables.

Conclusion: Anxiety and depression in health science students showed correlation with the province, internet use for education, and postponement of exams. These correlations could be common among students in other fields as well. A large-scale study covering a wider geographical area and various fields of education is necessary to further evaluate the impact of COVID-19 on (health sciences) students. The integration of mental health programs both as an intervention and a curriculum level among students is critical to ensure the health of the students.

Keywords: anxiety, depression, health science students, Nepal, COVID-19 pandemic

INTRODUCTION

COVID-19 is caused by the 2019 novel coronavirus or 2019-nCoV (1). This virus is in the same family of viruses as SARS. COVID-19 caused by the SARS-CoV-2 was first detected in Wuhan China in late December 2019 and has since spread all over the world (2). On January 30, 2020, the World Health Organization (WHO) declared the outbreak a public health emergency of international concern as the number of cases began to escalate across the globe (3).

The WHO declared the COVID-19 outbreak as a pandemic on March 11, 2020, when the confirmed cases reached 118,319 with 4,922 deaths worldwide (4). By May 18, 2020, there were 4,825,902 confirmed cases of COVID-19, with 317,101 deaths worldwide. According to the WHO, the case fatality rate was estimated to be around 2%. However, a few reports suggested that the rate ranged from 0.3 to 0.6% (5).

The COVID-19 pandemic has had a profound and pervasive impact on global mental health (6). It was reported that nearly all people affected by or during such global emergencies will experience some level of psychological distress, which for most will improve over time. The prevalence of mental disorders is expected to double compared to an emergency (7). The COVID-19 pandemic brought not only the risk of death from infection but also unbearable psychological pressure (8). A study done in French Universities showed that mental health-related quality of life was poorer than physical health ($p < 0.0001$) among health science students (9).

In Nepal, the first case of COVID-19 was reported on January 23, 2020 and the second case on March 23, 2020 (10). The government of Nepal announced a countrywide lockdown when the second case was announced (11, 12). Along with suggested physical distancing, people are also maintaining a certain social distance from friends and families. In addition, COVID-19 has been heavily stigmatized and can inevitably accelerate anxiety and depression (13). These circumstances have affected students in unprecedented ways because students generally have plans and ambitions for their future. Students faced an enormous disruption to their lives and education which has added a layer of uncertainty in their future. This has been a new and challenging context for students.

Health sciences students include those studying in the field of medicine and paramedics. Most of them have practical classes, field-work duties, and dates of graduation that have been postponed due to the pandemic. Many are instead taking classes online which may not be satisfactory and effective. A recent study on anxiety and depression during the COVID-19 pandemic among medical students in Nepal showed that a significant number of medical students were suffering from high levels of anxiety and depression. About 11.8 and 5.5% of medical students suffer from anxiety and depression, respectively (14). Another study found that 20.4% of students had a moderate level of anxiety, 6.6% had severe anxiety, and 2.8% had extreme levels of anxiety. Gender, age, level of education, and living arrangements were significantly associated with higher levels of anxiety (15). A study on the impacts of COVID-19 on college student's mental health in the United States showed that around 71% had increased stress and anxiety due to the COVID-19 outbreak. Multiple stressors were identified that contributed to increased levels of stress, anxiety, and depressive thoughts (16).

Most of the graduate and post-graduate level health science students are studying in either a semester or annual system. When the WHO declared the COVID-19 outbreak as a pandemic, many students were preparing to take final examinations (their exam schedules had been published) but a sudden announcement of complete lockdown by the government shattered the expectations of students. With the lockdown, universities were closed and exams were postponed. There was, and still is, a dilemma regarding the resumption of the academic activities. Amidst the uncertainty of all academic activities, and virtual classes; students suffer more from the separation and being physical/socially distanced from the college environment and thus are more likely to develop depression and anxiety.

Assessing the level of anxiety and depression among health science students showed the existence of health problems. A French online survey has shown 52.6% anxiety and 11.6% depression among health science students (9). It is critical to understand the mental health status of health science students and possible ways to mitigate such problems to protect them from anxiety and depression. The main objective of this study was to assess anxiety, depression, and associated factors that will guide interventions to maintain psychological well-being.

MATERIALS AND METHODS

Study Design and Setting

A web-based cross-sectional study was conducted among health science students studying in different provinces of Nepal. Graduate and post-graduate level students of selected colleges were invited to enroll in the study. Since the study design was web-based, only students who had internet access were able to fill out the online form.

Sample and Sampling

Health science students studying at graduate and postgraduate levels, aged 8 years and over were the most important selection criteria for participants. The Cochran formula was used to calculate the sample size ($n = Z^2pq/d^2$). Based on the study by Kunwar et al. prevalence of depression among health science students during COVID-19 was (p) = 0.41 (17) and the maximum allowable error was calculated to be (d) = 5%. The sample size was 372. Adding a 10% non-response rate, the final sample size for the study was 409. Colleges from different provinces were representatively selected. Altogether nine colleges were selected, among which one college from province 1 and province 2; three colleges from province 3; two colleges from province 4 and one college from province 5 and 6 was selected. A list of students of selected colleges was obtained from the head of the department; students were chosen proportionately to reach the sample for this study. In addition to coordination with the course manager, the selected students were reminded three times a week, during their online classes.

Data Collection

Anxiety and depression are influenced by socio-demographic factors. We used a structured questionnaire that has five parts: socio-demographic characteristics, educational factors, health-related factors, technological factors, anxiety (seven items), and depression (nine items). Data collection was done within 1 week in the 1st week of June 2020. Around 6–10 min was enough to fill in the questionnaire. They were regularly monitored to ensure they had access to the forms and submitted forms were checked for completeness. We followed-up with students who were disturbed due to internet issues to ensure their participation and that they completed the form.

Socio-Demographic Characteristics

Age, sex, religion, ethnicity, place of residence, living arrangements (own house/rent) were collected.

Education Factors

Educational data including the level of education, education systems, attendance of virtual classes, frequency and duration of virtual classes, pending assignments, postponement of the exam, time spent on study, and internet-related data were collected.

Health-Related Factors and Technological Factors

Diet pattern, exercise, source of internet and its strength, the device used for internet, technical ability to operate applications and related data were collected.

Generalized Anxiety Disorder Assessment (GAD-7)

Generalized Anxiety Disorder-7 (GAD-7), is a self-administered questionnaire developed by Robert L. Spitzer et al. with a sensitivity of 89% and specificity of 82% to assess the level of anxiety (18). It consists of seven items on a four-point Likert scale ranging from 0 to 3, in which 0 implies "not at all" and three implies "nearly every day." The level of anxiety was categorized into four groups as minimal, mild, moderate, and severe based on scoring 0–4, 5–9, 10–14, and 15–21, respectively. Accordingly, minimal and mild were merged; "<10" was the absence of depression, and moderate and severe were merged for the presence of depression "≥ 10." (18). The Cronbach's alpha for the anxiety was 0.8.

Patient Health Questionnaire-9 (PHQ-9) for Depression

PHQ-9 developed by primary care evaluation of mental disorders (PRIME MD) was used to assess depression levels among participants. It consists of nine items on a four-point Likert scale ranging from 0 to 3, where 0 implies "not at all" and three implies "nearly every day." The level of depression was categorized into five groups as minimal, mild, moderate, moderately severe, and severe based on scoring 0–4, 5–9, 10–14,15–19, and 20–27, respectively. Accordingly, minimal and mild were merged "<10;" and moderate, moderately severe, and severe was merged "≥ 10." The scores ($\geq$ 10) were used to determine the existence of depression (18). The Cronbach's alpha of the depression tool was 0.810.

Inclusion and Exclusion Criteria

Participants who filled in the online survey form, above the age of 18 years old were included in the study. The decision for participation was completely voluntary. The students with no proper access to the internet facility and those who were unable to send the filled forms within the given deadline were excluded from the study. Also, the students with a history of exposure to Covid patients, Covid positive cases, currently taking mental care, and those working in health facilities were excluded from the study to minimize the confounding effect in the design of the study. It was assured by confirming with the respective participants. If they met the exclusion criteria, the google form was automatically sent over.

Statistical Analysis

Data were collected and cleaned in Microsoft Excel. The data were imported to SPSS for further processing and analysis. Descriptive analysis such as frequency, percentage, mean and median was calculated. For inferential analysis, Chi squared test and logistic regression were performed. Anxiety and depression levels were assessed on the scoring. The association of scores was explored with socio-demographic characteristics, education-related factors, health-related factors, and technological-related factors.

RESULTS

The mean age of the respondents was 22.10 $\pm$ 2.928 years, ranging from 18 to 37 years, and more than half (55.7%) of the respondents were between the age of 21–25 years. More than three-fourths (83.1%) of the respondents were female and most (93.2%) of them followed Hinduism. More than two-thirds (67.7%) of the respondents were of upper caste groups and nearly half (48.2%) of them were living in municipalities. Most (87%) of the respondents were living in their own home (**Table 1**).

Most (41.3%) of the respondents were from Bagmati province and more than three-fourths (81.2%) of them had graduated. More than half (52.6%) of the respondents had a semester system and most (40.8%) of them were studying in the third and fourth semester of their 2nd year. Nearly half (47.9%) of the respondents were of public health stream and more than three fourths (81.7%) of them were attending virtual classes. Nearly three-fourths (71.9%) of the respondents had pending assignment/internal exams due to the lockdown and most (70.7%) of them had pending final exams, illustrated in **Table 2**.

More than half (67.7%) of the respondents had changes in diet or food habits during the lockdown and had the chance to sleep in during the day. More than half (61.9%) of the respondents exercised or played sports and more than half (63.1%) of them did not play offline games. Details are presented in **Table 3**. More than three-fourths (83.1%) of the respondents had Wi-Fi as the source of internet, and more than half (62.6%) had strong internet signals. Almost half (49.4%) of the respondents used a mobile device to access the internet (**Table 4**).

TABLE 1 | Socio-demographic characteristics of the respondents ($n = 409$).

Variables	Frequency (*n*)	Percentage (%)
Age		
≤20 Years	138	33.7
21-25 Years	228	55.7
>26 Years	43	10.6
Mean ± SD (Min-Max) 22.1±2.9 (18-37)		
Sex		
Male	69	16.9
Female	340	83.1
Religion		
Hinduism	381	93.2
Buddhism	20	4.9
Islam	4	1.0
Christianity	4	1.0
Ethnicity		
Dalit	10	2.4
Disadvantaged non-dalit terai caste	24	5.9
Religious minorities	3	0.7
Upper caste groups	277	67.7
Relatively advantaged janajati	95	23.2
Place of residence		
Rural municipality	31	7.6
Municipality	197	48.2
Sub-metropolitan	29	7.1
Metropolitan	152	37.2
Living arrangement		
Own home	359	87.8
Rent	50	12.2
Living in status		
With family	402	98.3
With friends	2	0.5
Without family	5	1.2

TABLE 2 | Education-related information of respondents.

Variables	Frequency (*n*)	Percentage (%)
Provinces		
Province one	33	8.1
Province two	25	6.1
Bagmati province	169	41.3
Gandaki province	140	34.2
Province five	29	7.1
Karnali province	13	3.2
Level of education		
Graduate	332	81.2
Post-graduate	77	18.8
Education system		
Semester	215	52.6
Annually	194	47.4
Grade		
First and second semester/first year	132	32.3
Third and fourth semester/second year	167	40.8
Fifth and sixth semester/third year	54	13.2
Seventh and eighth semester/fourth year	56	13.7
Stream/discipline		
Nursing	117	28.6
Public health	196	47.9
Pharmacy	31	7.6
MLT	51	12.5
Physiotherapy	14	3.4
Presence of virtual class		
Yes	334	81.7
No	75	18.3
Frequency of virtual class/week ($n = 334$)		
≤6 class/week	289	70.7
More than 6 class/week	45	11
Mean ± SD = 4.79 ± 3.48		
Pending of assignment/internal exam		
Yes	294	71.9
No	115	28.1
Pending of final exam		
Yes	289	70.7
No	120	29.3
Time spent in internet for educational purpose		
Don't spend	50	12.2
<4 h	307	75.1
More than 4 h	52	12.7
Frequency of contact with teachers		
No contact	113	27.6
Once times a day	169	41.3
More than one times	127	31.1

More than half (52.8%) of the respondents had minimal anxiety symptoms and more than half (57.9%) had minimal depressive symptoms. The prevalence of anxiety and depression was 15.7 and 10.7%, respectively. Details are illustrated in **Table 5**.

Final exam postponement was significantly associated with anxiety ($p < 0.005$) (**Table 6**). For students whose final exam was not postponed, the odds were 2.2 times higher than among the students whose final exam was postponed (OR = 2.2, 95%CI: 1.1–4.4). Province and hours spent on the internet per day for education were significantly associated with depression ($p<0.05$). With reference to students who spent less than the mean hours on the internet every day for education, the odds were 2.1 times higher among the students who spent more than mean hours on the internet per day for education (OR = 2.1, 95%CI: 1.1–4.2), as presented in **Table 7**.

DISCUSSION

The study revealed that every one in 10 (10.7%) and nearly one in seven (15.7%) health sciences students who had internet access was suffering from moderate to severe depressive and anxiety symptoms. The findings showed a strong association between

final exam postponement and anxiety. Sleeping during the day, hours spent on the internet, and coming from select provinces were associated with depression.

TABLE 3 | Health-related information of respondents.

Variables	Frequency (*n*)	Percentage (%)
Diet/change in food habit		
Yes	277	67.7
No	132	32.3
Rest/sleep		
<average (≤6 h)	45	11
Normal (7–8 h)	216	52.8
More than average (≥9 h)	148	36.2
Exercise/sports		
Yes	253	61.9
No	156	38.3
Play offline games		
Yes	151	36.9
No	258	63.1

TABLE 4 | Technological related information.

Variables	Frequency (*n*)	Percentage (%)
Source of internet		
Wi-Fi	340	83.1
Mobile data	48	11.7
Both	21	5.1
Strength of internet		
Strong	256	62.6
Weak	153	37.4
Time spent in internet per day		
<5 h	217	53.1
More than 5 h	192	46.9
Device to access internet		
Mobile and laptop	180	44.0
Mobile	202	49.4
Laptop	24	5.9
Desktop	3	0.7

Anxiety

The study showed that 52.8, 31.5, 10.3, and 5.4 percent of points were scored in minimal, mild, moderate, and severe anxiety, respectively. In contrast, slightly lower percent points in minimal (46.5%) and mild (18.7%), but higher of those in moderate (20.5%) and severe (14.3%) were observed in school adolescents from grades nine to 12 in Nepal (19). However, these adolescents were lower in age and might have less access to the internet. In addition, the current study findings contradict those of a study of Bangladeshis carried out by Islam S. et al. This study showed 18, 21, 47.3, and 13.8 percent of points for minimal, mild, moderate, and severe anxieties, respectively. It should also be noted that nearly all (98.2%) medical and allied health sciences students were Facebook users (20), showing that they have internet access.

This study reveals no association between engaging in exercise ($p = 0.31$, OR 0.7; 0.4–1.3) and anxiety, whereas the study done by Islam et.al shows a significant association between exercise and anxiety ($p = 0.009$, OR = 1.72; 95%, CI = 1.15–2.59). Respondents not engaging in physical exercise were 1.72 times more likely than the respondents taking physical exercise to have anxiety (21).

Depression

Our study shows 57.9% minimal depression, 31.3% mild depression, 8.1% moderate, 2.4% moderately severe, and 0.2% severe depression. This contradicts findings by Islam et.al which shows 9.5% minimal depression, 11% mild depression, 50.2% moderate, 15.3% moderately severe, and 4% severe depression (21).

Our study shows that students who spend more time on the internet were 2.18 times more likely to be depressed than respondents spending less time on the internet ($p = 0.021$, OR = 2.1, CI = 1.1–4.2), whereas similar study done by Islam and et.al showed that the respondents using the internet <2 h/day were 0.53 times less likely than the respondents using the internet more than 4 h/day to be depressed ($p = 0.033$, OR = 0.53; 95% CI = 0.29–0.95).

In the present study, no statistically significant association was found between any of the socio-demographic variables, including education level, province, sex, religion, ethnicity, place of residence, staying partner, living arrangement, education system, and faculty of education. A previous study of Bangladeshi medical students also reported no significant relationship between socio-demographic variables and depression or anxiety

TABLE 5 | The rate of different severities of anxiety and depressive symptoms.

Variables	Anxiety symptoms		Depressive symptoms	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Minimal	216	52.8	237	57.9
Mild	129	31.5	128	31.3
Moderate	42	10.3	33	8.1
Moderately	-	-	10	2.4
Severe	22	5.4	1	0.2

TABLE 6 | Bi-variate analysis between Anxiety and different variables ($n = 409$).

Characteristics	Anxiety		χ^2	*P*-value	OR	CI
	Anxious	Non-anxious				
Educational level						
Graduate	53 (16.0%)	279 (84%)	0.0.133	0.715	0.877	0.435–1.771
Post Graduate	11 (14.3%)	66 (85.7%)				
Sex						
Male	10 (14.5)	59 (85.5)	2.084	0.772	1.114	0.536–2.313
Female	54 (15.9)	286 (84.1)				
Living arrangement						
Home	54 (15)	305 (85)	0.817	0.366	1.412	0.666–2.992
Rent	10 (20)	40 (80)				
Attending virtual class						
Yes	50 (15)	284 (85)	0.634	0.426	0.767	0.399–1.475
No	14 (18.7)	61 (81.3)				
Pending assignment/ internal exams						
Yes	50 (17)	244 (83)	1.463	0.226	1.478	0.782–2.794
No	14 (12.2)	101 (87.8)				
Final exam postpone						
Yes	53 (18.3)	236 (81.7)	5.405	**0.020**	2.225	1.119–4.427
No	11 (9.2)	109 (90.8)				
Exercise/play sports daily						
Yes	36 (14.2)	217 (85.8)	1.011	0.315	0.758	0.442–1.301
No	28 (17.9)	128 (82.1)				
Internet strength						
Strong	36 (14.1)	220 (85.9)	1.303	0.254	1.369	0.797–2.350
Weak	28 (18.3)	125 (81.7)				
Ability to operate virtual class application						
Yes	53 (15.4)	292 (84.6)	0.136	0.712	0.875	0.429–1.783
No	11 (17.2)	53 (82.8)				
Sleep per day						
Less than average	9 (20)	36 (80)	0.761	0.643	-	-
Normal	32 (14.8)	184 (85.2)				
More than average	23 (15.5)	125 (84.5)				
Hours of self-study per day						
<=mean hour	31 (16.8)	154 (83.2)	0.315	0.575	0.858	0.503–1.464
>mean hour	33 (14.7)	191 (85.3)				
Hours spent on the internet per day for education						
<=mean hours	49 (15.1)	275 (84.9)	0.325	0.569	1.203	0.637–2.270
>mean hours	15 (17.6)	70 (82.4)				
Frequency of virtual class per week						
≤4.79 class	25 (16.7)	125 (83.3)	0.186	0.666	0.886	0.512–1.533
>4.79 class	39 (15.1)	220 (84.9)				
Duration of virtual class per day						
≤2.31 h	31 (14.2)	187 (85.8)	0.401	0.527	1.219	0.660–2.249
>2.31 h	20 (16.8)	99 (83.2)				
Hours spent on the internet per day						
≤5.85 h	28 (12.9)	189 (87.1)	2.638	0.104	1.558	0.910–2.666
>5.85 h	36 (18.8)	156 (81.2)				
Hours spent on offline games per day						
≤half hour	41 (16)	215 (84)	0.174	0.677	0.887	0.506–1.557
>half hour	22 (14.5)	130 (85.5)				

Bold values represent statistical association.

TABLE 7 | Bi-variate analysis between depression and different variables ($n = 409$).

Characteristics	Depression		χ^2	*P*-value	OR	CI
	Depressed	Non-depressed				
Educational level						
Graduate	39 (11.7)	293 (88.3)	1.797	0.180	0.522	0.199–1.371
Post graduate	5 (6.5)	72 (93.5)				
Provinces						
Province 1	4 (12.1)	29 (87.9)	11.471	**0.031**		
Province 2	3 (12)	22 (88)				
Province 3	10 (5.9)	159 (94.1)				
Gandaki province	20 (14.3)	120 (85.7)				
Province 5	3 (10.3)	26 (89.7)				
Province 6	4 (30.8)	9 (69.2)				
Sex						
Male	6 (8.7)	63 (91.3)	0.368	0.544	1.321	0.536–3.259
Female	38 (11.2)	302 (88.8)				
Attending virtual class						
Yes	34 (10.2)	300 (89.8)	0.634	0.426	0.737	0.346–1.566
No	10 (13.3)	65 (86.7)				
Pending assignment/ internal exams						
Yes	36 (12.2)	258 (87.8)	2.408	0.121	1.866	0.840–4.147
No	8 (7)	107 (93)				
Final exam postpone						
Yes	30 (10.4)	259 (89.6)	0.146	0.702	0.877	0.447–1.720
No	14 (11.7)	106 (88.3)				
Exercise/play sports daily						
Yes	22 (50)	231 (91.3)	2.938	0.086	0.580	0.310–1.087
No	22 (14.1)	134 (85.9)				
Ability to operate virtual class application						
Yes	33 (9.6)	312 (90.4)	3.267	0.071	0.510	0.243–1.070
No	11 (17.2)	53 (82.8)				
Sleep per day						
Less than average	10 (22.2)	35 (77.8)	7.003	**0.043**	2.653	1.152–6.112
Normal	21 (9.7)	195 (90.3)			1	Ref
More than average	13 (8.8)	135 (91.2)			0.894	0.433–1.847
Hours of self-study per day						
≤mean hour	16 (8.6)	169 (91.4)	1.565	0.211	1.509	0.789–2.884
>mean hour	28 (12.5)	196 (87.5)				
Hours spent on internet per day for education						
>mean hours	15 (17.6)	70 (82.4)	5.304	**0.021**	2.180	1.109–4.284
≤mean hours	29 (9)	295 (91)			1	Ref
Frequency of virtual class per week						
≤4.79 class	16 (10.7)	134 (89.3)	0.002	0.964	1.015	0.530–1.945
>4.79 class	28 (10.8)	231 (89.2)				
Hours spent on internet per day						
≤5.85 h	21 (9.7)	196 (90.3)	0.562	0.453	1.270	0.679–2.376
>5.85 h	23 (12)	169 (88)				
Hours spent on offline games per day						
≤half hour	30 (11.7)	226 (88.3)	0.624	0.430	0.764	0.392–1.492
>half hour	14 (9.2)	138 (90.8)				

Bold values represent statistical association.

(21). The present study only obtained significant associations with (i) place of residence /province and anxiety; (ii) sleep per day and depression; (iii) hours spent on the internet per day for education and depression; and, (iii) postpone of final exams and depression. A similar study conducted in Bangladesh also reported significant associations between lack of sleep satisfaction and depression, excessive daily internet use, and depression (21).

POLICY IMPLICATION

Based upon these insights into the psychological aspects of the pandemic, psycho-social counselors should be used by educational institutions, responsible for the health of the students. Mental health issues are prominent during pandemic situations, thus psycho-social aspects should be addressed at the initial stages. Educational institutions have to initiate policies and take actions that contribute to the promotion of mental health.

CONCLUSION

Anxiety and depression in health science students showed a correlation with province, internet use for education, and postponement of exams. These correlations could be common among students of other fields as well. A large-scale study covering a wider geographical area and various fields of education is necessary to further evaluate the impact of COVID-19 on (health sciences) students. The integration of mental health programs both as an intervention and as part of the curriculum is critical to ensure the health of the students.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study received ethical approval from Nepal Health Research Council (No: 397/2020P) on 3rd June, 2020. Permission was also obtained from the selected colleges. All participants were fully informed regarding study objectives and written informed consent was obtained from participants by ticking off to agree to participate in research in Google form. Confidentiality of the data were fully maintained. All data were stored in the computer database which was accessible only to the researcher and was password protected.

AUTHOR CONTRIBUTIONS

RY, SM, DY, SB, HK, and EK: research conceptualization. RY, SB, SP, PP, RN, EK, and JP: supervised the data collection and writing-original draft. RY, SB, PP, RN, DY, HK, and CA: formal analysis. DY, SM, HK, CA, and RY: writing-review and editing. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

We are deeply grateful to all the selected colleges and program coordinators who have supported this study during data collection and all the respondents who participated and used their valuable time to fill out the form. The authors would like to thank Dr. Bipin Adhikari, Oxford University for reviewing the manuscript, and Dr. Shelly Xu, Nova Southern University, USA for editing English language and technical suggestions.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 22 March 2021
doi: 10.3389/fmed.2021.600415

Whom Should Be Saved? A Proposed Ethical Framework for Allocating Scarce Medical Resources to COVID-19 Patients Using Fuzzy Logic

Heba Saadeh[1*†], *Maha Saadeh*[2†] *and Wesam Almobaideen*[1,3]

[1] Computer Science Department, King Abdullah II School of Information Technology, The University of Jordan, Amman, Jordan, [2] Computer Engineering and Informatics, School of Science and Technology, Middlesex University Dubai, Dubai, United Arab Emirates, [3] Electrical Engineering and Computing Sciences, Rochester Institute of Technology in Dubai, Dubai, United Arab Emirates

OPEN ACCESS

Edited by:
Maysa Al-Hussaini, King Hussein Cancer Center, Jordan

Reviewed by:
Rolf Bass, Retired, Berlin, Germany
Domenico Criscuolo, Italian Society of Pharmaceutical Medicine, Italy

***Correspondence:**
Heba Saadeh
heba.saadeh@ju.edu.jo

[†]*These authors have contributed equally to this work*

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *30 August 2020*
Accepted: *22 February 2021*
Published: *22 March 2021*

Citation:
Saadeh H, Saadeh M and Almobaideen W (2021) Whom Should Be Saved? A Proposed Ethical Framework for Allocating Scarce Medical Resources to COVID-19 Patients Using Fuzzy Logic. Front. Med. 8:600415. doi: 10.3389/fmed.2021.600415

COVID-19 is a global pandemic that affected the everyday life activities of billions around the world. It is an unprecedented crisis that the modern world had never experienced before. It mainly affected the economic state and the health care system. The rapid and increasing number of infected patients overwhelmed the healthcare infrastructure, which causes high demand and, thus, shortage in the required staff members and medical resources. This shortage necessitates practical and ethical suggestions to guide clinicians and medical centers when allocating and reallocating scarce resources for and between COVID-19 patients. Many studies proposed a set of ethical principles that should be applied and implemented to address this problem. In this study, five different ethical principles based on the most commonly recommended principles and aligned with WHO guidelines and state-of-the-art practices proposed in the literature were identified, and recommendations for their applications were discussed. Furthermore, a recent study highlighted physicians' propensity to apply a combination of more than one ethical principle while prioritizing the medical resource allocation. Based on that, an ethical framework that is based on Fuzzy inference systems was proposed. The proposed framework's input is the identified ethical principles, and the output is a weighted value (per patient). This value can be used as a rank or a priority factor given to the patients based on their condition and other relevant information, like the severity of their disease status. The main idea of implementing fuzzy logic in the framework is to combine more than one principle when calculating the weighted value, hence mimicking what some physicians apply in practice. Moreover, the framework's rules are aligned with the identified ethical principles. This framework can help clinicians and guide them while making critical decisions to allocate/reallocate the limited medical resources during the current COVID-19 crisis and future similar pandemics.

Keywords: COVID-19, ethical framework, ethical principles, fuzzy logic, resource allocation, scarce resources, WHO ethical guidelines

INTRODUCTION

The novel coronavirus 2019 (COVID-19) is a global respiratory pandemic that is highly contagious emerged in Wuhan city of China (1). It had negatively affected all the countries worldwide and disturbed the everyday lives of billions of citizens worldwide. It changed the way people used to work, learn, interact, communicate, and travel (2, 3). The social, economic, and psychological impacts of COVID-19 are essential; however, the physiological impact on the health of the infected individuals and the patients of chronic diseases and/or patients who need emergent care is crucial since it has a direct, apparent, and immediate effect on the health care system of the country (4–8). The COVID-19 fatality rate is alarming (around 107 million causalities and more than two millions death cases, as of 7th of February, 2021), and the death cases had been recorded for all ages and various health conditions (9, 10), especially with the emerging of new strains of COVID-19 (11).

Italy has been one of the first countries severely affected by the spread of COVID-19 outside China. Ten percent of positively tested patients in Italy needed intensive care to overcome the acute respiratory distress syndrome. Moreover, due to the exponential rise of the number of COVID-19 patients, there was an actual risk of running out of Intensive Care Unit (ICU) beds, ventilators, and other medical resources, including face masks and shields (12, 13). Many medical centers in Italy respond to the largest outbreak of COVID-19 outside Asia by developing and applying their response plans (14). As the number of COVID-19 cases is still increasing worldwide, mainly due to the second wave and virus mutations, in addition to the limitation of medical resources, doctors and medical professionals are left with the hardest decision to make: whom should be saved first? The decision to select one patient over the others is affected by principles, which may vary based on cultural, religious, and humanity-related reasons (15–17).

It is vital to have a comprehensive, ethical, and applicable framework/plan to be used when needed for a sudden and massive crisis. Previous pandemics such as influenza also required high demand from the health systems, and protocols to prevent, control, and mitigate the effects of influenza had been provided (18). Similarly, medical centers and hospitals provided recommendations for containing and managing COVID-19, with a particular interest in the best practice of scarce medical resource allocation. The guiding principles discussed by Emanuel et al. (19) to allocate resources during COVID-19 recommended that the ICU workers act in a way that strives to save the most number of lives and/or maximize the life-years saved. This means "allocating scarce resources to patients who are sick enough to benefit but also have the best chance of survival" (20). Although this guidance is essential, it might cause a bias since this principle does not uphold all persons' protected rights (21). According to the World Health Organization (WHO), excluding population groups from being allocated medical resources would be inappropriate (22). Moreover, resource allocation should be guided by well-established and broadly-applicable ethical principles when there is insufficient supply to meet everyone's needs.

DeJong et al. (23) provide practical ethical suggestions to guide clinicians and medical centers while allocating limited medications for COVID-19 inpatients in the US. They suggested four ethical principles: firstly, the benefit from reducing mortality should be assessed using the best available evidence. Allowing policies should be revised as evidence develops, and medications should be prioritized during the shortage. Secondly, the choices of each patient should be respected. However, when there is an insufficient supply of medications, it may not be possible to follow individual patients and their physicians' preferences. Thirdly, in order to avoid discrimination and mitigate health disparities, scarce medications should be allocated fairly. Lastly, allocation policies should be made accountable, responsive to the concerns of those affected, transparent, and comparable to the situation, including the progression of the epidemic and the proportion of the supply and demand of medications. Moreover, Brown and Goodwin (24) pointed out that resource allocation guidance should be in alliance with anti-discriminatory criteria such as disability, socioeconomic status, race, and insurance status.

Favoring young patients (youngest first) was the outcome of an online survey completed by 586 US participants. The aim was to elicit the general public preferences to allocate ventilators for COVID-19 patients (25). This result is consistent with the proposed guiding ethical principles by Emanuel et al. (19), summarized in treating patients equally, prioritizing the worst-off, and maximizing social and individual benefits. This is also aligned with the Italian physicians' guidelines; give higher priority to the young patients when assigning intensive care supplies (16, 17). Another recent study, conducted in Jordan, collected a total of 754 responses from five different public groups: religion scholars (3.9%), physicians (22.0%), medical students (21.5%), allied health practitioners (16.2%), and lay people (36.3%). The survey was based on nine ethical principles for allocating medical resources: sickest-first, waiting list (order), youngest first, service, random, monetary contribution, survival, instrumental value, and individual behavior (26). Four groups (excluding physicians) favor sickest-first despite the age, while the physicians tend to choose combined criteria when allocating the scarce medical resources (26).

Usually, allocating medical resources is carefully assessed per-case in order to ensure the maximum benefits. However, at the time of crises, health care systems experienced extensive pressure and shortened in medical resources, despite the country's wealth. This is what most of the countries faced during the current pandemic, COVID-19, and hence allocating scarce medical resources was not a straight forward process. Combining more than one ethical principle to determine who should be given medical attention might be a good process to follow. This paper aims to identify the most commonly recommended ethical principles and provide recommendations for their applications. Furthermore, propose an ethical framework using fuzzy logic that guides clinicians' decisions in allocating medical resources to COVID-19 patients. This framework gives weight to patients based on five ethical principles identified according to WHO guidelines and state-of-the-art practices proposed in the literature. However, the proposed framework is solely based

on the ethical principles applied when allocating the currently available scarce medical resources to the current patients arriving at a hospital. The differences between rich and developing countries and considering per-hospital resources in addition to the availability of resources at different times in the same hospital were not within the scope of the proposed ethical framework.

IDENTIFIED ETHICAL PRINCIPLES

Based on current state-of-the-art practices proposed in the literature during the COVID-19 pandemic, five ethical principles that were commonly suggested and recommended are identified. The five principles are: anti-discrimination, prioritize the worst off, social effects, patient's history, and clinical evidence.

Fairness/Equality/Anti-discrimination

Allocate medical resources randomly among eligible patients. Resource allocation should not exclude patients based on race, age, religion, disability, origin, sexual orientation, gender, perceived quality of life, or any other type of discrimination. According to WHO, this principle must promote specific ethical values such as transparency, inclusiveness, consistency, and accountability (22). Transparency means that the decisions and justifications should be made public. Inclusiveness is relayed to allow decisions affected entities to influence the decision-making process and the decision itself. Consistency is to treat all persons in the same categories in the same way. Finally, accountability means that decision-makers should justify their allocation decisions and be held responsible (22).

Prioritize the Worst Off

To allocate medical resources to those most at risk or those in greatest medical need. This principle can be applied when it maximizes the expected post-treatment life-years. Thus, favoring younger patients or even sickest patients if it maximizes survival years (19).

Relational/Social Effects

To consider family responsibilities, such as children or elderly caretakers, and people who contributed or will have a potential contribution to the community, such as physicians, clinicians, and healthcare providers. This principle is being referred to as maximizing social benefits.

Patient's History

Patients already receiving a medical resource and/or drugs for other severe conditions should continue to receive it.

Clinical Evidence

Medical resource allocation should be evidence-based. This means allocating the resources to patient groups who have been shown by rigorous randomized clinical trials (RCTs) to benefit the most from the treatment provided.

RECOMMENDATIONS FOR THE APPLICATIONS OF THE IDENTIFIED ETHICAL PRINCIPLES

According to the WHO guidelines and the literature's best practices, the main recommendations on how to implement and apply the identified ethical principle are summarized below.

Fairness/Equality/Anti-discrimination

World Health Organization recommends that "each person's interest should count equally unless there are good reasons that justify the differential prioritization of resources" (22). WHO also advises that fairness must promote specific ethical values such as transparency, inclusiveness, consistency, and accountability (22). The equality principle justifies the allocation of resources by a lottery (22). According to DeJong et al. (23), a "first-come, first-served" approach should be avoided because it disadvantages those who experience barriers to seeking health care. Instead, a random allocation, such as a lottery, is the fairest way for drug allocation among eligible patients.

Moreover, they recommended that scarce medications be allocated fairly and be made accountable, transparent, proportionate to the situation, and responsive to those affected (23). However, from George Washington University Milken Institute, Adnan Hyder has pointed out that random allocation is challenging for patients with a similar prognosis since it assumes agreement among clinicians of prognostic indicators (27). Brown and Goodwin advised that ethical recommendations must be supplemented with explicit guidance against discrimination or an attempt to balance the concern for maximizing prognosis with concerns about social justice (24). Similarly, according to Liddell et al. (21), "principles must uphold the protected rights of all persons." Unless the patient/legal representative consents or unless ventilation is not clinically indicated, it is considered a criminal offense and a civil wrong to physically remove intubation.

Moreover, this could be a breach of Article 3 of the European Convention on Human Rights, which protects patients from inhuman and degrading treatment (21). DeJong et al. (23) recommended that "prioritization should not exclude patients based on age, disability, religion, race, or ethnicity, national origin, gender, sexual orientation, or perceived quality of life". However, Scheidegger et al. had recommended that age is a risk factor for mortality and must be taken into account (28). Kirkpatrick et al. (20) had also recommended that it is necessary to have special consideration to ensure fair distributions of medical resources, especially to patients with disabilities. The "first-come, first-served" approach is not the right approach for resource allocation. As stated by Berlinger et al. (29), "a critically ill patient waiting for an ICU bed might be better able to benefit from this resource than a patient already in the ICU whose condition is not improving." The random ethical principle (26) is highly recommended to ensure fairness. However, the order of registration (first-come, first-serve), monetary (contribution to

the costs of the treatment), and youngest first ethical principles should be avoided since these contradict the fairness principle.

Prioritize the Worst Off

According to the World Health Organization, this principle is appropriate to guide the allocation of resources for people at risk, such as providing vaccines for healthcare providers (22). Emanuel et al. (19) recommended that medical resources "should go first to front-line healthcare workers and those who care for ill patients and those who keep critical infrastructure operating." Likewise, Scheidegger et al. (28) had recommended that "professionals whose health is at greater risk in the event of infection with the coronavirus are to be especially protected." Based on their survey, Yousef et al. (26) have highlighted that the sickest patients are recommended to be considered first for scarce medical resources allocation. Moreover, the likelihood to survive the longest is also considered a priority for scarce medical resource allocation.

Relational/Social Effects

World Health Organization recommends giving priority to those who contributed or will have a potential contribution to the community, such as clinicians, healthcare providers, and first responders (22). Ethical analysis needs to account for relational effects representing a different value for decisions (27). However, a person's relationship with dependents is hard to assess in a crisis, and the assessment risks becoming a judgment of social worth (30). Emmanuel et al. (19) recommend that medical resources "should go first to front-line healthcare workers and others who care for ill patients and who keep critical infrastructure operating." Similarly, Yousef et al. (26) had considered giving priority to those who have essential roles for keeping society operational or have contributed in the past to the common good.

Patient's History

For existing FDA-approved medications, DeJong et al. (23) recommended that, with good evidence, patients already receiving the drug for other severe conditions or severe chronic diseases should continue to receive it.

Clinical Evidence

DeJong et al. (23) recommended that if there is no evidence that patients who suffer from special health conditions such as coronary artery disease, diabetes, and hypertension show a lower level of therapy response compared to other patients, then the former type of patients should be provided with new therapies. Moreover, they suggested that patient groups receive priority if sound evidence emerged that they have more considerable clinical benefits than others (23). This principle can guide the allocation of scarce resources that confer substantially different benefits to different individuals (22). Kirkpatrick et al. (20) had stated that reallocation of medical resources might occur after time-limited trials to see the evidence of recovery or improvement; otherwise, these resources may be reallocated to other patients. Scheidegger et al. (28) had recommended that the highest priority and intensive care should be given to patients whose condition will be improved with it but will suffer without it.

PROPOSED FUZZY ETHICAL FRAMEWORK

Allocating scarce medical resources at the time of crises, like COVID-19, is not a straight forward process and holds a bit of uncertainty. It is sometimes hard to apply only one principle, like youngest first, since physicians tend to assess the need by applying more than one principle at once to maximize the benefits. Therefore, a combined criterion (based on more than one principle) is often more preferred. This is highlighted in a recent comprehensive study conducted in Jordan to assess general public opinions regarding allocating scarce medical resources, and physicians tend to choose combined criteria while deciding who should be given medical attention first (26). Based on that, an ethical framework that combined multiple ethical principles to prioritize medical resource allocation decisions is proposed. Fuzzy Logic (31) was used to model this framework to handle the companion uncertainty.

The proposed fuzzy framework (**Figure 1**) is centered on the five identified ethical principles (previous section). The idea is to give the patient a weight that can serve as a decision-making factor when scarce medical resources are allocated. This weight is calculated based on the combination of these five ethical principles. For example, if a patient satisfies multiple principles, he/she will get a higher weight than others and hence more likely to get medical resources than others. The fuzzy framework can prioritize the different ethical principles in different settings, and this can vary based on different cultural, religious, and humanity-related factors.

Fuzzy Logic Overview

The fuzzy logic, first proposed by Zadeh in 1965, is defined as a set of elements with a degree of membership. Thus, instead of having a step value such as 0 or 1, a value can be between 0 and 1, like 0.4. The advantage of fuzzy logic is that it describes the problem in terms of linguistic variables, like age: old or young, making it a powerful tool for managing the vagueness and uncertainty efficiently (31). A Fuzzy inference system is an inference system based on fuzzy logic to infer values using a predefined set of rules. The inference system consists of three main steps: fuzzification, rules evaluation, and defuzzification (32). The inputs and outputs are variables that can have real numbers values. In the fuzzification step, real number inputs are mapped to the fuzzy domain by converting each value into a fuzzy value (linguistic term). For example, if the variable can have any value in the range [0, 1], say 0.3, then the fuzzy value that corresponds to this value is Low. On the other hand, if the input is 0.8, then the fuzzy value is High. Any value in between can be Moderate. In the second step, a set of predefined rules are evaluated. The rule has the following format assuming n fuzzy values for the input variable and m fuzzy values for the

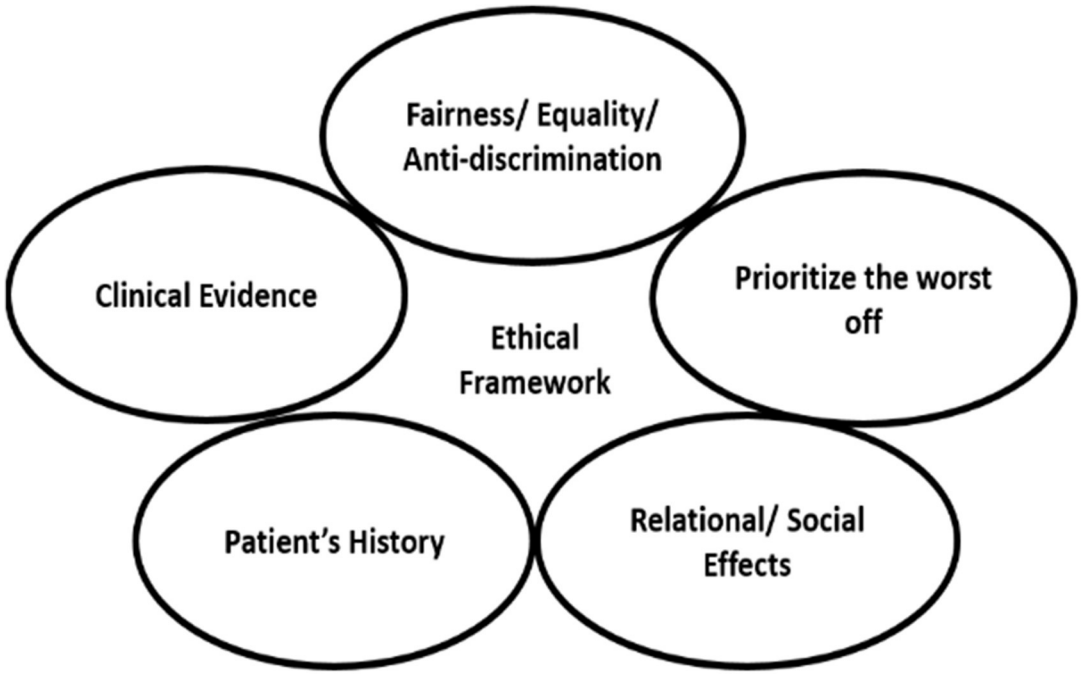

FIGURE 1 | The identified five ethical principles for the proposed fuzzy ethical framework of scarce medical resource allocation.

output variable:

$$IF\{Input - variable\ is\ Value_n\}THEN$$
$$\{Output - Variable\ is\ Value_m\}$$

The previous step's fuzzy output value is mapped back to the real numbers' domain in the last step.

Details of the Proposed Fuzzy Framework

The proposed ethical framework that is based on the fuzzy logic (**Figure 2**) takes the following inputs:

1. Condition Severeness (CS): this input is related to the "prioritize the worst off" ethical principle. This input's value is determined by the physicians/clinicians based on the patient's disease condition. The value is between 0 and 1. For example, values 0.3 or less indicate a non-severe condition, while 0.8 or more indicate a severe condition and any values in between indicate moderate condition.
2. Social Value (SV): this input is related to the "relational/social effects" ethical principle. This input's value is determined by the physicians/clinicians based on the patient's social impact. The value is between 0 and 1. For example, a nurse who is the only breadwinner for his/her family can be assigned a social value of 0.8, which indicates a high social impact, i.e., healthcare provider and family support, on the other hand, the social value for a single nurse can be 0.5 indicates a lower social impact, i.e., healthcare provider only.
3. Resource Usage History (RUH): this input is related to the "patient's history" ethical principle. This input's value is determined by the physicians/clinicians based on the patient's record on receiving a particular medical resource. The value is between 0 and 1. For example, a patient who is already receiving a medical resource can be assigned a RUH value of 0.8, which indicates a high priority to continue receiving the medical resource. On the other hand, a value of 0.3 indicates that the patient received medical resources in the past. A value of 0 indicates no previous record of receiving a particular medical resource.
4. Clinical Evidence (CE): this input is related to the "clinical evidence" ethical principle. The value of this input is determined by the physicians/clinicians based on any evidence of the benefit of receiving a particular medical resource. The value is between 0 and 1. For example, a patient who showed recovery or improvement evidence can be assigned a value of 0.8, which indicates a high priority to receive the medical resource. On the other hand, a value of 0.3 indicates that the patient's condition is improving slowly, thus, a lower priority to receive it. A value of 0 indicates no improvement of patient condition is noticed after receiving the medical resource.

The inference system's output is a weighted value (W), which indicates the level of the combined interaction between the four different ethical principles that were met. This output is calculated as a result of predefined rules (shown below). This weighted value can take five fuzzy values: VeryLow (VL), Low (L), Moderate (M), High (H), and VeryHigh (VH). These fuzzy values are then mapped to a value between 0 and 1. Below is an example of some fuzzy rules proposed for the ethical framework.

Fuzzy Inference Rules

IF {CS is H & SV is H & RUH is H & CE is H} THEN {W is VH}

IF {CS is H & SV is H & RUH is H & CE is L} THEN {W is H}

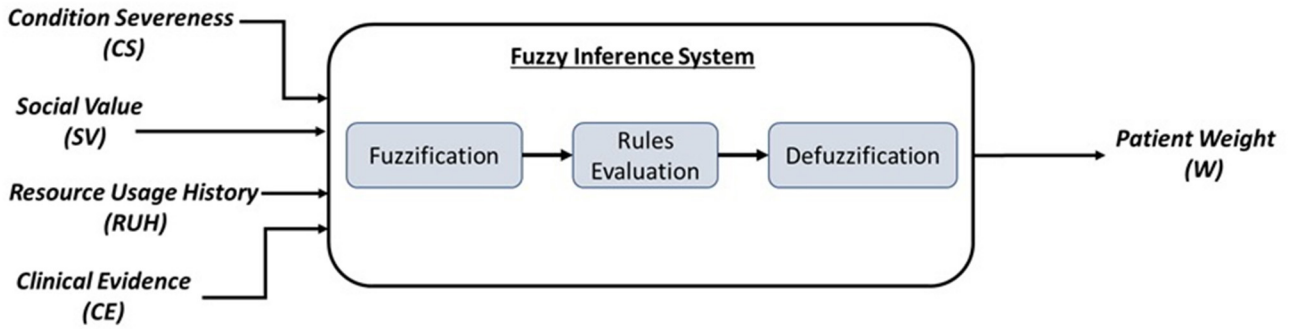

FIGURE 2 | The proposed fuzzy ethical framework components. Inputs: four ethical principles. Processing: three main stages. Output: a weight or decision factor per patient to determine his/her priority in receiving a medical resource.

IF {CS is H & SV is H & RUH is L & CE is L} THEN {W is M}
IF {CS is H & SV is L & RUH is L & CE is L} THEN {W is L}
IF {CS is L & SV is L & RUH is L & CE is L} THEN {W is VL}

- According to the first rule, if all the four ethical principles were favorably satisfied, then the weight is VeryHigh.
- According to the second rule, if three ethical principles were favorably satisfied, then the weight is High
- According to the third rule, if two ethical principles were favorably satisfied, then the weight is Moderate
- According to the fourth rule, if only one ethical principle was favorably satisfied, then the weight is Low
- And according to the last rule, if all the four ethical principles were not satisfied, then the weight is VeryLow

Note that the "Fairness/Equality/Anti-discrimination" ethical principle is implicitly satisfied by not considering the patient's age and gender in the framework. Moreover, this ethical principle is also satisfied when two or more patients have equal weights; accordingly, a random selection can be applied.

CONCLUSION

The massive disruption caused by the COVID-19 pandemic had uncovered the lack of readiness in the health systems regarding staff members and medical resources. The rapid and increasing number of infected patients in a short time and the severe medical complications accompanying the disease overwhelmed the health care infrastructure of many counties. Thus, clinicians had been in desperate need of practical and ethical recommendations to guide them while allocating and reallocating scarce resources for and between COVID-19 patients. This research identified the most commonly recommended ethical principles in accordance with WHO guidelines and literature's best practices and provide recommendations for their applications. Furthermore, it proposed an ethical framework based on fuzzy logic that can help clinicians and guide them in their decisions while allocating limited medical resources, like ICU beds and ventilators, to COVID-19 patients. This framework is aligned with the identified ethical principles and can also be applied in a similar future pandemic. Finally, expanding the current proposed fuzzy framework to consider not only ethical principles but also other per-hospital resource availability and other different restrictions globally worth investigating.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.600415/full#supplementary-material

Supplementary Figure 1 | The proposed ethical framework using the Mamdani inference system implemented in Matlab.

Supplementary Figure 2 | The membership functions of input variables.

Supplementary Figure 3 | The membership functions of the output variable.

Supplementary Figure 4 | Sample of the fuzzy inference rules.

Supplementary Figure 5 | The output weight variable is VeryHigh when all ethical principles are satisfied for a particular patient.

Supplementary Figure 6 | The output weight variable is Low when a single ethical principle is satisfied for a particular patient.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX

This appendix discusses the implementation of the proposed ethical framework using the Matlab Fuzzy Logic Toolkit. Firstly, we need to implement the structure of the fuzzy inference system. The proposed ethical framework consists of four input variables that correspond to the identified ethical principles, which are Condition Severeness (CS), Social Value (SV), Resource Usage History (RUH), and Clinical Evidence (CE) and one output variable, which is the Weight (W). **Supplementary Figure 1** shows the proposed framework as implemented by Matlab using Mamdani fuzzy inference. Each input variable is mapped to the following fuzzy values:

- Low is represented by a trapezoidal membership function, which takes four values to specify the range (0, 0, 0.1, 0.4). This means that any input value in this range will be considered as Low.
- Moderate is represented by a triangular membership function, which takes three values to specify the range (0.25, 0.5, 0.75). This means that any input value in this range will be considered as Moderate.
- High is represented by a trapezoidal membership function, which takes four values to specify the range (0.6, 0.9, 1, 1). This means that any input value in this range will be considered as High.

As illustrated in **Supplementary Figure 2**, the membership functions are overlapped to allow inputs to take two values in different membership functions. For example, an input value of 0.3 is considered both Low and Moderate since it intersects with both functions. The output variable W is represented in five fuzzy values (**Supplementary Figure 3**) as the following:

- VeryLow is represented by a trapezoidal membership function, which takes four values to specify the range (0, 0, 0.15, 0.3). This means that any output value in this range will be considered as VeryLow.
- Low is represented by a triangular membership function, which takes three values to specify the range (0.15, 0.3, 0.45). This means that any output value in this range will be considered as Low.
- Moderate is represented by a triangular membership function, which takes three values to specify the range (0.35, 0.5, 0.65). This means that any output value in this range will be considered as Moderate.
- High is represented by a triangular membership function, which takes three values to specify the range (0.55, 0.7, 0.85). This means that any output value in this range will be considered as High.
- VeryHigh is represented by a trapezoidal membership function, which takes four values to specify the range (0.7, 0.85, 1, 1). This means that any output value in this range will be considered as VeryHigh.

Secondly, after implementing the fuzzy inference inputs and output, we added the fuzzy rules. **Supplementary Figure 4** shows a sample of these rules. The fuzzy values for input variables will be matched with each rule. The rule will be applied when the condition part is satisfied (fully matched with the fuzzy inputs values); otherwise, the rule will not be selected. **Supplementary Figure 5** shows the applied rule when inputs have high values (when all ethical principles are met), which is rule number 1. As illustrated, the weight, in this case, is VeryHigh = 0.865. The scenario in **Supplementary Figure 6** is applied when the patient satisfies only a single ethical principle in which the weight is Low = 0.3.

frontiers in Medicine

ORIGINAL RESEARCH
published: 30 March 2021
doi: 10.3389/fmed.2021.620444

Ethical Challenges Related to the Novel Coronavirus (COVID-19) Outbreak: Interviews With Professionals From Saudi Arabia

Ghiath Alahmad, Hanie Richi, Ala'a BaniMustafa and Adel F. Almutairi*

King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia

The new and dangerous coronavirus disease (COVID-19) has posed a serious challenge to the ability of healthcare systems of many countries to contain the spread of the disease and to mitigate its various consequences. The disease posed many ethical challenges both in itself and in the methods used in its management. Although the ethical principles that healthcare operates under are universal, a thorough understanding of the ethical difficulties it poses necessitates consideration of contextual, societal, and cultural factors. This study provides an in-depth exploration of the ethical challenges related to the COVID-19 pandemic outbreak in relation to healthcare providers, medical researchers, and decision-makers in Saudi Arabia. Four themes were extracted from participants' responses, namely, ethical challenges about disease-control measures, challenges to actions in certain groups, challenges regarding software programs, and finally ethics in research practices. Each theme likewise contained sub-themes. The themes and sub-themes were discussed in light of the ethical principles: autonomy, beneficence, non-beneficence, and justice, as well as other principles, such as protecting confidentiality, privacy, and preventing stigma and discrimination.

Keywords: ethical challenges, COVID-19, professionals, ethical principles, Saudi Arabia

OPEN ACCESS

Edited by:
Maysa Al-Hussaini, King Hussein Cancer Center, Jordan

Reviewed by:
Peter David Stonier, King's College London, United Kingdom
Modupe O. Coker, Rutgers, The State University of New Jersey, United States

****Correspondence:***
Ghiath Alahmad
ghiathalahmad@hotmail.com; ahmadg@ngha.med.sa

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *22 October 2020*
Accepted: *08 March 2021*
Published: *30 March 2021*

Citation:
Alahmad G, Richi H, BaniMustafa A and Almutairi AF (2021) Ethical Challenges Related to the Novel Coronavirus (COVID-19) Outbreak: Interviews With Professionals From Saudi Arabia. Front. Med. 8:620444. doi: 10.3389/fmed.2021.620444

BACKGROUND

Novel diseases, such as Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome, that appeared within the past 20 years received interest in societies all around the globe. The new and dangerous disease COVID-19, which had its first outbreak bin December 2019 in Wuhan, China, and is known to cause severe pneumonia, has shaken healthcare systems all over the world (1). This alarmingly contagious virus is known to spread from one person to another through direct close contact in a similar manner to influenza, through respiratory droplets released when the infected person coughs or sneezes (2). Recently, coronavirus has spread to many parts of the world, through the travelers and Affected more than 41,093,074 people in 217 countries and the countries in the Gulf Cooperation Council (GCC) have 897,790 cases (as of October 21, 2020) (3–5). The death toll has reached 4,702 people, and unfortunately this figure is increasing. The World Health Organization officially assigned the outbreak to pandemic status on March 11, 2020.

The outbreak of COVID-19 has posed challenges to many countries and their ability to contain the spread of the virus. The evaluation of past experience with epidemic diseases can help shape the

response to future challenges. Planning strategies to tackle infectious disease outbreaks and advance preparation can lead to a rapid and strategic response to create a road to recovery. However, logistical challenges are linked to the recognition and identification of infectious disease outbreaks, which can impede the planning of effective strategies for control (6). Among the ethical concerns, for example, is the outbreak of an unknown organism.

When the strain of a virus that is causing a certain infectious disease is unknown, it is impossible to know what vaccines or medications are most appropriate should be looked to for the development of a treatment plan to combat the outbreak. The first development plan for pandemic vaccine preparation and stocking prior to an infectious disease outbreak poses the challenge of what to research, develop, and keep and stock for a what-if situation, upon which it can be made available for distribution and administration before the strain becomes known. One example of this can be seen in the case of HIV in the 1980s, which could not be diagnosed at that time, due to the poor state of knowledge of the disease and its agent. It was not until the year 2003 that a better understanding of the nature of the virus became available (7). It was only at this point that drug development, effective testing, and more scientific diagnoses emerged. Recent years have shown advances in the testing of HIV vaccines in clinical trials (8). This is similar to the case of the novel coronavirus (COVID-19), in particular regarding to unavailability of a vaccine, which may raise ethical concerns among researchers.

Due to the unavailability of a COVID-19 vaccine and to time pressure, experiments may be conducted that do not follow approved and well-established procedures, such as the performance of a thorough series of animal experiments before testing on humans. Even after an effective vaccine is developed, healthcare facilities will doubtless face a shortage vaccine due to the need for them all over the world. This poses the following question: how should healthcare organizations and their regulators handle this crisis? A rubric according to which the limited supply of vaccines can be administered to those who matter most is necessary. A potential order of prioritization might run as follows:

Healthcare practitioners who in direct contact with patients should be the first priority, followed by citizens at the highest risk, such as 65-year-olds who are already ill, and then individuals who have been hospitalized more broadly (8).

It is likely that in the case of an infectious disease outbreak, such as that of COVID-19, it can overwhelm medical care systems, as was seen in Italy, for example. In particular, the number of patients who needed ventilation outstripped intensive care unit capacity in many parts of Italy (9). This prompted criticism of government planners along both ethical and legal dimensions in regard to their failure to predict and adapt to the possibility of a pandemic disease (10). The most pressing matter here is deciding what to do when it reaches the point where hospitals cannot accept patients due to their capacities having been overwhelmed.

One potential remedy is to make alternative sites available and to use equipped volunteer caregivers. In addition, agencies should be most concerned about patients who have limited or even no health insurance coverage; that is, they should must respond with kindness, not simply leave patients to die. The challenge here is to honor the commitment to patient well-being and consequently, to the patient's civil rights.

Epidemic and pandemic disease outbreaks inevitably impact a country's economy negatively. It is necessary for public health planning and preparedness take into account death and citizens in a state of despair (7, 11–15). A major role that they play is taking cost into consideration and assigning the balance between benefit and risk. This entails the provision of appropriate healthcare needs that include agreement on fair procedures and conformity to legal rights, while ensuring a reasonable budget to keep disease under control.

Screening procedures to support early diagnosis and treatment are critical in an epidemic outbreak to patient recovery and to prevent further disease spread and to moderate government expenditure (6).

Most people who think that they have had exposure will voluntarily agree to be tested, but some may pose difficulties on this point, presenting a challenge for Public Health Services or healthcare authorities, who may have to authorize mandatory testing. This authorization, however, should only be used if voluntary and advisory means are unsuccessful.

In response to the effort to contain the spread of the debilitating infectious disease outbreak of COVID-19 and other potential pandemics or outbreaks that may follow, healthcare authorities and policy makers in many countries issued a statement that affected individuals should be quarantined or subjected to involuntary confinement (15). The ethical challenge here is in justifying how harmful it would be for an affected individual to mingle with the public at large. Quarantine may be appropriate if the disease is highly contagious. At this moment, it is mandatory that the individual to be quarantined has access to necessities, such as medical care and food and to be informed about his/her family to maintain quality of life. Here, it is important for there to be a balance between the spread of a disease and freedom from restrictions.

The question of whether it is appropriate to name quarantined individuals in the media is also concerning. From a public health practice point of view, this should be done because it allows doctors to trace infected individuals' location, perform medical evaluation if necessary, and help them with their treatment if needed. Individuals, however, must be granted the right to maintain their privacy (15, 16).

During the present COVID-19 pandemic, one way to prevent disease spread is to cancel public events, closing schools, workplaces, sporting venues, and restaurants (17). Doing this can be quite challenging, as school closings and rescheduling make it difficult to cover planned lessons. Further, such closures can produce immense economic impacts, especially on businesses such as restaurants, shopping centers, and entertainment venues.

Saudi Arabia has is observing the pandemic with great interest and conducting important research on COVID-19, and Saudi universities and research centers are establishing research programs and redirecting the financial support necessary to such efforts. Saudi Arabia ranked twenty-fifth in the world and first in

the Arab world in terms of its scientific publishing on COVID-19 (18), searching PubMed (on October 20, 2020) showed that there are 677 scientific papers published by researchers in Saudi Arabia, although none of these covered the ethical aspects of the pandemic. Saudi officials did attempt to establish ethical controls in the response to and management of COVID-19, as well as in researching it, particularly with regard to the National Committee of Bioethics, which issued a statement on research controls in times of epidemics and emergencies.

In this research project, we investigate ethical issues related to the COVID-19 outbreak. These findings will help address ethical questions at the individual, social, and organizational levels and will help develop guidelines that can be used by fellow clinicians, researchers, and policy makers in Saudi Arabia. We especially focus on the following issues, which are important but little researched issues in the Middle East.

METHODS

Study Design

This study adopted a qualitative research approach. In order to explore ethical challenges related to the COVID-19 pandemic in depth among professionals in Saudi Arabia, we conducted 24 interviews, with frontline healthcare providers (physicians and nurses) who specialize in treating infectious diseases, in addition to stakeholders and experts in the programs that manage COVID-19 outbreak, such as researchers and decision makers in Saudi Arabia, in King Abdul-Aziz Medical City, which includes King Abdullah Specialized Hospital and King Abdullah International Medical Research Center, in Riyadh, Saudi Arabia. Purposive sampling was used to recruit the participants (19), face to face interviews were conducted until saturation was reached (20). The interviews were conducted between May and September 2020. In order to identify the themes of importance, three interviews with three professional from different backgrounds were conducted. None of these three interviews were included in this study.

Participants and Data Collection

A phenomenological approach was used to collect data (19). Each semi-structured interview was conducted over 45–60 min. We began each encounter by giving a description of this study, explaining its objectives, assuring participants of their confidentiality, and asking for voluntary informed consent. The interviews used open-ended questions, following the interview guide, and began with demographic data. The interview questions were used to cover ethical considerations in relation to these topics, among others: outbreak of an unknown disease agent, vaccine shortages, drug treatment, experimental drugs, care shortages, occasions for screening, quarantine for suspected or confirmed infection, confidentiality and privacy, airlifts, travel restrictions, and cancelation of public events.

The interviews were conducted face to face and were audio-taped and transcribed. The interviews were conducted in places convenient to the interviewees.

Data Analysis

The inductive approach to qualitative data analysis was employed, which revolves around finding patterned meaning in data (21). Several particular steps were used, which including coding, searching, reviewing, defining themes, and identifying them. NVivo 11 software was used for analysis. The analysis was performed iteratively, which required the analyzer to move back and forth across the listed actions. The collected data were analyzed separately by the research team, and then the outcomes were compared to strengthen the analysis. Four main themes were produced by the analyses, and each theme contained subthemes.

Ethical Considerations and Consent Documents

Ethical approval was obtained from the IRB office at King Abdullah International Medical Research Centre KAIMRC, and informed consents were collected before starting the interviews. No identifier will be used, and privacy and confidentiality will be completely protected. Appropriate informed consent for qualitative research will be used.

RESULTS

Participant Characteristics

Individual Interviews were conducted with 24 healthcare providers and researchers working in Riyadh, Saudi Arabia, at King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, and King Abdullah Specialized Hospital in the National Guard for Health Affairs. All of the interviewees expressed their interest in working on COVID-19, describing it, managing it, and conducting medical research on it.

Nine of the participants were specialists in infectious diseases, five worked in experimental medicine, and two worked in intensive care units. Others had positions at laboratories where samples from COVID-19 patients were tested. Seven participants were IRB members who had examined research proposals for studies of COVID-19.

Seven of the participants were female, and the remainder were male. The interviews were with a variety of ages ranging from 30 to 60 years. Finally, 14 were Saudis, and the others were non-Saudis of different nationalities (**Table 1**).

Themes

Four main themes were found, each with a number of subthemes (**Table 2**).

Theme 1: Ethical Challenges Regarding Measures Taken to Control COVID-19

Preventing public gatherings and applying restrictions

The majority of participants were positive about the actions and decisions that the government took to ban various types of gathering. One participant explained:

"The measures taken by government to close down many economic activities and prevent social gatherings were necessary, and it was successful. It effectively reduced disease spread."

TABLE 1 | Characteristics of participants.

#	Sex	Nationality	Job Title	Specialty	Institute	Department
1	M	Non-Saudi	Research Scientist	Infectious Disease	KAIMRC	Medical Genomics Research
2	F	Saudi	Post-Doctoral Researcher	Infectious Disease	KAIMRC	Infectious Disease
3	F	Non-Saudi	Research Associate	Experimental Medicine	KAIMRC	Experimental Medicine
4	M	Saudi	Adjunct Research Scientist, Infectious Diseases Research	Infectious Disease	KAIMRC	Infectious Disease
5	M	Saudi	Post-Doctoral Researcher	Experimental Medicine	KAIMRC	Experimental Medicine
6	M	Saudi	Operations Administrator Laboratory Services	Laboratory	KAIMRC	Research Operation
7	M	Non-Saudi	Senior Research Scientist	Infectious Disease	KAIMRC	Nanomedicine
8	M	Non-Saudi	Associate Research Scientist	Experimental Medicine	KAIMRC	Experimental Medicine
9	M	Non-Saudi	Chairman, Senior Research Scientist	Infectious Disease	KAIMRC	Medical Research Core Facility
10	M	Non-Saudi	Research Scientist	Experimental Medicine	KAIMRC	Experimental Medicine
11	M	Non-Saudi	Clinical Research Coordinator	Infectious Disease	KAIMRC	Research Office
12	M	Non-Saudi	Senior Research Scientist	Experimental Medicine	KAMC	Experimental Medicine
13	M	Non-Saudi	Clinical Research Coordinator	IRB	KAIMRC	Institutional Review Board
14	M	Saudi	ICU consultant	Intensive Care Unit	KAMC	Intensive Care Unit
15	M	Saudi	ID Consultant	Infectious Disease	KAMC	Infectious Disease
16	M	Saudi	Professor of Genetics	Infectious Disease	KFSH	KFSH & RC
17	M	Non-Saudi	ICU consultant	Intensive Care Unit		Intensive Care Unit
18	F	Saudi	Associate Professor	IRB/Pharmacology	KSAU-HS	College of Pharmacy, KSAU-HS
19	M	Saudi	Chairman, Infectious Disease Research	Infectious Disease	KAIMRC	Infectious Disease Research Unit
20	M	Saudi	Assistant Professor Physiology	IRB/Physiology	SSAU	College of Medicine, KSAU-HS
21	F	Saudi	Assistant Professor of Pharmacology and Toxicology	IRB/Pharmacology	KSAU-HS	College of Pharmacy, KSAU-HS
22	F	Saudi	Consultant	IRB/Dental	KAMC	Orthodontics Division, Dental Service
23	F	Saudi	Consultant	IRB/Gynecology	KASCH	Division of Gynecology Oncology, Department of Oncology
24	F	Saudi	Consultant	IRB/Pediatric	KASCH	Pediatric, Intensivist–PICU-KASCH

Another said:

"The decision for shutdown—although it limited freedom and caused harm to some groups—it is ultimately in line with society's interests. This type of decision is really ethical."

Another participant said:

"COVID-19 status is like a wartime status, where difficult decisions must be made to protect people."

Closing schools and change teaching methods

One participant said:

"Although it was difficult, shifting teaching from the usual method to online teaching for millions of students at various stages from primary school to the university, was a huge step but in the correct direction."

Work changes in institutions and companies

Restrictions on gatherings were not limited to the people outside institutions but also inside them, including academic institutions, research centers, and hospitals.

One participant said:

"Our meetings now take place through Microsoft Teams. Teaching lectures as well. This was a positive step because it increases attendance percentages and is highly effective."

However, this opinion was not shared by all interviewees. Another participant said:

"The quality of performance in these online meetings is not the same as in usual physical meetings, which allows better communication, especially because in the most cases, people don't use video calls but only audio calls."

Prayer, the Umrah, and the Hajj

One of the restrictions that has been widely accepted by the participants is banning communal prayers in mosques and doing them only individually in homes.

A participant said:

"The decision to temporarily stop prayers in mosques was an excellent and necessary decision. It came early, at the correct time, and was effective in preventing disease spread."

Another said:

"The decision to stop communal prayers is compatible with Islamic law because it prevents harm to others."

Another participant explained:

"Temporarily banning prayers in mosques was a painful but wise and logical decision."

TABLE 2 | Themes and sub-themes.

Theme 1: Ethical challenges regarding measures taken to control COVID-19	Preventing public gatherings and applying restrictions
	Closing schools and change teaching methods
	Work changes in institutions and companies
	Banning Communal Prayer, the Umrah, and the Hajj
Theme 2: Ethical challenges regarding procedures and actions for certain groups	Screening of certain groups
	Isolation
	Protecting volunteers and healthcare providers
Theme 3: Ethical challenges of detecting COVID-19 and confidentiality issues	Software programs
	Exposing infected people names
Theme 4: Ethical challenges in COVID-19 research	Quantity of research and publication
	Uncertainty
	Resource distribution
	Not following correct experimental path

This was echoed in the ban on Umrah, a pilgrimage with some similarity to the Hajj, in which many visit Mecca and Medina, the two Muslim holy cities. One participant said:

"Banning Umrah at this time is an ethical and logical decision, and it is in accord with Islamic law."

One participant said:

"The decision that was made to limit the pilgrimage (Hajj) to very few pilgrims, closer to hundreds than to the usual few millions, was very wise, and it matches Islamic and ethical principles."

Theme 2: Ethical Challenges Regarding Procedures and Actions for Certain Groups

Screening of certain groups

The government introduced some restrictions for certain groups that are either exposed to more danger than others or that may cause disease spread. These restrictions included mandatory screening, isolation, and restricted transportation and visits.

One participant said:

"In some crowded collections of people where it is impossible to socially distance and where the health circumstances are not appropriate, screening of these groups specifically is very important and beneficial to the whole community in general."

Another said:

"Screening is important in some places, such as airports; however, surely we will not stop people in the streets for screening, this is not acceptable."

A participant said:

"Doing compulsory screening is a serious and painful issue, and we cannot do this in usual cases and forever. We can only do it when there is a strong justification for it."

One of the participants explained the compulsory screening of specific groups who were poor and living in a lousy environment:

"Doing free of charge screening of these vulnerable persons will help in offering them better protection and more justice."

Isolation

Isolation was applied for 14 days for two groups, namely, those returning from outside the country and those who have tested positive of COVID-19. The majority of interviewees agree on the isolation made by authorities.

One participant said:

"The government has done everything to bring home all nationals who are living abroad and offer them a good isolation environment, including hotels, and good and healthy places to reside."

Patient isolation is ethical obligation, as expressed by research participants. A researcher said:

"Quarantine limits freedom and social interactions and cause disturbance to social life. We must accept these social effects for good reason."

Harm prevention is a professional and ethical duty of healthcare providers.

One respondent said:

"If we know that someone is hiding an infection, we cannot simply ignore that. Action should be taken, starting with giving advice to this person and ending with reporting to the authorities."

Protecting volunteers and healthcare providers

The participation of healthcare providers in fighting against COVID-19 is considered to constitute a noble act because they are putting themselves at risk to help protect people and the community.

A participant said:

"Being close to COVID-19 patients—even only to do tests—increases the possible harm to healthcare providers. We should be grateful for and appreciate this kind of sacrifice."

Protection should be offered for these groups. One participant said:

"Healthcare providers should have sufficient protection because if they get infected, they will put those people around them at risk as well."

However, no pressure should be placed to force people to do any work that may put them in danger.

A participant said:

"Healthcare provider should not be abused by asking them to do some relevant or risky tasks."

Theme 3: Ethical Challenges of Detecting COVID-19 and Confidentiality Issues

Software programs

Some Software programs have been used to help control COVID-19 spread. General tendencies regarding the permissions enjoyed by such programs was expressed by the participants, however, they thought that more conditions should be taken into account. A participant said:

"Software tracking healthy and infected people has benefits; however, to minimize harm, we should review methods of

collecting and storing, manipulating, and utilizing information by any third party."

Another participant said:

"We should know enough and have enough information about any program of this type and its dimensions."

A participant said:

"The use of this type of software by governments and official authorities can be justified, but never by private parties."

Exposing infected people names

Our participants indicated that revealing the names of people who are infected or in touch with infected people may have some benefit.

A participant said:

"Revealing names is in fact helpful for protecting people."

However, according to some, revealing names will affect confidentiality and privacy.

One participant warned about the consequences of breaching confidentiality and revealing names:

"Knowing that a certain person is infected or potentially infected may lead to stigma against him."

A participant said:

"Fear of stigma may prevent others from declaring that they have COVID-19."

However, another participant expressed a different point of view:

"Stigma about COVID-19 is not strong as it is in other diseases, especially in genetic conditions. On the other hand, stigma can lead to bad results."

To avoid any negative series of events, some measures should be taken to keep from revealing any names, according to one participant:

"Any revealing of names should only be done by institutions to protect their employees."

Theme 4: Ethical Challenges in COVID-19 Research

Quantity of research and publication

It was noted that there has been great interest in research and publishing on COVID-19. For around half of our participants, this raised the question whether we really need all of it. One expressed this concern:

"We have at KAIMRC around 140 research proposals that use different methods and have different objectives. That seems good, but I doubt we need this number of studies."

Another participant:

"We need more information to develop a better understanding of the virus and the disease, however."

Another researcher did not see any problem in doing more research. He explained:

"Unlike MERS, which had few patients, the number of COVID-19 patients is large, and therefore they will not be exhausted by the medical experiments conducted on them, as happened to MERS patients."

Uncertainty

The largest challenge in dealing with COVID-19 is that we do not know what information to trust, and every day there is new information coming in that should be judged, discussed, and evaluated separately, although this information may not always be correct, and may even be contradictory.

One participant said:

"Although there is a huge amount of information, articles, lectures, and interviews, we have little concretely grounded knowledge."

Resource distribution

Conducting excessive research on COVID-19 may have a negative effect on resource distribution as expressed by many of the interviewees, which was expressed by one of the participants:

"I do appreciate that we need many clinical trials in order to find medications and develop vaccines; however, this will come at the expense of other research about other diseases. We need to have balance."

Another participant had a different opinion:

"Here, we have enough resources to conduct all needed research. For example, cancer research did not stop although it costs a lot."

Another participant considered that the change in resource distribution was acceptable, and he said:

"This is temporary, and everything will come back again after COVID-19 outbreak is finished."

Not following correct experimental path

Hurrying to publish papers may be risky and distort the relationship of mature and misleading information. According to nearly half of interviewees, the desire for rapid results may lead to a push to avoid following accepted steps in clinical trials. One of the participants expressed:

"Clinical trials seeking to find vaccines face the problem that they aren't follow the established stages of vaccine development, including animal experiments."

The same participant also said:

"The hope of finding effective and safe treatment faces the same problem, namely, passing stages before their time to get results in as soon as possible. This may have negative effects on the efficacy and safety of these new drugs."

DISCUSSIONS

The participants in this study expressed ethical challenges related to fighting COVID-19 especially those regarding preventing public gatherings, social or religious events, and questions. In particular, the challenges discussed related to limiting freedom, economic harms, social impact, ethical challenges related to forced screening and isolation, software that can affect freedom and decision making, and confidentiality, privacy, and the possibility of stigma and discrimination. Moreover, the participants mentioned the ethical challenges that accompany research and studies and how for this type research is beneficial to patients and communities, as well as how resources can be distributed for this kind of research, most importantly not following the correct scientific steps for conducting clinical trials.

In this discussion, we cover different dimensions of these challenges and their effects in the light of ethical standards and principles.

Facing COVID-19 Is an Ethical Duty

The state has an ethical duty because it is responsible for preventing gatherings and the transmission of disease among its population. Additionally, the citizens have an ethical duty not to participate, whether intentionally or unintentionally, in spreading this disease.

While COVID-19 is still being spread, the community, governments, and individuals must take action to reduce the spread of disease, including but not limited to preventing gatherings, decreasing economic activities, controlling teaching in schools and universities, and taking some other measures. This all is in pursuit of a high and important purpose, namely, to protect people during disasters. This has resulted in a Royal Decree in Saudi Arabia for this purpose, which later played a role in containing the disease the country (22, 23), which falls under the category of due diligence, which have been stated in the general international law (24) and the International Human rights law (25). This matches other aspects of law as well, such as Article 11 of the European Social Charter (26) and Article 12-1 of the International Covenant of Economic, Social and Cultural Rights (ICESCR) (27), among others.

The prevention of gathering also matches the Islamic law that Saudi Law is built on, which mentions the duty to protect persons and prevent harms. An example commonly used in support of this point is early Islamic states, where rulers forced people to isolate to prevent infectious disease (28).

On the other hand, the ethical duties that push people to accept social distancing has a different foundation, most importantly the feeling of responsibility, protecting oneself, avoiding disease, and self-interest, beyond altruism, with little concern for freedom, controlling the population for public interest and to protect others.

This ethical duty and necessity manifest as the need to prevent harm, produce benefits, respecting confidentiality and privacy, increasing justice, freedom, and responsibility, preserving and not wasting resources, protecting the vulnerable, and finally research integrity.

Ethical Duties in the Light of Bioethical Principles

The ethical that must be faced in COVID-19, can be summarized as the offer of a maximal amount of protection to society and the community and providing the highest standard of healthcare to patients, following international bioethical principles, which are similar to and largely match the ethical values of Saudi society.

The idea of doing no harm can is the clearest principle to follow for any step in controlling COVID-19, which would include banning gatherings and imposing social distance, and changing teaching to online teaching to offer protection to students and their families. Moreover, temporarily halting prayers in mosques that once hosted them five times per day may be its clearest manifestation, and this can be considered as among the strongest measures, which reflects the government intention to do what is necessary to control Covid-19. This decision received support from the religious authorities and Fatwa bodies (29).

Similarly, stopping the Umrah and reducing the Hajj to a very limited numbers of pilgrims, although it was a major drop in expected income to the state, follow suit. These decisions in the face of economic loss represent the government's desire to take all necessary steps.

Moreover, screening, isolation, and reporting also come under the principle of do no harm, and all were accepted by all of our research participants. These measures are similar to others taken by other countries around the world and are compatible with the recommendations of similar organizations and authorities (30), with the results of other authors (31).

The measure of preventing gatherings is supported by the do no harm principle and also by the beneficence principles, an important item for bioethics. While social distancing policies did contribute to preventing the spread of disease, they also offered protection to people, a direct personal benefit; likewise, institutions that enabled online communication among their employees contributed effectively to protecting them and consequently protecting their interests as a clear benefit.

Moreover, praying at home instead of at mosques goes beyond preventing the transmission of disease to others but also preventing them from being infected. Scanning also goes beyond protecting others, bringing direct benefit to the person who is screened, who can know what steps are necessary to take in the event of infection.

Due to the serious effects of COVID-19, which are increasing in vulnerable groups, such as elderly people, offering protection to them and preventing disease transmission among them should be considered an absolute ethical duty.

However, although social distance in all of its forms, screening, and isolation are important, they nevertheless contradict the autonomy principle, especially the measures are obligatory and compulsory. However, these imperatives should remain at an ethically acceptable level and be included under the headings of both individual responsibility and social solidarity (28).

One of the most important considerations, with comes with the risk of ethical violation, is that of privacy and confidentiality (32). In particular, this should caution against revealing the names of COVID-19 patients, which implies the need for a mechanism regarding revealing names and the importance of this measure (33).

Privacy and confidentiality are also at risk due to the use of software programs for detecting patients on their mobiles, which may be an important method for controlling the spread of the coronavirus (34), such that rapid tracing and discovery of newly infected cases can decrease the spread (35).

The risk will increase as violations occur and stigma or discrimination develops, which can involve risk to the lives of healthcare providers, patients, and survivors (36).

Participant concerns regarding stigma have been noted by other studies (37–39). Fear of stigma and discrimination can result in people hiding their symptoms of their infections, avoiding treatment, and avoiding testing until their condition

deteriorates (40), which will have a negative impact on the preventing of disease spread (41).

While performing compulsory screening for all may not be ethically acceptable, doing it for some vulnerable groups may offer them protection and achieve a certain degree of justice (42).

While the participants have many concerns regarding conducting research on COVID-19, social distancing did not negatively affect the number of medical studies. This relates to some questions that faced researchers in their research, such as ethical, legal, and management procedures needed to use information and confidential data (43).

Even though there is a critical need to do research in studies of COVID-19, accelerating them will have negative impact on medical research integrity, as was mentioned by our participants in this study and by mentioned by other authors (44, 45).

The solution comes from finding a balance between the benefits of doing research on the one hand and the risk of offering fast and immature knowledge, which can lead to incorrect clinical decisions, on the other (44).

Moreover, rapid medical research on COVID-19 especially clinical trials may in fact bring a higher degree of risk to participants, which contradicts the ethical principle to do no harm (46).

Doing unnecessary and rapid research can have a negative impact on other resources, especially when those resources are limited, rather than using them in study of other diseases, especially when these diseases have a significant impact.

These issues and ethical challenges in doing research on COVID-19 require the development of mechanisms to review research projects with special committees created for this purpose.

CONCLUSION

The participants in this study presented a range of opinions concerning the ethical aspects of the medical response to COVID-19, especially about preventing gatherings, doing screenings, and doing isolation, along with conducting research to develop new treatments or vaccines. The participants recalled the importance of preventing harm, beneficence, protecting vulnerable groups, maintaining confidentiality and privacy, and preventing stigma and discrimination. They also mentioned the important of maintaining research integrity to improve protection and avoid mistakes. However, some other issues remain neglected in our study, such as questions regarding intensive care, which requires further research.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The IRB at the National Guard Health Affairs. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors conceived and designed the study and contributed equally to the writing of this article. All authors contributed to manuscript revision and approved the final version of the manuscript.

FUNDING

King Abdullah International Medical Research Center KAIMRC funded this research (Grant Number: RYD-20-419810-57810).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 31 March 2021
doi: 10.3389/fmed.2021.618185

Deficiencies in Planning Interventional Trial Registration of COVID-19 in China

*Xiaodan Li[1], Shengzhao Zhang[2,5], Yiling Zhou[3], Ying Liu[2], Youlian Zhou[3], Sheyu Li[3,4] and Na Su[2,5]**

[1] Department of Gastroenterology, West China Hospital, Sichuan University, Chengdu, China, [2] Department of Pharmacy, West China Hospital, Sichuan University, Chengdu, China, [3] Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, China, [4] Department of Guideline and Rapid Recommendation, Cochrane China Center, MAGIC China Center, Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu, China, [5] West China School of Pharmacy, Sichuan University, Chengdu, China

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Edited by:
Maysa Al-Hussaini,
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Reviewed by:
Frits Lekkerkerker,
Consultant, Amsterdam, Netherlands
Haavi Morreim,
University of Tennessee Health Science Center (UTHSC), United States

***Correspondence:**
Na Su
zoya159@163.com

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: 16 October 2020
Accepted: 09 March 2021
Published: 31 March 2021

Citation:
Li X, Zhang S, Zhou Y, Liu Y, Zhou Y, Li S and Su N (2021) Deficiencies in Planning Interventional Trial Registration of COVID-19 in China. Front. Med. 8:618185. doi: 10.3389/fmed.2021.618185

Background: The coronavirus disease 2019 (COVID-19) pandemic has affected the world since late 2019. The efforts to control the spread of the virus need to be supported by credible evidence. Therefore, we analyzed the rationality of the timeline and geographic distribution of COVID-19 trial registration in mainland China.

Methods: We searched the Chinese Clinical Trial Registry (ChiCTR, http://www.chictr.org.cn/) and International Clinical Trials Registry Platform (ICTRP, https://www.who.int/ictrp/en/) using keywords including novel coronavirus, coronavirus pneumonia, 2019-nCoV, COVID-19, and SARS-COV-2 from 1 December 2019 to 27 April 2020 and included interventional randomized and non-randomized trials including patients with confirmed cases of COVID-19 in mainland China. The registered trials were reviewed, and data were independently extracted by two reviewers based on the inclusion criteria.

Results: A total of 263 registered interventional trials were included in the study. We defined the sample size index (SI) as the total number of patients needed by the trials divided by the total number of patients diagnosed with COVID-19. A total of 84,341 patients had been diagnosed with COVID-19 in China as of 26 April 2020, and the included trials had a combined sample size of 31,156 patients (SI: 0.37). After control of the COVID-19 epidemic was achieved in China (February 18, 2020), the SI was 1.54, suggesting that the number of patients needed by the trials was greater than the number of newly diagnosed patients. The SIs in 8 out of 26 provinces in mainland China were >1.

Conclusions: Our results suggested a clear over registration of COVID-19 trials in China, especially after control of the pandemic was achieved, preventing the generation of high-quality evidence.

Keywords: COVID-19, SARS-CoV-2, interventional trials, registries, China, sample size index

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has affected the world since late 2019 (1, 2). The efforts to control the spread of the virus need to be supported by credible evidence, and the performance of clinical trials and publication of the results substantially assist in the public health control and clinical management of the disease (3, 4). However, a waste of research resources has also been reported (5, 6). China was the first country to respond to the pandemic and published the earliest randomized controlled trials (RCTs) pertaining to COVID-19 (7–10). Since the number of newly diagnosed cases dramatically dropped in China starting in late February, many ongoing trials may face competition with other trials with regard to recruitment because of the limited number of patients. In addition, new trials pertaining to COVID-19 were still registered. In the current study, we analyze the rationality of the timeline and geographic distribution of COVID-19 trial registration in mainland China.

MATERIALS AND METHODS

Data Source

We searched the Chinese Clinical Trial Registry (ChiCTR, http://www.chictr.org.cn/) and International Clinical Trials Registry Platform (ICTRP, https://www.who.int/ictrp/en/) using keywords including novel coronavirus, coronavirus pneumonia, 2019-nCoV, COVID-19, and SARS-COV-2 from 1 December 2019 to 27 April 2020 and included interventional randomized and non-randomized trials that included patients with confirmed cases of COVID-19 in mainland China. Registered trials were included if they: (1) involved patients with confirmed cases of COVID-19; (2) were interventional clinical trials; (3) were single-arm or controlled; and (4) were conducted in mainland China.

Two authors (XL, SZ) obtained the number of patients in each province from the National Health Commission of the People's Republic of China (http://www.nhc.gov.cn/).

Data Extraction

Two authors (XL, SZ) independently extracted the number of confirmed cases with COVID-19 in each province per day and the following data of included clinical trials, registration number, date of registration, public title, applicant's institution, ethical approval, study type, study design, study phase, inclusion criteria, exclusion criteria, randomization, blinding, study period, funding, interventions, sample size, research setting, main outcomes, and surrogate outcomes including adverse events, imageological examination, laboratory examination, viral nucleic acid, pulmonary function, measuring scale assessing and recovery time/length of stay. These extracted data were cross-checked, and any discrepancies were resolved through discussion or negotiation with a third party.

The trial location was defined as the province where patients were recruited. For a multicenter trial which did not report exact number or percentage of participants from each province, its sample size would be evenly distributed among these provinces by one author (YZ).

Data Analyses

The data were double-entered and cross-checked using Excel 2019 for the preliminary extraction of the data pertaining to the registered trials. We summarized the number of newly confirmed cases per day, the cumulative number of confirmed cases, sample size of newly registered trials per day, and the cumulative sample size of registered trials from 1 December 2019 to 27 April 2020. We calculated sample size index (SI) using the total number of patients needed by the trials divided by the total number of patients diagnosed with COVID-19. An SI >1 suggests some trials could not be completed unless some patients were involved in more than one trial. We divided the data into two groups using February 18 as the cut-off point. We generated heat maps and time diagrams in R Studio (version 3.6.1).

RESULTS

A total of 721 registered studies were retrieved, including 625 from ChiCTR and 96 from the WHO ICTRP. After screening the registration information, 263 registered trials with a total sample size of 31,156 participants were included in the final analysis. The reasons for the exclusions were as follows: (1) epidemiologic studies ($n = 125$); (2) not related to COVID-19 ($n = 70$); (3) revocation of authorization ($n = 52$); (4) not interventional studies ($n = 172$); (5) discharged patients ($n = 34$); (6) duplicate registration ($n = 5$). A total of 84,341 patients had been diagnosed with COVID-19 by 26 April 2020, and the overall SI was 0.37. This suggests that every one in three patients with COVID-19 needed to participate in a trial to facilitate the completion of all trials.

Baseline Characteristics of Registered Trials

The registered study locations were distributed across 26 provinces and municipalities in mainland China, and 26 were multicentre clinical studies. The first trial was registered on 23 January 2020. There were 183 RCTs (69.6%), 38 non-randomized controlled trials (14.4%), and 42 single-arm trials (16.0%). Only 191 registered trials (72.6%) obtained ethical approval, and 38 (20.8% among the RCTs) used blinding. The median sample size was 78 (range: 4 to 1,000). There were 240 (91.3%) principle investigators who belonged to medical institutions. As shown in **Table 1**, the interventions included drug therapy (138, 52.5%), non-drug therapy (47, 17.9%) and alternative therapy (78, 29.7%). Alternative therapy including Chinese traditional medicine (72, 27.4%), non-drug therapy in Chinese traditional medicine (5, 1.9%) and other alternative therapy (1, 0.4%). The outcomes included patient-important outcomes (70, 26.6%) and surrogate outcomes (193, 73.4%).

Over Registration of Trials Based on the Timeline

As shown in **Figure 1**, the number of new patients diagnosed with COVID-19 per day was greater than the number of new patients needed by the trials per day during the COVID-19 outbreak until February 18, which made recruitment feasible. On February

TABLE 1 | The baseline of the included registered trials.

		Number (*n*)
The number of registered trials		263
Intervention	Drug therapy	138
	Non-drug therapy	47
	Alternative therapy	78
	Chinese Traditional Medicine	72
	Non-drug therapy in Chinese Traditional Medicine	5
	Other alternative therapy	1
Outcome	Patient-important outcome(s)	70
	Surrogate outcome(s)	193

Drug therapy: Drugs for gastrointestinal disorders; Drugs for blood and blood forming organs; Drugs for cardiovascular; Hormone; Anti-infectious drugs; Antitumor and immune drugs; Nervous system drugs; Antiparasitic drugs; Respiratory system durgs; Other drugs; A combination of the two drugs (western medicine); Triple therapy (western medicine).
Non-drug therapy: Respiratory support; Respiratory rehabilitation training; Dialysis treatment; nutrition support; Psychological therapy; Microecology/Light therapy/Mongolian medicine; Stem cell therapy.
Chinese Traditional Medicine: Traditional Chinese Medicine decoction pieces; Chinese Traditional medicine; Traditional Chinese medicine injection; Combination of Chinese and western medicine.
Non-drug therapy in Chinese Traditional Medicine: Acupoint treatment; Others.
Other alternative therapy: probiotics.
Patient-important outcome(s): Death or cure; Cure rate.
Surrogate outcome(s): Adverse outcomes; Imageological examination; Laboratory examination; Viral Nucleic Acid; Pulmonary function; Measuring scale assessing; Recovery time/length of stay.

18, 982 new patients were needed by the trials, and there were 1,751 new patients diagnosed with COVID-19 (SI: 0.56), but on February 19, 1850 new patients were needed by the trials, and 723 new patients were diagnosed with COVID-19 (SI: 2.56). From starting on February 19 until 26 April, the number of new patients diagnosed with COVID-19 per day and the number of new patients needed by the trials per day fluctuated slightly, and on April 26, the number of new patients needed by the trials per day was greater than the number of new patients diagnosed with COVID-19 per day.

As shown in **Figure 2**, 74,279 patients had been diagnosed with COVID-19 as of 18 February 2020 in China, at which point the registered trials needed to include 15,640 patients (SI: 0.21). After 18 February 2020, only 10,062 patients were newly diagnosed with COVID-19, but the inclusion of 15,516 new patients (SI: 1.54) was planned by the registered trials. The trials registered after 18 February 2020 needed too many patients to complete, and these trials may not be feasible.

Over Registration of Trials by Location

Among the 26 provinces with registered trials in mainland China, the SIs of eight provinces were >1 (**Figure 3**). The top-five provinces were Beijing (SI: 4.64), Shanghai (SI: 3.85), Guizhou (SI: 2.72), Zhejiang (SI: 2.24), and Guangdong (SI: 1.74). All of these provinces except Guizhou Province are in East China. This means that the patients in Beijing would have to participate in an average of 4.64 trials to facilitate the completion of all the trials. The SI was 0.2 in Hubei Province, of which the cumulative confirmed cases represented 82.3% of total ones in China as of 26 April in China.

DISCUSSION

Our study showed that the timeline and geographic distribution of the COVID-19 trial registration in mainland China were unreasonable. The imbalanced distribution of the trial registration may be associated with the capacity for medical research across provinces. Novel therapies are urgently needed to address the COVID-19 crisis; however, our results suggest that many trials registered after 18 February, and those registered in the provinces with SIs >1 may not be completed because of competition for participants. This over-registration leads to the failure of trials. Many trials have had to terminate after recruiting a small number of patients before they could generate credible conclusions. Well-designed multicentre trials addressing important questions changed current practices relatively more efficiently (11), especially given the limited number of patients.

According to the basic information of the registered clinical trials included in this study, only 2/3 of the trials were randomized, and 20% of them performed blinding. The minimum sample size of the included registered studies was only 4, which is inadequate, making it difficult to produce meaningful conclusions. This suggests that the overall quality of the designs of these trials needs improvement, which is consistent with previous reports (12, 13). The median sample size of each trial was limited, but the overall sample size was large due to the fact that there were many trials. Over-registration may lead to excess trials, leading to the overexploitation of research sources by underpowered trials.

Over-registration may be caused by lacking of collaborations between researchers and institutes and the imbalanced distribution of medical services and research resources. The hospitals treating most patients with COVID-19 may not have the capacity to plan and conduct the trials. The feasibility of these trials thus may not be adequately considered, including the relevance of the topic, the appropriateness of the study design, and the calculation of the sample size. As there is no feedback system auditing trials without results, investigators may not adequately consider the consequences of the premature suspension of the trial on the availability of adequate financial support for COVID-19 research. A credit system to audit these prematurely suspended trials (e.g., not allowing investigators of these trials to register again in the system) may also help reduce over-registration.

Based on our analysis, the proportion of the surrogate outcome was too high. The registered studies used surrogate outcomes as the study endpoints instead of patient-important outcomes, which is a serious violation of the original intent of the registration of clinical trials involving patients with both mild and severe disease, making it impossible to determine the effectiveness of the interventions even if the studies are successfully performed. In addition, although Chinese traditional medicine therapy is important in China, it is over-represented in the registered trials. Instead of

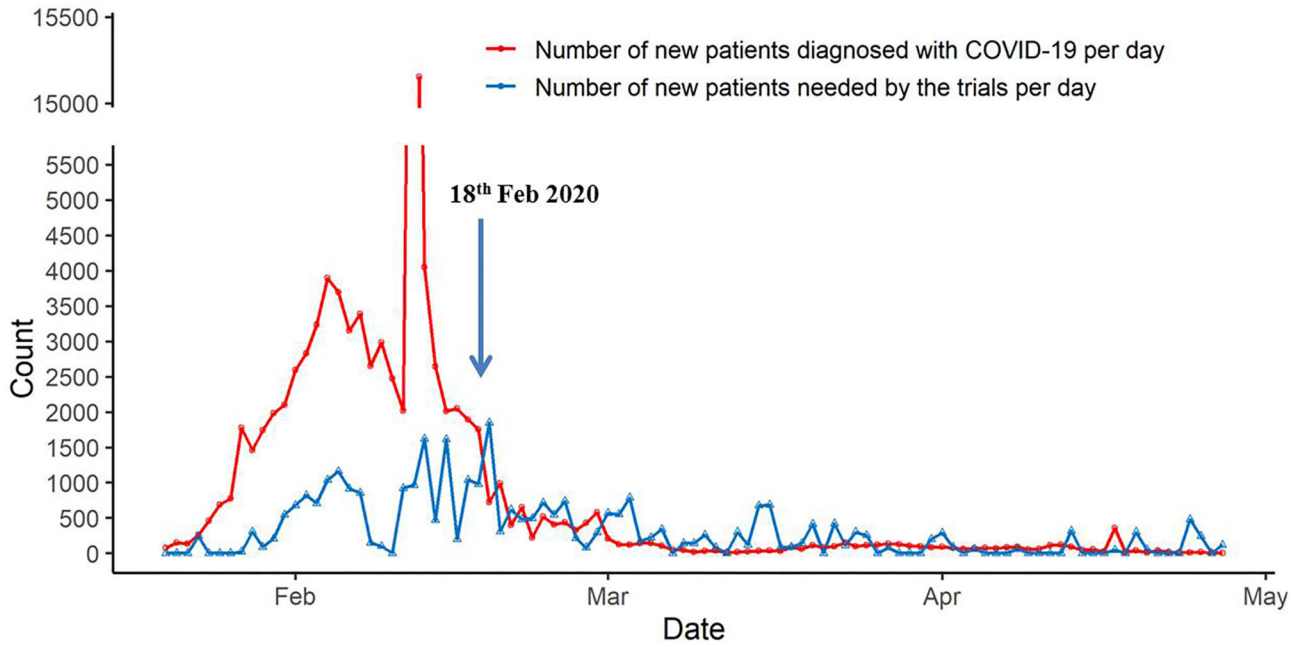

FIGURE 1 | The timeline of new sample size needed by the trials and the new cases with COVID-19.

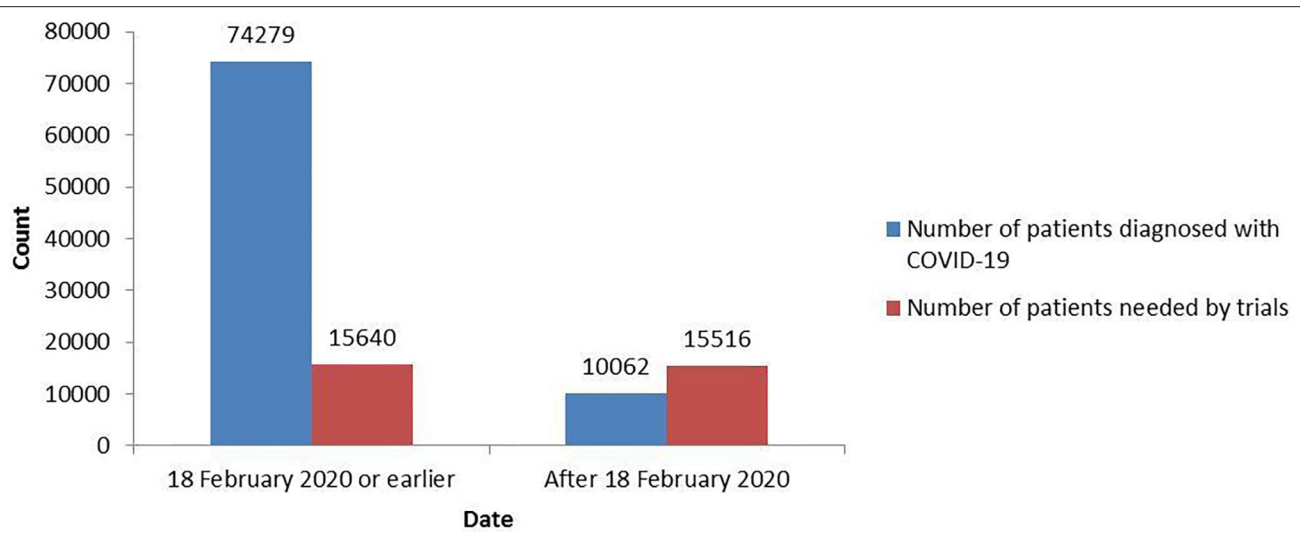

FIGURE 2 | The total number of patients needed by the COVID-19 trials and the total number of patients diagnosed with COVID-19 before and after 18 February 2020.

focusing on Chinese traditional medicine, we should perform more clinical trials on antiviral drugs, such as chloroquine and lopinavir/ritonavir.

Paul P. Glazious et al., in an editorial in the BMJ (14), pointed out that the number of COVID-related registered trials is large, but too many of them have small sample sizes, inaccurate designs and duplicate aims, which not only limits the possible benefits of the research but also wastes a substantial amount of resources. Sanders et al.'s review in JAMA (15) concluded that the number of relevant trials is growing rapidly, but there is still a substantial lack of RCTs among the currently registered studies, and to date, no effective drug treatment has been identified. The timely registration of trials should culminate in the publication of study results; however, the results thus far published have limited clinical implications. It should also be noted that the indirectness between clinical trials and real-world practice (16). Observational studies based on real-world data are equally necessary.

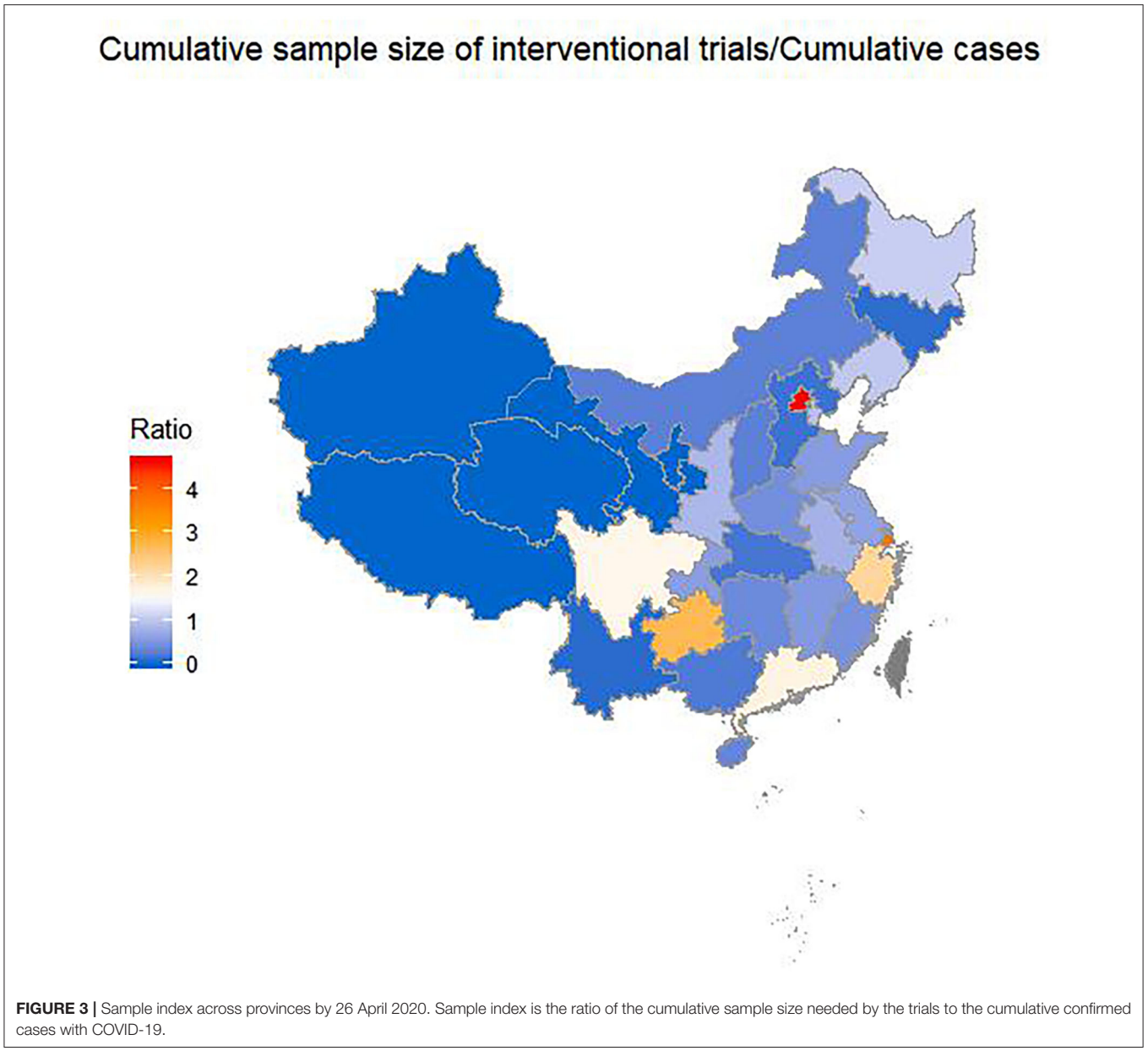

FIGURE 3 | Sample index across provinces by 26 April 2020. Sample index is the ratio of the cumulative sample size needed by the trials to the cumulative confirmed cases with COVID-19.

CONCLUSION

Our study shows a clear over-registration of trials pertaining to COVID-19 in China, especially after control of the pandemic was achieved. We call for the proper regulation of trial registration and broader collaboration before designing a trial, especially during this public health crisis in China and other countries. A credit system to prevent the investigators of prematurely terminated trials from registering another study may be necessary in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

XL, SL, and NS: conceiving this study. XL, SZ, and YoZ: collecting the data. YL and YiZ: performing the analyses and illustrated the figures. XL, YL, SL, and NS: writing draft. All authors contributed to the article and approved the submitted version.

FUNDING

NS was supported by grants from Health Commission Program (Grant Number 2020-111) and 1.3.5 Project for

Disciplines of Excellence, West China Hospital, Sichuan University (Grant Number 2018HXFH048). SL was supported by grants from the National Natural Science Foundation of China (Grant Number 21534008), Sichuan Science and Technology Program (Grant Number 2019YFH0150), and 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (Grant Number ZYGD18022 and 2020HXF011).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 15 April 2021
doi: 10.3389/fpsyt.2021.580067

Adverse Psychological Reactions and Psychological Aids for Medical Staff During the COVID-19 Outbreak in China

Qinji Su[1†], *Xiaoyun Ma*[2†], *Shun Liu*[2], *Shaogang Liu*[3], *Bernard A. Goodman*[4], *Miaoyu Yu*[1*] *and Wenbin Guo*[1,5*]

[1] Mental Health Center, The Second Affiliated Hospital, Guangxi Medical University, Nanning, China, [2] Department of Epidemiology, School of Public Health, Guangxi Medical University, Nanning, China, [3] Guangxi Key Laboratory of Chemistry and Engineering of Forest Products, School of Chemistry and Chemical Engineering, Guangxi University for Nationalities, Nanning, China, [4] School of Physical Science and Technology, Guangxi University, Nanning, China, [5] Department of Psychiatry, National Clinical Research Center for Mental Disorders, The Second Xiangya Hospital of Central South University, Changsha, China

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Edited by:
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Universidad Internacional de La Rioja, Spain
Muhammad Salman,
University of Lahore, Pakistan

***Correspondence:**
Wenbin Guo
guowenbin76@csu.edu.cn
Miaoyu Yu
yuliuyu01@sina.com

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Public Mental Health, a section of the journal Frontiers in Psychiatry

Received: 04 July 2020
Accepted: 18 March 2021
Published: 15 April 2021

Citation:
Su Q, Ma X, Liu S, Liu S, Goodman BA, Yu M and Guo W (2021) Adverse Psychological Reactions and Psychological Aids for Medical Staff During the COVID-19 Outbreak in China. Front. Psychiatry 12:580067. doi: 10.3389/fpsyt.2021.580067

Background: The outbreak of the novel coronavirus disease COVID-19 caused panic and psychological stress throughout the World. We investigated the extent of adverse psychological reactions in two medical staff groups in China, and explored the importance of online psychological assistance for them.

Methods: A cross-sectional online survey including Hospital Anxiety and Depression Scale (HADS) and Insomnia Severity Index (ISI) was utilized to assess anxiety, depression, and insomnia. Propensity score matching (PSM) was applied to match sex and age between the two groups. Differences in the prevalence of adverse psychological reactions between the two groups were compared by a Chi-square test. A multivariate logistic regression analysis was utilized to search for associated adverse psychological reaction factors of two groups.

Results: A total of 2,920 medical staff took part in the survey, including 470 frontline and 2,450 non-frontline medical staff. The risk of the frontline group experiencing anxiety, depression, insomnia-early, insomnia-middle, and insomnia-late were 1.16, 1.28, 1.26, 1.22, 1.28 times those of the non-frontline group after PSM. For frontline medical staff, the spinsterhood state (OR = 1.23, 95% CI: 1.00–1.51; $P = 0.05$) was a risk factor for anxiety. Bachelor or college degree (OR = 2.23, 95% CI: 1.24–4.02, $P = 0.01$) and a contact history with COVID-19 patients (OR = 1.62, 95% CI: 1.10–2.40; $P = 0.02$) were risk factors for insomnia. For non-frontline medical staff, being a woman (OR = 1.49, 95% CI: 1.08–2.06, $P = 0.01$) was a risk factor for anxiety, whilst being in a middle age group was a protective factor for anxiety (OR = 0.70, 95% CI: 0.50–0.99, $P = 0.04$) and depression (OR = 0.65, 95% CI: 0.45–0.93, $P = 0.02$). Being a woman (OR = 1.47, 95% CI: 1.14–1.89, $P = 0.003$) and working in a COVID-19 unit (OR = 1.31, 95% CI: 1.11–1.54, $P = 0.001$) were risk factors for insomnia, whilst the spinsterhood state (OR = 0.80, 95% CI: 0.67–0.95; $P = 0.01$) was a protective factor for insomnia. Online forms of psychological aid were all popular with medical staff.

Conclusions: The prevalence of anxiety, depression, and insomnia in frontline medical staff was significantly higher than in the non-frontline group. Appropriate intervention methods should be adopted according to the different influencing factors of the two groups. Online psychological aid was the preferred mechanism for relieving psychological problems.

Keywords: COVID-19, medical staff, anxiety, depression, insomnia

INTRODUCTION

The rapid spread of the novel coronavirus disease COVID-19 resulted in a pandemic affecting more than 100 countries in the first few months of 2020 (1), and created an unprecedented challenge to patients and health care systems (2). According to the World Health Organization (WHO), as of 21 May 2020 confirmed cases numbered 4,893,186 with a death toll of 323,256 (3). In China, a total of 82,971 confirmed cases and 4,634 deaths were reported by the National Health Commission of China for the period to 24:00 on May 20 (4).

The generation of virus-laden respiratory droplets combined with high transmissibility led to rapid human-to-human transmission of COVID-19 (5, 6). Faced with such a critical respiratory infectious disease, varying degrees of anxiety, depression, stress, and psychological reactions were observed in Chinese citizens at the beginning of the outbreak of COVID-19 (7). Furthermore, residents of Hong Kong experienced high perceived susceptibility and severity (8), whilst Twitter users experienced increased anxiety, depression and indignation, and decreased Oxford happiness index (9). In order to alleviate the adverse psychological reactions of social groups, the State Council issued a guideline for a hotline to provide psychological support, counseling, crisis intervention, and other services for various groups involved in epidemic prevention and control (9). However, no specific attention was paid to psychological intervention for medical staff. With the rapid increase in the number of patients with COVID-19 dependent on health care systems, medical staff experienced acute physical and mental burdens, as a result of a soaring workload, separation from families, and fear of becoming infected themselves. This was especially concerning for frontline medical staff who were directly engaged in diagnosis, treatment, and care for patients with COVID-19 (10, 11). Previous studies based on the SARS outbreak in 2003 reported that medical staff suffered adverse psychological reactions, such as, stress, psychological distress, anxiety, depression, and insomnia (12–14), and recent research has suggested that the COVID-19 outbreak posed a huge threat for the development of anxiety, depression, and insomnia in medical staff (15–17). Such negative psychological reactions not only weaken the attention, understanding, and decision-making ability of medical staff, but also result in deterioration in physical health, reluctance to work in potentially dangerous environments, with resignation from hospitals even being considered (18–20).

Anxiety and depression are the most common emotional responses when people are faced with unknown or known threats, which frequently coexist (21, 22). Long periods of anxiety and depression can disrupt normal physiological functions, as well as the immune system (23), and may also be a cause of insomnia (15). Furthermore, poor sleep quality is also detrimental to the functioning of the immune system, and thus, increases vulnerability to the virus (24). On the basis of evidence from the SARS outbreak in 2003, we hypothesized that frontline medical staff might be prone to suffer from anxiety, depression, and insomnia as a result of the high-stress situation of the COVID-19 outbreak, and that it is critical that they receive regular assessments of their mental health status for timely identification of problems and for addressing their psychological status.

Psychological aids from mental health workers can usually detect mental health problems, and provide targeted suggestions for medical staff. However, because of the high transmissibility of COVID-19, there was little free time available for frontline medical staff, and face-to-face counseling was no longer appropriate for them. A recent cross-sectional survey showed that psychotherapy has a major role to relieve the stress level of Spanish healthcare workers during the outbreak of COVID-19 (25). As a consequence, we investigated the contents and forms of psychological aid preferred by medical staff, and our findings may thus provide policy advice for the prevention and treatment of mental health problems in other prolonged high stress situations.

In this study, we aimed to assess the levels of anxiety, depression, and insomnia and compared results between frontline and non-frontline medical staff groups. Moreover, we specifically aimed to identify latent influencing factors of adverse psychological reactions in the two medical staff groups in order to provide evidence for alleviating the severity of anxiety, depression, and insomnia disorders in medical staff in the future. Furthermore, the survey of psychological aid modes should be of value to medical practitioners involved in control of the COVID-19 pandemic.

METHODS

Study Design and Data Collection

A cross-sectional online survey was designed to assess the mental health status of medical staff. We adopted a free online questionnaire survey platform (SO JUMP; http://www.sojump.com) (26, 27) *via* the WeChat or QQ of the tencent social media network and DingTalk to collect data from respondents. In order to ensure the quality of the questionnaire, we carried out a preliminary survey, and then modified it according to feedback from respondents. The questionnaire information is

detailed in **Supplementary Materials 1, 2**. In order to guarantee confidentiality of personal information, respondents were permitted to answer questionnaires anonymously from 3 to 17 February, 2020. Informed consent was obtained from each participant, and the study was approved by the Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University (No. 2020-KY0004).

Demographic Information

All subjects enrolled in the survey were medical staff. Demographic information focused on sex (men and women), age (≤28, 29–40, >40), educational level (<Undergraduate/junior college, Undergraduate/junior college, ≥Postgraduate), marital status (widowed/divorced, married, single), medical staff group (frontline and non-frontline), region (non-risk, low-risk, medium-risk, and high-risk), history of contact with patients with COVID-19 (positive and negative), and the COVID-19 unit (positive and negative). The frontline medical staff were engaged directly in diagnosis, treatment, and care for patients with COVID-19. The classification of zone was based on the epidemic risk level query website (https://bmfw.www.gov.cn/yqfxdjcx/index.html). Most subjects enrolled in the present study were from a low-risk zone. Positive COVID-19 unit meant this hospital received and treated patients with COVID-19.

Hospital Anxiety and Depression Scale

The Chinese version of HADS was used to identify the presence of anxiety and depression disorder in the medical staff (28). This questionnaire comprised two subscales of anxiety (HADS-A) and depression (HADS-D), and each subscale contained seven self-assessment screening items. The score of each item was deemed as 0 (never), 1 (mild), 2 (moderate), or 3 (severe). Overall, the total scores of HADS-A and HADS-D were classified as normal (0–7) and anxiety or depressive (8–21) with higher scores indicating higher levels of symptoms.

Insomnia

In order to investigate whether the respondents had symptoms of insomnia and to assess its severity, we designed four questions according to the Chinese version of the Insomnia Severity Index (ISI) (29, 30); these were classified as insomnia-early, insomnia-middle, and insomnia-late. Insomnia - early means difficulty initiating sleep, insomnia-middle means difficulty maintaining sleep, and insomnia-late means waking up too early and not being able to fall back asleep. In addition to these questions, we attempted to evaluate sleep quality through questions of sleep mode satisfaction. The answer to each question was evaluated as 0 (never), 1 (mild), 2 (moderate), 3 (severe), or 4 (extremely severe), and classified in two levels: normal (0) and abnormal (1–4).

Psychological Aid

We designed three questions to probe whether psychological aid was necessary in order to perform medical work, and assessed the need for psychological aid, along with its forms and contents. For the questions on "the forms of psychological aid" and "the contents of psychological aid," participants were able to choose more than one option.

Statistical Analysis

Respondents were divided into frontline and non-frontline medical staff groups, and their demographic information and mental health status scores were presented as frequency distributions (numbers and percentages). The 1:1 ratio propensity score matching (PSM) method was applied to match sociodemographic characteristics such as sex and age between frontline and non-frontline medical staff groups in order to eliminate the influence of confounding factors. The statistical magnitude of the L1 measure was used to evaluate the effect of matching. The statistical magnitude of L1 measure was lower, and the effect of matching was improved.

A Chi-square test was used to determine if there were significant differences in prevalence for anxiety, depression, and insomnia symptoms between the frontline and non-frontline medical staff groups. A Spearman's rank correlation was conducted to explore any relationship between the anxiety and depression symptoms. Furthermore, we used stratified analyses to explore the correlative and influencing factors of adverse psychological reactions in two groups. First of all, the potential associated factors for adverse psychological reactions of the two groups was performed by Chi-square test. Then, we conducted a multivariate logistic regression analysis to seek out potential influencing factors for anxiety, depression, and insomnia symptoms in two groups. The odds ratios (ORs) and 95% confidence interval (CI) were applied to describe the relationship between mental health status and influencing factors. SPSS 22.0 software (IBM, Armonk, NY, USA) was applied to analysis all of the statistical results, which were plotted using GraphPad Prism 8.0 (La Jolla, CA, USA). All analyses were two sided, with $P < 0.05$ considered to be statistically significant.

RESULTS

Demographic Characteristics

In general, a total of 2,920 eligible questionnaires were collected from 470 (16.1%) frontline and 2,450 (83.9%) non-frontline medical staff. The majority of participants were women (86.8%). We divided them into three age groups. The middle age group (29–40) had the largest proportion (51.4%), followed by the younger age group (33.1%) and the older age group (15.5%). The majority of their academic qualifications were undergraduate or junior college (85.4%). Married persons accounted for the largest proportion (66.4%), and 2,337 (80.0%) respondents lived in non-risk regions, whilst 583 (20.0%) respondents admitted that they had been exposed to confirmed or suspected cases of COVID-19. Furthermore, 1,766 (60.5%) work units of participants administered and treated patients with COVID-19. Full demographic details are shown in **Table 1**.

We divided the participants into frontline and non-frontline medical staff groups, the ratio of men to women is about 1:3 in frontline medical staff, while the ratio is about 1:8 in non-frontline medical staff group. There is a statistical difference in sex between two groups by the Chi-square test ($\chi^2 = 49.00$, *df*

TABLE 1 | Comparison of basic information between frontline and non-frontline medical staff.

Basic information	Total (%)	The medical staff group		χ2	*P*
		Frontline	Non-frontline		
Overall(%)	2,920 (100%)	470 (16.1%)	2,450 (83.9%)		
Sex				49.00	**<0.001**
Men	385 (13.2%)	109 (23.2%)	276 (11.3%)		
Women	2,535 (86.8%)	361 (76.8%)	2,174 (88.7%)		
Age				10.13	**0.01**
≤28	967 (33.1%)	132 (28.1%)	835 (34.1%)		
29–40	1,501 (51.4%)	273 (58.1%)	1,228 (50.1%)		
>40	452 (15.5%)	65 (13.8%)	387 (15.8%)		
Education level				2.96	0.23
<Undergraduate/junior college	150 (5.1%)	18 (3.9%)	132 (5.4%)		
Undergraduate/junior college	2,493 (85.4%)	401 (85.3%)	2,092 (85.4%)		
≥Postgraduate	277 (9.5%)	51 (10.9%)	226 (9.2%)		
Marital status				0.88	0.65
Widowed/divorced	74 (2.5%)	11 (2.3%)	63 (2.6%)		
Married	1,940 (66.4%)	321 (68.3%)	1,619 (66.1%)		
Spinsterhood	906 (31.0%)	138 (29.4%)	768 (31.3%)		
Region				35.98	**<0.001**
No-risk region	2,337 (80.0%)	346 (73.6%)	1,991 (81.3%)		
Low-risk region	31 (1.1%)	9 (1.9%)	22 (0.9%)		
Medium-risk region	538 (18.4%)	106 (22.6%)	432 (17.6%)		
High-risk region	14 (0.5%)	9 (1.9%)	5 (0.2%)		
Contact history				443.43	**<0.001**
Positive	583 (20.0%)	261 (55.5%)	322 (13.1%)		
Negative	2,337 (80.0%)	209 (44.5%)	2,128 (86.9%)		
COVID-19 work unit				59.28	**<0.001**
Positive	1,766 (60.5%)	359 (76.4%)	1,407 (57.4%)		
Negative	1,154 (39.5%)	111 (23.6%)	1,043 (42.6%)		

The bold values indicate that the differences are statistically significant.

$= 1$, $P < 0.001$). Similarly, the distribution of age was different between the two groups, and the difference was also statistically significant ($\chi^2 = 10.13$, $df = 2$, $P = 0.006$). However, the distribution of the education level and marital status were not statistically significant between two groups ($\chi^2 = 2.96$, $df = 2$, $P = 0.23$; $\chi^2 = 0.88$, $df = 2$, $P = 0.65$). Therefore, we matched the two groups by sex and age through propensity score matching (PSM). The results showed that 470 frontline medical staff and 470 non-frontline medical staff were matched through sex and age. The statistical magnitude of L1 measure was reduced after matching (0.14 vs. 0.01), and the difference in sex and age was not statistically significant (both $\chi^2 < 0.001$, $df = 1$ or $df = 2$, $P = 1.00$) after matching, indicating it was a good PSM.

Comparisons of the Symptoms of Adverse Psychological Reactions Between Frontline and Non-frontline Groups After PSM

As shown in **Table 2**, the proportion of frontline medical staff experiencing anxiety was higher than for non-frontline medical staff (30.0 vs. 24.3%). Result unveiled that frontline medical staff may be more prone to anxiety compared to the non-frontline medical staff ($\chi^2 = 3.92$, $df = 1$, $P = 0.05$). As for depression, 123 (26.2%) frontline medical staff suffered varying degrees of depression, whereas, 86 (18.3%) non-frontline medical staff admitted to having similar symptoms. Statistical results indicate that the frontline medical staff may be more prone to depression ($\chi^2 = 8.42$, $df = 1$, $P = 0.004$). Furthermore, Spearman's rank correlation showed a positive correlation between the total scores for anxiety and depression ($r_s = 0.75$, $df = 2918$, $P < 0.001$), suggesting that medical staff may suffer from depression accompanying anxiety.

In addition, 60.6% (285) of frontline medical staff suffered from varying degrees of insomnia-early, whereas, the corresponding proportion of non-frontline medical staff was 49.1% (231), the difference was statistically significant ($\chi^2 = 12.53$, $df = 1$, $P < 0.001$). 53.0% (249) of frontline medical staff suffered from varying degrees of insomnia-middle, compared to 43.0% (202) of non-frontline medical staff, the difference was statistically significant ($\chi^2 = 9.42$, $df = 1$, $P = 0.002$). Similarly, the proportion of frontline medical staff was higher than non-frontline medical staff for insomnia late (55.7 vs. 43.6%). The difference was statistically significant ($\chi^2 = 13.83$, *df*

TABLE 2 | Comparisons of the symptoms of adverse psychological reactions between frontline and non-frontline groups after PSM.

Adverse psychological reactions	Total (%)	The medical staff group		OR	OR95% CI	χ2	*P*
		Frontline	Non-frontline				
N	940	470	470				
Anxiety						3.92	0.05
Normal	685 (72.9%)	329 (70.0%)	356 (75.7%)	1.00 (reference)			
Abnormal	255 (27.1%)	141 (30.0%)	114 (24.3%)	1.16	1.00–1.36		
Depression						8.42	0.004
Normal	731 (77.8%)	347 (73.8%)	384 (81.7%)	1 (reference)			
Abnormal	209 (22.2%)	123 (26.2%)	86 (18.3%)	1.28	1.07–1.52		
Insomnia-early						12.53	<0.001
Normal	424 (45.1%)	185 (39.4%)	239 (50.9%)	1 (reference)			
Abnormal	516 (54.9%)	285 (60.6%)	231 (49.1%)	1.26	1.11–1.43		
Insomnia-middle						9.42	0.002
Normal	489 (52.0%)	221 (47.0%)	268 (57.0%)	1 (reference)			
Abnormal	451 (48.0%)	249 (53.0%)	202 (43.0%)	1.22	1.07–1.39		
Insomnia-late						13.83	<0.001
Normal	473 (50.3%)	208 (44.3%)	265 (56.4%)	1 (reference)			
Abnormal	467 (49.7%)	262 (55.7%)	205 (43.6%)	1.28	1.12–1.45		
Sleep mode satisfaction						5.14	0.02
Normal	158 (16.8%)	66 (14.0%)	92 (19.6%)	1 (reference)			
Abnormal	782 (83.2%)	404 (86.0%)	378 (80.4%)	1.21	1.04–1.40		

PSM, Propensity Score Matching.

$= 1, P < 0.001$). For sleep mode satisfaction, more frontline than non-frontline medical staff expressed dissatisfaction with sleep patterns (86.0 vs. 80.4%), and this result was highly significant ($\chi^2 = 5.14$, $df = 1$, $P = 0.02$). Thus, overall frontline medical staff had more problems with sleeping.

Potential Correlative Factors for Anxiety and Depression in Two Medical Staff Groups by Stratification Analysis

We used stratified analyses to explore the correlative factors of anxiety and depression in two groups. The Chi-square test analysis showed that only the marital status was related with the occurrence of anxiety ($\chi^2 = 7.13$, $df = 2$, $P = 0.03$), while other factors were not associated with the symptom of anxiety among frontline medical staff. For the symptom of depression, we failed to identify the factors associated with depression among frontline group.

For non-frontline medical staff, the sex ($\chi^2 = 5.20$, $df = 1$, $P = 0.02$), the age ($\chi^2 = 9.05$, $df = 2$, $P = 0.01$), and the marital status ($\chi^2 = 5.83$, $df = 2$, $P = 0.05$) were related to the incidence of anxiety. Also, the age ($\chi^2 = 13.17$, $df = 2$, $P = 0.001$), the education level ($\chi^2 = 6.41$, $df = 2$, $P = 0.04$), and the marital status ($\chi^2 = 7.30$, $df = 2$, $P = 0.03$) were related to the incidence of depression. The detail information are shown in **Table 3**.

Potential Correlative Factors for Insomnia in Two Medical Staff Groups by Stratification Analysis

Among frontline medical staff, the education level was connected with insomnia-early ($\chi^2 = 7.36$, $df = 2$, $P = 0.03$). Whereas, the education level ($\chi^2 = 5.86$, $df = 2$, $P = 0.05$), the contact history ($\chi^2 = 9.68$, $df = 1$, $P = 0.002$) and working in COVID-19 work unit ($\chi^2 = 6.60$, $df = 1$, $P = 0.01$) were related to insomnia-middle. However, we failed to find out the factors associated with insomnia-late and sleep mode satisfaction in frontline medical staff. The detail information were shown in **Table 4**.

Among non-frontline medical staff, the sex ($\chi^2 = 10.77$, $df = 1$, $P = 0.001$), the marital status ($\chi^2 = 8.13$, $df = 2$, $P = 0.02$), and working in COVID-19 work unit ($\chi^2 = 11.59$, $df = 1$, $P = 0.001$) were associated with insomnia-early. Whereas, the sex ($\chi^2 = 8.93$, $df = 1$, $P = 0.003$) and working in COVID-19 work unit ($\chi^2 = 14.26$, $df = 1$, $P < 0.001$) were correlated to insomnia-middle. Also, we found that the age ($\chi^2 = 30.79$, $df = 2$, $P < 0.001$), the marital status ($\chi^2 = 8.37$, $df = 2$, $P = 0.02$), the contact history ($\chi^2 = 8.72$, $df = 1$, $P = 0.003$), and working in COVID-19 work unit ($\chi^2 = 13.99$, $df = 1$, $P < 0.001$) were related to insomnia-late. What's more, we discovered that the sex ($\chi^2 = 10.32$, $df = 1$, $P < 0.001$), the education level ($\chi^2 = 7.14$, $df = 2$, $P = 0.03$), and working in COVID-19 unit ($\chi^2 = 9.13$, $df = 1$, $P = 0.003$) were correlated to sleep mode satisfaction. The detail information are shown in **Table 4**.

Potential Influencing Factors of Adverse Psychological Reactions of Two Medical Staff by Stratification Analysis

Among frontline and non-frontline medical staff, we found a series of factors that were related to anxiety, depression, and insomnia by univariate analysis. Therefore, we used the statistically significant variables obtained from univariate analysis to conduct a further multivariate logistic regression to find out

TABLE 3 | Factors associated with the symptoms of anxiety and depression in two groups.

	Frontline medical staff								Non-frontline medical staff							
	Anxiety		χ2	*P*	Depression		χ2	*P*	Anxiety		χ2	*P*	Depression		χ2	*P*
	Normal	Abnormal			Normal	Abnormal			Normal	Abnormal			Normal	Abnormal		
N	329	141			347	123			1,862	588			1,968	482		
Sex			0.42	0.52			0.14	0.70			5.20	**0.02**			1.38	0.24
Men	79 (24.0%)	30 (21.3%)			82 (23.6%)	27 (22.0%)			225 (12.1%)	51 (8.7%)			229 (11.6%)	47 (9.8%)		
Women	250 (76.0)	111 (78.7)			265 (76.4%)	96 (78.0%)			1,637 (87.9%)	537 (91.3%)			1,739 (88.4%)	435 (90.2%)		
Age			3.42	0.18			0.25	0.88			9.05	**0.01**			13.17	**0.001**
≤28	102 (31.0%)	32 (22.7%)			101 (29.1%)	33 (26.8%)			666 (35.8%)	171 (29.1%)			703 (35.7%)	134 (27.8%)		
29–40	184 (55.9%)	87 (61.7)			198 (57.1%)	73 (59.3%)			912 (49.0%)	314 (53.4%)			972 (49.4%)	254 (52.7%)		
>40	43 (13.1%)	22 (15.6)			48 (13.8%)	17 (13.8%)			284 (15.3%)	103 (17.5%)			293 (14.9%)	94 (19.5%)		
Education level			1.84	0.40			3.00	0.22			0.32	0.85			6.41	**0.04**
<Undergraduate/junior college	15 (4.6%)	3 (2.1%)			16 (4.6%)	2 (1.6%)			103 (5.5%)	29 (4.9%)			100 (5.1%)	32 (6.6%)		
Undergraduate/junior college	277 (84.2%)	124 (87.9%)			291 (83.9%)	110 (89.4%)			1,588 (85.3%)	504 (85.7%)			1,698 (86.3%)	394 (81.7%)		
≥Postgraduate	37 (11.2%)	14 (9.9%)			40 (11.5%)	11 (8.9%)			171 (9.2%)	55 (9.4%)			170 (8.6%)	56 (11.6%)		
Marital status			7.13	**0.03**			2.69	0.26			5.83	**0.05**			7.30	**0.03**
Widowed/divorced	6 (1.8%)	5 (3.5%)			8 (2.3%)	3 (2.4%)			43 (2.3%)	20 (3.4%)			45 (2.3%)	18 (3.7%)		
Married	215 (65.3%)	106 (75.2%)			230 (66.3%)	91 (74.0%)			1,215 (65.3%)	404 (68.7%)			1,286 (65.3%)	333 (69.1%)		
Spinsterhood	108 (32.8%)	30 (21.3%)			109 (31.4%)	29 (23.6%)			604 (32.4%)	164 (27.9%)			637 (32.4%)	131 (27.2%)		
Region			1.11	0.77			1.81	0.61			3.24	0.36			4.02	0.26
No-risk region	238 (72.3%)	108 (76.6%)			260 (74.9%)	86 (69.9%)			1,527 (82.0%)	464 (78.9%)			1,614 (82.0%)	377 (78.2%)		
Low-risk region	7 (2.1%)	2 (1.4%)			7 (2.0%)	2 (1.6%)			15 (0.8%)	7 (1.2%)			18 (0.9%)	4 (0.8%)		
Medium-risk region	77 (23.4%)	29 (20.6%)			73 (21.0%)	33 (26.8%)			316 (17.0%)	116 (19.7%)			332 (16.9%)	100 (20.7%)		
High-risk region	7 (2.1%)	2 (1.4%)			7 (2.0%)	2 (1.6%)			4 (0.2%)	1 (0.2%)			4 (0.2%)	1 (0.2%)		
Contact history			0.02	0.89			2.00	0.16			2.69	0.10			2.11	0.15
Positive	182 (55.3%)	79 (56.0%)			186 (53.6%)	75 (61.0%)			233 (12.5%)	89 (15.1%)			249 (12.7%)	73 (15.1%)		
Negative	147 (44.7%)	62 (44.0%)			161 (46.4%)	48 (39.0%)			1,629 (87.5%)	499 (84.9%)			1,719 (87.3%)	409 (84.9%)		
COVID-19 work unit			0.01	0.94			0.00	0.99			2.15	0.14			1.10	0.30
Positive	251 (76.3%)	108 (76.3%)			265 (76.4%)	94 (76.4)			1,054 (56.6%)	353 (60.0%)			1,120 (56.9%)	287 (59.5%)		
Negative	78 (23.7%)	33 (23.7%)			82 (23.6%)	29 (23.6%)			808 (43.4%)	235 (40.0%)			848 (43.1%)	195 (40.5%)		

The bold values indicate that the differences are statistically significant.

TABLE 4 | Factors associated with the symptoms of insomnia in two groups.

	Frontline medical staff															
	Insomnia-early		χ2	*P*	Insomnia-middle		χ2	*P*	Insomnia-late		χ2	*P*	Sleep mode satisfaction		χ2	*P*
	Normal	Abnormal			Normal	Abnormal			Normal	Abnormal			Normal	Abnormal		
N	185	285			221	249			208	262			66	404		
Sex			0.48	0.49			0.03	0.87			0.003	0.96			0.05	0.83
Men	46 (24.9%)	63 (22.1%)			52 (23.5%)	57 (22.9%)			48 (23.1%)	61 (23.3%)			16 (24.2%)	93 (23.0%)		
Women	139 (75.1%)	222 (77.9%)			169 (76.5%)	192 (77.1%)			160 (76.9%)	201 (76.7%)			50 (75.8%)	311 (77.0%)		
Age			3.30	0.19			2.79	0.25			0.31	0.86			0.52	0.77
≤28	45 (24.3%)	89 (31.2%)			56 (25.3%)	78 (31.3%)			62 (29.8%)	72 (27.5%)			18 (27.3%)	116 (28.7)		
29–40	110 (59.5%)	161 (56.5%)			130 (58.8%)	141 (56.6%)			118 (56.7%)	153 (58.4%)			37 (56.1%)	234 (57.9%)		
>40	30 (16.2%)	35 (12.3%)			35 (15.8%)	30 (12.0%)			28 (13.5%)	37 (14.1%)			11 (16.7%)	54 (13.4%)		
Education level			7.36	**0.03**			5.86	**0.05**			4.36	0.11			3.75	0.15
<Undergraduate/junior college	7 (3.8%)	11 (3.9%)			9 (4.1%)	9 (3.6%)			6 (2.9%)	12 (4.6%)			5 (7.6%)	13 (3.2%)		
Undergraduate/junior college	149 (80.5%)	252 (88.4%)			180 (81.4%)	221 (88.8%)			173 (83.2%)	228 (87.0%)			52 (78.8%)	349 (86.4%)		
≥Postgraduate	29 (15.7%)	22 (7.7%)			32 (14.5%)	19 (7.6%)			29 (13.9%)	22 (8.4%)			9 (13.6%)	42 (10.4%)		
Marital status			2.10	0.35			1.71	0.43			0.05	0.98			0.78	0.68
Widowed/ divorced	6 (3.2%)	5 (1.8%)			7 (3.2%)	4 (1.6%)			5 (2.4%)	6 (2.3%)			1 (1.5%)	10 (2.5%)		
Married	130 (70.3%)	191 (67.0%)			153 (69.2%)	168 (67.5%)			141 (67.8%)	180 (68.7%)			48 (72.7%)	273 (67.6%)		
Spinsterhood	49 (26.5%)	89 (31.2%)			61 (27.6%)	77 (30.9%)			62 (29.8%)	76 (29.0%)			17 (25.8%)	121 (30.0%)		
Region			3.07	0.38			1.45	0.69			4.69	0.20			3.68	0.30
No-risk region	136 (73.5%)	210 (73.7%)			162 (73.3%)	184 (73.9%)			150 (72.1%)	196 (74.8%)			45 (68.2%)	301 (74.5%)		
Low-risk region	6 (3.2%)	3 (1.1%)			6 (2.7%)	3 (2.1%)			7 (3.4%)	2 (0.8%)			3 (4.5%)	6 (1.5%)		
Medium-risk region	40 (21.6%)	66 (23.2%)			49 (22.2%)	57 (22.9%)			48 (23.1%)	58 (22.1%)			16 (24.2%)	90 (22.3%)		
High-risk region	3 (1.6%)	6 (2.1%)			4 (1.8%)	5 (2.0%)			3 (1.4%)	6 (2.3%)			2 (3.0%)	7 (1.7%)		
Contact history			3.42	0.06			9.68	**0.002**			0.08	0.78			0.50	0.48
Positive	93 (50.3%)	168 (58.9%)			106 (48.0%)	155 (62.2%)			117 (56.3%)	144 (55.0%)			34 (51.5%)	227 (56.2%)		
Negative	92 (49.7%)	117 (41.1%)			115 (52.0%)	94 (37.8%)			91 (43.8%)	118 (45.0)			32 (48.5%)	177 (43.8%)		
COVID-19 work unit			1.97	0.16			6.60	**0.01**			2.97	0.09			0.20	0.66
Positive	135 (73.0%)	224 (78.6%)			157 (71.0%)	202 (81.1%)			151 (72.6%)	208 (79.4%)			49 (74.2%)	310 (76.7%)		
Negative	50 (27.0%)	61 (21.4%)			64 (29.0%)	47 (18.9%)			57 (27.4%)	54 (20.6%)			17 (25.8%)	94 (23.3%)		

(Continued)

TABLE 4 | Continued

	Non-frontline medical staff															
	Insomnia-early		χ2	*P*	Insomnia-middle		χ2	*P*	Insomnia-late		χ2	*P*	Sleep mode satisfaction		χ2	*P*
	Normal	Abnormal			Normal	Abnormal			Normal	Abnormal			Normal	Abnormal		
N	1,166	1,284			1,365	1,085			1,321	1,129			454	1,996		
Sex			10.77	**0.001**			8.93	**0.003**			2.86	0.09			10.32	**<0.001**
Men	157 (13.5%)	119 (9.3%)			177 (13.0%)	99 (9.1%)			162 (12.3%)	114 (10.1%)			75 (16.5%)	201 (10.1%)		
Women	1,009 (86.5%)	1,165 (90.7%)			1,188 (87.0%)	986 (90.9%)			1,159 (87.7%)	1,015 (89.9%)			379 (83.5%)	1,795 (89.9%)		
Age			1.17	0.56			4.08	0.13			30.79	**<0.001**			0.70	0.71
≤28	386 (33.1%)	451 (35.1%)			484 (35.5%)	353 (32.5%)			489 (37.0%)	348 (30.8%)			151 (33.3%)	686 (34.4%)		
29–40	595 (51.0%)	631 (49.1%)			681 (49.9%)	545 (50.2%)			671 (50.8%)	555 (49.2%)			235 (51.8%)	991 (49.6%)		
>40	185 (15.9%)	202 (15.7%)			200 (14.7%)	187 (17.2%)			161 (12.2%)	226 (20.0%)			68 (15.0%)	319 (16.0%)		
Education level			3.33	0.19			3.04	0.22			2.95	0.23			7.14	**0.03**
<Undergraduate/junior college	59 (5.1%)	73 (5.7%)			75 (5.5%)	57 (5.3%)			63 (4.8%)	69 (6.1%)			20 (4.4%)	112 (5.6%)		
Undergraduate/junior college	987 (84.6%)	1,105 (86.1%)			1,152 (84.4%)	940 (86.6%)			1,129 (85.5%)	963 (85.3%)			378 (83.3%)	1,714 (85.9%)		
≥Postgraduate	120 (10.3%)	106 (8.3%)			138 (10.1%)	88 (8.1%)			129 (9.8%)	97 (8.6%)			56 (12.3%)	170 (8.5%)		
Marital status			8.13	**0.02**			0.70	0.71			8.37	**0.02**			0.59	0.74
Widowed/divorced	24 (2.1%)	39 (3.0%)			32 (2.3%)	31 (2.9%)			25 (1.9%)	38 (3.4%)			11 (2.4%)	52 (2.6%)		
Married	802 (68.8%)	817 (63.6%)			907 (66.4%)	712 (65.6%)			859 (65.0%)	760 (67.3%)			307 (67.6%)	1,312 (65.7%)		
Spinsterhood	340 (29.2%)	428 (33.3%)			426 (31.2%)	342 (31.5%)			437 (33.1%)	331 (29.3%)			136 (30.0%)	632 (31.7%)		
Region			1.16	0.76			0.52	0.92			4.17	0.24			1.97	0.58
No-risk region	954(81.8%)	1,037 (80.8%)			1,110 (81.3%)	881 (81.2%)			1,059 (80.2%)	932 (82.6%)			374 (82.4%)	1,617 (81.0%)		
Low-risk region	12 (1.0%)	10 (0.8%)			12 (0.9%)	10 (0.9%)			10 (0.8%)	12 (1.1%)			6 (1.3%)	16 (0.8%)		
Medium-risk region	198 (17.0%)	234 (18.2%)			241 (17.7%)	191 (17.6%)			250 (18.9%)	182 (16.1%)			73 (16.1%)	359 (18.0%)		
High-risk region	2 (0.2%)	3 (0.2%)			2 (0.1%)	3 (0.3%)			2 (0.2%)	3 (0.3%)			1 (0.2%)	4 (0.2%)		
Contact history			0.001	0.98			1.88	0.17			8.72	**0.003**			1.05	0.31
Positive	153 (13.1%)	169 (13.2%)			168 (12.3%)	154 (14.2%)			149 (11.3%)	173 (15.3%)			53 (11.7%)	269 (13.5%)		
Negative	1,013 (86.9%)	1,115 (86.8%)			1,197 (87.7%)	931 (85.8)%			1,172 (88.7%)	956 (84.7%)			401 (88.3%)	1,727 (86.5%)		
COVID-19 work unit			11.59	**0.001**			14.26	**<0.001**			13.99	**<0.001**			9.13	**0.003**
Positive	628 (53.9%)	779 (60.7%)			738 (54.1%)	669 (61.7%)			713 (54.0%)	694 (61.5%)			232 (51.1%)	1,175 (58.9%)		
Negative	538 (46.1%)	505 (39.3%)			627 (45.9%)	416 (38.3%)			608 (46.0%)	435 (38.5%)			222 (48.9%)	821 (41.1%)		

The bold values indicate that the differences are statistically significant.

TABLE 5 | Factors of influencing adverse psychological reactions in frontline group by logistic regression analysis.

	β	SE	Wald	OR	OR 95% CI	*P*
Anxiety						
Marital status						
Widowed/divorced (control)						
Married	0.54	0.29	3.58	1.71	0.98–2.99	0.06
Spinsterhood	0.20	0.11	3.72	1.23	1.00–1.51	**0.05**
Insomnia-early						
Education level						
<Undergraduate/junior college (control)						
Undergraduate/junior college	0.73	0.56	1.69	2.07	0.69–6.21	0.19
≥Postgraduate	0.80	0.30	7.09	2.23	1.24–4.02	**0.01**
Insomnia-middle						
Education level						
<Undergraduate/junior college (control)						
Undergraduate/junior college	0.72	0.56	1.61	2.04	0.68–6.17	0.21
≥Postgraduate	0.70	0.31	5.05	2.01	1.09–3.69	**0.03**
Contact history						
Negative (control)						
Positive	0.48	0.20	5.89	1.62	1.10–2.40	**0.02**
COVID-19 work unit						
Negative (control)						
Positive	0.37	0.23	2.50	1.45	0.92–2.29	0.11

The bold values indicate that the differences are statistically significant.

the latent influencing factors of two groups. For frontline medical staff, the results unveiled that the spinsterhood state (OR = 1.23, 95% CI: 1.00–1.51; $P = 0.05$) was a risk factor for anxiety compared to widowed/divorced. Bachelor or college degree was the risk factor for insomnia-early (OR = 2.23, 95% CI: 1.24–4.02, $P = 0.01$) and insomnia-middle (OR = 2.01, 95% CI: 1.09–3.69; $P = 0.03$). In addition, the COVID-19 patients contact history (OR = 1.62, 95% CI: 1.10–2.40; $P = 0.02$) was a risk factor for insomnia-middle. The detail information are shown in **Table 5**.

For non-frontline medical staff, the women (OR = 1.49, 95% CI: 1.08–2.06, $P = 0.01$) was a risk factor for the occurrence of anxiety, while middle age group was a protective factor not only for anxiety (OR = 0.70, 95% CI: 0.50–0.99, $P = 0.04$) but also for depression (OR = 0.65, 95% CI: 0.45–0.93, $P = 0.02$). The women (OR = 1.47, 95% CI: 1.14–1.89, $P = 0.003$) and working in a COVID-19 unit (OR = 1.31, 95% CI: 1.11–1.54, $P = 0.001$) were risk factors for insomnia-early, while the spinsterhood state (OR = 0.80, 95% CI: 0.67–0.95; $P = 0.01$) was a protective factor for insomnia-early. Also, the women (OR = 1.47, 95% CI: 1.14–1.90, $P = 0.003$) and working in a COVID-19 unit (OR = 1.30, 95% CI: 1.10–1.52, $P = 0.002$) were risk factors for insomnia-middle. Working in a COVID-19 unit (OR = 1.37, 95% CI:1.16–1.61 $P < 0.001$) was a risk factor for insomnia-late, while the spinsterhood state (OR = 0.76, 95% CI: 0.61–0.95; $P = 0.02$) was a protective factor for insomnia-late. As for sleep mode satisfaction, the women (OR = 1.58, 95% CI: 1.17–2.15; $P = 0.003$) and working in a COVID-19 unit (OR = 1.33, 95% CI: 1.09–1.64, $P = 0.01$) were risk factors. The detail information are shown in **Supplementary Table 1**.

Psychological Aid

As a result of the high-pressure working environment during the COVID-19 pandemic, medical staff were susceptible to psychological problems. Therefore, we further investigated the need for psychological aid for all medical staff. The results showed that 53.0% (1,526) thought it necessary for medical staff to provide and receive psychological help. The provision of online forms for psychological aid, WeChat or QQ group counseling (66.6%), public account publicity (64.8%), and propaganda on TV and radio (60.6%) were the three most popular procedures (**Figure 1A**). Furthermore, medical staff were more inclined to be familiar with "how to self-alleviate psychological reactions" (81.2%), "how to help others relieve psychological reactions" (70.5%) and "common psychological reactions" (64.1%) (**Figure 1B**).

DISCUSSION

In the present study, we observed that a number of medical staff suffered from adverse psychological reactions to varying degrees during the outbreak of COVID-19. The results showed that frontline medical staff were at greater risk for anxiety, depression, and insomnia compared to non-frontline medical staff, and that there was an increased prevalence of anxiety and depression disorders at the height of the COVID-19 pandemic. Similar conclusions that frontline medical staff in high-risk departments were more susceptible to feelings of anxiety, depression, and insomnia compared with non-frontline staff have also been reported (16, 31–34). However, we also discovered a positive correlation between anxiety and depression, and the co-existence of anxiety and depression in this specific population of medical staff in relation to the adverse stressors which were present during the COVID-19 pandemic. There is also evidence that the flourishing of both conditions altogether is not exclusive to medical staff, and there is generally a high probability of comorbidity in both disorders (35, 36). Furthermore, medical staff suffered from varying degrees of insomnia symptoms, including insomnia-early, insomnia-middle, and insomnia-late in agreement with the report of a higher percentage of medical staff experiencing sleep problems compared with other occupational groups during the past 3 months (37). Therefore, for the welfare and improving immunity of medical staff against the virus, work units should arrange reasonable working times, and ensure that such staff have adequate sleep quality.

We investigated the related factors of adverse psychological reactions in frontline and non-frontline medical staff, respectively. For frontline medical staff, we discovered that the marital status was connected with anxiety and the education level, history of contact with patients with COVID-19 and working in COVID-19 unit were connected with insomnia. These adverse reactions were more severe among frontline medical staff, possibly due to a skyrocketing workload, worrying

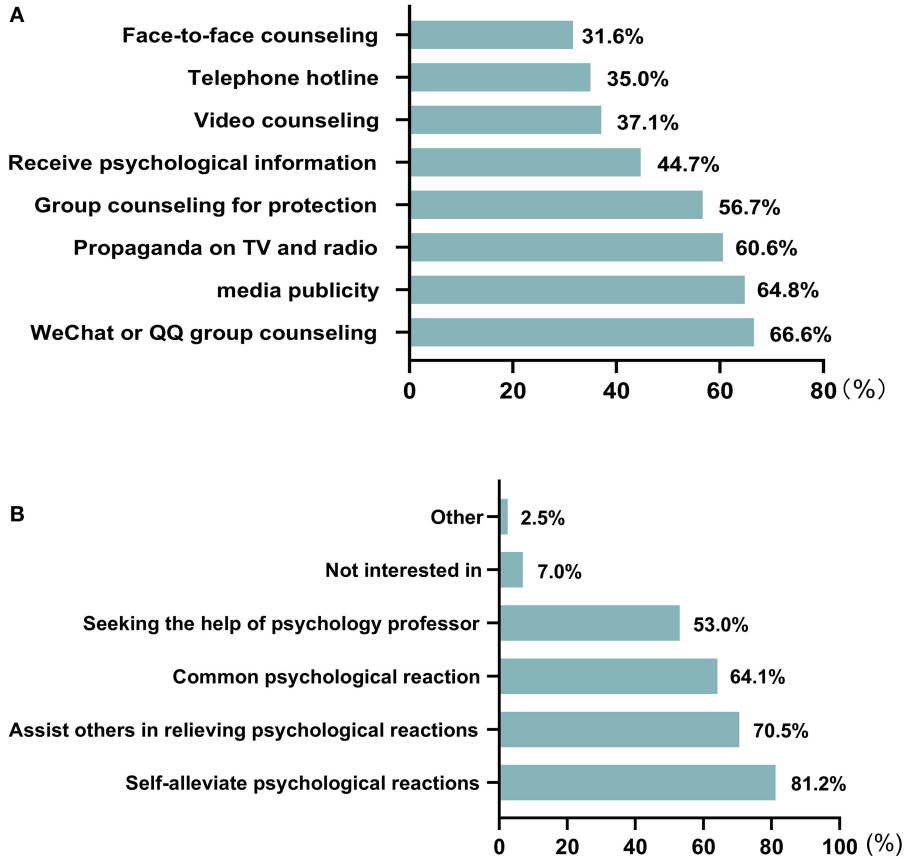

FIGURE 1 | Findings on the psychological aid needs. **(A)** The choice of medical staff for psychological aid forms. **(B)** The choice of medical staff for content of psychological aid.

about infected virus from COVID-19 patients and fearing of transmitting the virus to family numbers. For non-frontline medical staff, the age, and the marital status were not only related to anxiety, but also related to depression. However, the sex was related to anxiety and the education level was related to depression. In addition, the sex, the age, the marital status, the educational level, the history of contact with patients with COVID-19 and working in a COVID-19 unit were associated with the occurrence of insomnia. It was suggested that the marital status was a common associated factor for anxiety and the education level, history of contact with patients with COVID-19 and working in COVID-19 unit were common associated factors for insomnia in two medical groups. Besides, the adverse psychological reactions of non-frontline workers may be influenced by more factors, such as, the sex and age. Hence, we should pay attention to the mental health of all medical staff who have direct or indirect contact with the COVID-19 patients, giving targeted guidance on mental health.

We also explored the underlying factors that influence adverse psychological reactions. In particular, spinsterhood people were more prone to anxiety among frontline medical staff. What's more, having a bachelor's degree and a contact history of COVID-19 patient were more likely to suffer from insomnia among frontline medical staff. As expected, men were less susceptible to anxiety than women in non-frontline medical staff, which is consistent with a number of previous studies (15, 38–40). However, working at a COVID-19 unit were a risk factors for insomnia among the non-frontline group, but not among frontline group, which is inconsistent with the report of Su et al. (13) that SARS unit nurses had higher proportions of insomnia compared to non-SARS unit nurses during the SARS epidemic in Taiwan. Furthermore, we found that people in the middle age group were at lower risk for anxiety and depression in non-frontline medical staff, which was in line with previous research, which reported that older respondents were less susceptible to anxiety and depression disorder than younger people (13, 37). It was suggested that middle age group medical workers have more experience in epidemics than younger health workers. They are more psychologically resilient and may play a vital role in this epidemic.

Generally speaking, the sudden outbreak of COVID-19 led to increased workload, reduced rest time, worry about family infection, and reduced family activities for medical staff, which may have contributed to the presentation of mental health problems (41, 42). Previous studies have shown that at least 50% of medical staff needed psychological assistance (33, 43), which is

consistent with the present study. Hence, it is vital for medical staff to obtain appropriate psychological aid and care. As we know, choosing the best way to conduct psychological counseling achieves the most satisfactory effects, and the development of internet technology is of great benefit and allows adoption of online forms for conducting psychological aid (41). By using this approach, we could not only effectively reduce the risk of virus transmission, but also increase crowd participation. In our survey, we concluded that medical staff preferred forms of WeChat or QQ group counseling, and public account publicity rather than face-to-face counseling. In addition, we sought to understand what psychological knowledge medical staff needed in order to provide targeted guidance. In our study, "how to self-alleviate psychological reactions," "how to help others relieve psychological reactions" and "common psychological reactions" were the most popular contents for medical staff, and we should carry out more psychological knowledge guidance and training in these areas.

In this study, we had a sufficiently large sample size for a proper statistical analysis. The application of a PSM to eliminate the influence of confounding factors improved the authenticity and reliability of the conclusions, and the use of validated questionnaires and assessment of the value of psychological aids also contribute to the significance of the research. However, there were some limitations in the present study. First, this was a cross-sectional survey and our participants were not followed up. Thus, it is difficult to know how their mental health state will alter during the development of the COVID-19 pandemic, and a longitudinal study is needed to investigate the psychological effects on this population in future. Second, our data were collected *via* WeChat, DingTalk, and other social platforms, and the limitation of using social media for distributing questionnaires (i.e., medical staff who didn't use these social software were not enrolled in this study), may bias the results. Also, the clinical variables recollected in an online platform may not be entirely reliable, but this was the only way to collect the data because of confinement as a result of precaustions against the spread of COVID-19. Finally, the subjects enrolled in the present study were all medical staff and mostly from a low-risk zone. Previous studies have focused on participants in the high-risk zone, and there was no previous study sample from a low-risk zone. Nevertheless, the present study shows that the medical staff from a low-risk zone, especially frontline staff, experienced anxiety, depression, and insomnia as a result of the COVID-19 pandemic, and thus suggests that attention should be also paid to the mental health of medical staff in the low-risk zone.

Overall, the COVID-19 outbreak resulted in medical staff suffering from increases in certain mental health problems, and frontline medical staff were at greater risk for adverse psychological reactions than non-frontline staff. Identifying the underlying factors may contribute to the formulation of effective measures for relieving anxiety, depression, and insomnia symptoms among medical staff. Finally, we expect government and health systems to focus increasingly on the mental health of medical staff, especially the frontline group, and mental health care should have an indispensable role in global epidemic prevention and control.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Informed consent was obtained from each participant, and the study was approved by the Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University.

AUTHOR CONTRIBUTIONS

BG analyzed the data and contributed to the interpretation of results. WG, XM, and QS designed the study. QS, XM, and SGL completed the data collection. MY and WG made critical revisions and approved the final manuscript. All the authors including SL, QS, and XM wrote the first draft of the manuscript.

FUNDING

This study was supported by grants from the National Key R&D Program of China (Grant No. 2016YFC1307100), National Natural Science Foundation of China (Grant No. 81771447), Development and application of medical and health appropriate technology of Guangxi (Grant No. S2019014), Young and Middle-aged Teachers' Basic Ability Support Project of Guangxi Universities (Grant No. 2020KY03029), and Key Clinical Specialty Construction Project of Guangxi.

ACKNOWLEDGMENTS

We would like to thank Dr. Zhikun Zhang, Meiying Lei, Yuming Li for their assistance in completing this project. The authors also thank all individuals who served as the research participants.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.580067/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 07 May 2021
doi: 10.3389/fmed.2021.589550

Nurses' Ethics in the Care of Patients During the COVID-19 Pandemic

Aladeen Alloubani[1]*, *Wejdan Khater*[2], *Laila Akhu-Zaheya*[2], *Maysa Almomani*[2] and *Safa Alashram*[3]

[1] Nursing Research Unit, King Hussein Cancer Center, Amman, Jordan, [2] Department of Adult Health Nursing, Faculty of Nursing, Jordan University of Science and Technology, Irbid, Jordan, [3] Consultancy of Secretary General, Civil Service Bureau, Amman, Jordan

Working during an epidemic can be physically, emotionally, and morally demanding for nurses. In addition to caring for patients, nurses are also responsible for looking after themselves and their families. The current study aimed to explore nurses' ethics in the care of patients during the coronavirus disease 2019 (COVID-19) pandemic. A descriptive qualitative approach was adopted in order to gain an in-depth understanding of nurses' experiences of caring for patients with coronavirus. A purposive sample of 10 nurses working with patients with COVID-19 was recruited. Interviews were held with the nurses, and content analysis of the interviews was conducted. Each interview was transcribed, and the text was coded into manageable categories on the word, word sense, phrase, sentence, and theme levels before analysis. Three major themes related to the nurses' ethical commitments during the COVID-19 crisis emerged during the data analysis. These themes are as follows: the obligation of nurses to provide care for patients regardless of their medical diagnosis; the ethical dilemma faced by nurses of whether to care for patients or protect themselves from the virus; and finally, the responsibility of nurses to care for themselves.

Keywords: ethical, COVID-19, nurses, dilemma approach, care

OPEN ACCESS

Edited by:
Thalia A. Arawi, American University of Beirut Medical Center, Lebanon

Reviewed by:
Domenico Criscuolo, Italian Society of Pharmaceutical Medicine, Italy
Lisa Kristina Dannenberg, University Hospital of Düsseldorf, Germany

***Correspondence:**
Aladeen Alloubani
aa.12567@khcc.jo

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *30 July 2020*
Accepted: *08 March 2021*
Published: *07 May 2021*

Citation:
Alloubani A, Khater W, Akhu-Zaheya L, Almomani M and Alashram S (2021) Nurses' Ethics in the Care of Patients During the COVID-19 Pandemic. Front. Med. 8:589550. doi: 10.3389/fmed.2021.589550

INTRODUCTION

Nurses have always played an essential role in the provision of healthcare (1, 2). However, particularly during disasters and pandemics, nurses are exposed to greater risk and are required to work to their full capacity under risky circumstances. Working during an epidemic can be particularly demanding for nurses. Furthermore, nurses may often find themselves faced with moral dilemmas when working during pandemics, as they must balance between caring for patients while looking after themselves and their families (3).

In situations where there are limited resources available, such as the lack of personal protective equipment for healthcare providers during the COVID-19 pandemic, nurses must place their lives at risk in order to provide patient care (4, 5). Thus, nurses may feel unsafe, exposed to higher risks, and in need of professional, legal, and moral support while providing care during emergencies and crises (6).

Three main ethics challenges are likely to affect nurses in distinct ways, including nurses' safety, patients, families, and friends; the distribution of scarce resources; and the change in nature of nurses' relationships with patients and families (7).

As per Interpretive Statement 8.4 provided within the Code of Ethics for Nurses with Interpretive Statements (2015), all necessary actions performed by nurses and avoidance of action by nurses in the context of patient care can bring about outcomes that may be an accidental

violation of human rights (8). Nurses must practice caution when deciding whether or not to participate in patient care in every situation, and this requires them to analyze the pros and cons of the situation so that they may be able to justify their actions when required to do so.

AIM

The current study aimed to explore nurses' ethics in the care of patients during the COVID-19 pandemic.

METHODS

Design

A descriptive qualitative approach was used to gain an in-depth understanding of nurses' experiences of caring for patients with coronavirus. The descriptive qualitative approach used in this study focused on answering "who," "what," and "where" questions related to the ethical experiences of nurses caring for patients with coronavirus (9). Moreover, this study was highly concerned with capturing the experiences and feelings of the respondents, as well as identifying specific trends in the study participants and personal characteristics. The use of a descriptive qualitative approach ensures that the information obtained from the respondents complies with scientific requirements (10).

Sample and Setting

A purposive sample of 10 nurses working with patients with COVID-19 was recruited. Purposive sampling allows researchers to decide what needs to be known and set out to find participants who can and are willing to provide the most relevant information by virtue of knowledge or experience (11). Hence, purposive sampling was viewed to be suited to the aim of understanding nurses' ethical behaviors, attitudes, and practices during the COVID-19 pandemic. The sample size was determined based on data saturation, which refers to "the repetition of discovered information and confirmation of previously collected data" [(12), p. 122].

The study was carried out at two different hospitals in Jordan, one located in Amman, the capital of Jordan, and the other in the North Region of Jordan. The two selected hospitals are government hospitals that were the only hospitals receiving patients with confirmed COVID-19 diagnosis at the time of data collection. The inclusion criteria included being a nurse who provided direct nursing care for patients with COVID-19 and agreeing to participate in the study. Meanwhile, nurses who were working at the selected hospitals but in units that were not receiving confirmed COVID-19 cases were excluded.

Interview Outline

The interview questions were developed based on a review of relevant articles in the literature and experts' opinions. Semi-structured, open-ended interviews that lasted between 30 and 90 min each were held *via* Zoom with 10 nurses. The interviews were guided by an interview guideline, and all interviews were held in Arabic. The interviews were tape-recorded, transcribed verbatim in Arabic, translated into English, and then analyzed using thematic analysis. The transcripts were translated from Arabic into English by the research team and then checked by a qualified translator and one of the study participants, so as to ensure the highest level of accuracy.

Data Collection

The study aim and significance were explained to the participants prior to data collection, and the interviews were scheduled at the participants' convenience. The data collection process was an iterative process that included collecting, coding, and analyzing data (13). The interviews were conducted by the research team members, most of whom had previous experience conducting qualitative interviews. One-on-one interviews were held through the software application Zoom, and all interviews were recorded and kept strictly private and confidential.

The participants were informed that they had the right to withdraw from the study at any time without consequences, and that all collected data would be kept confidential. During data collection, the researchers built rapport with the respondents but made sure not to interfere with or impact their responses. To enhance the data authenticity and avoid any bias, several strategies were employed by the researchers, including active listening, unconditional acceptance, and clarification. In order to increase the reliability of the results, the interviewer summarized each interview to the interviewee at the end in order to allow the participant to check for and clarify any misconceptions or add additional information.

Content Analysis

Thematic analysis was used for analyzing the data. All audiotaped interviews were carefully transcribed verbatim. Manual analysis was performed by the research team through constant reading and rereading, coding, and analysis of the data collected from the participants. Each interview was analyzed using the same process until all transcripts had been analyzed. The process of coding, categorizing, and originating the major themes were discussed with all research team members to ensure accuracy and consistency.

Content analysis of the translated transcripts was conducted, whereby the transcripts were coded into manageable categories on the word, word sense, phrase, sentence, and theme levels and then examined using either conceptual analysis or relational analysis. The researchers cross-checked their interpretations to validate the accuracy of the findings. Finally, to ensure the credibility of the results, member checks were carried out, where researchers shared the study's results with the participants in order to confirm that the findings were reflective of their experiences (14).

Ethical Consideration

Prior to conducting the study, ethical approval was obtained from the institutional review board of Jordan University of Science and Technology. In order to maintain their privacy, the participants were informed that the interviews would be recorded, and each participant was able to choose a convenient location for the interview to be held through Zoom. Since the interviews were held *via* Zoom, a waiver of documentation of

TABLE 1 | Participants demographics characteristics.

Participants (Nurse No code)	Gender	Age (year)	Education level	Total number of experiences (year)
NH1	Male	35	BS	14
NH2	Female	33	BS	12
NH3	Female	34	Master	13
NH4	Male	32	BS	12
NH5	Male	52	BS	31
NK1	Male	26	Master	5
NK2	Female	32	BS	12
NK3	Male	30	Master	10
NK4	Male	26	BS	5
NK5	Female	26	BS	5

TABLE 2 | Themes and subthemes.

Theme	Sub themes
Nurses are obligated to provide care for patients regardless	We are always available for patients
	Patient with Covid-19 has the right to be cared for
	What if this patient one of my family members
Ethical dilemma	Nurses should not be forced: it should be voluntary
	It is community and professional commitment
Nurses are responsible to protect themselves	

informed consent was requested. Finally, all collected data were stored on a password-protected computer.

RESULTS

Demographic Data

Fifteen participants were invited to participate, of whom 10 (66.6%) agreed to participate and were therefore interviewed (**Table 1**). Of the 10 nurses, six were male, and four were female. The mean age of the participants was 32.6 years ($R = 26–52$), and the average number of years of experience was 11.9 years. As for educational level, all of the nurses held Bachelor of Science in Nursing (BSN) degrees, and three of the nurses also held master's degrees. All of the participating nurses had started caring for patients with COVID-19 since the virus had started spreading in Jordan (March 2, 2020).

Themes

Three major themes related to the nurses' ethical commitment during the COVID-19 pandemic emerged during the data analysis (**Table 2**). These themes are as follows: the obligation of nurses to provide care for patients regardless of their medical diagnosis, the ethical dilemma faced by nurses of whether to care for patients or protect themselves from the virus, and the responsibility of nurses to care for themselves.

The Obligation of Nurses to Provide Care for Patients Regardless of Their Medical Diagnosis

This theme describes nurses' perception of their ethical commitment to provide care for patients regardless of their medical diagnoses. This theme included three subthemes: nurses should always be available for patients; patients with COVID-19 have the right to Be cared for; and patients should be treated as if they were family members.

Nurses Should Always Be Available for Patients

The nurses believed that it was their duty as nurses to care for patients regardless of their diagnoses. The nurses also expressed that they were committed to being available for their patients when they needed them and providing the best care possible. One participant said:

> *"For me, it is my role as a nurse to take care of people"* (NK3).

Another participant emphasized the importance of providing nursing care to the best of one's ability:

> *"You need to work with all you have, with humanity, and with passion, and to try to give 100%"* (NH2).

Although the nurses expressed facing several challenges in caring for patients with COVID-19, they believed that this was part of their responsibilities. One participant reported:

> *"It* [nursing] *is a humanitarian profession; even if there are challenges, we need to give patients their rights…that is a must"* (NK3).

Another participant said:

> *"It doesn't make sense for someone with my experiences to no help people, as this is my job. It's important that I'm sincere toward my job"* (NH10).

Patients With COVID-19 Have the Right to Be Cared for

The participating nurses highlighted that COVID-19 patients had the same right of being cared for as did other patients. They emphasized that patients had the right to receive the care they needed because being COVID-19 patients was not their fault. One participant said:

> *"Whatever the case, they are not responsible for their disease; they need someone to take care of them... that's the idea"* (NH3).

The participating nurses also expressed that COVID-19 patients are like patients with any other infectious disease, and that the only difference is that COVID-19 is a new virus. Thus,

the nurses believed that COVID-19 patients had the same right to receive nursing care as did other patients. One nurse said:

"As nurses, what is our job? What is needed from us? It is our job to provide nursing care for all patients … After all, patients with COVID-19 are like other patients, except that they have a new disease" (NK4).

Another participant indicated:

"I mean, patients with coronavirus are like other patients, except that the virus they have been infected with is new. Since I now have experience dealing with the virus, I have no problem taking care of COVID-19 patients" (NK5).

Patients Should Be Treated as if They Were Family Members

The participating nurses perceived all patients as if they were their family members. The nurses asked themselves the question of what they would do if the COVID-19 patient was one of their family members and needed someone to take care of them. Therefore, they treated COVID-19 patients the way they would have liked their family members to be treated. One nurse reported:

"The motive behind my voluntary work with patients despite the challenges is the idea that each patient could have been one of my family members" (NH1).

Another participant said, *"I kept saying that these patients have nothing to do with the being infected …he/she could be my father, my mother, my sister...you should consider patients as family members …. I used to work with pregnant women with COVID-19, and I kept thinking that this could have been my wife who was pregnant during these times"* (NK2).

Ethical Dilemma

The thematic analysis of the interviews showed that the nurses were caught in an ethical dilemma. On the one hand, they felt that they should not be forced to work with COVID-19 patients, and on the other hand, they felt a national and professional sense of commitment to not saying no. Two subthemes emerged from this theme: first, working with COVID-19 patients should Be voluntary and not obligatory, and second, nurses have a community and professional commitment to caring for all patients.

Working With COVID-19 Patients Should Be Voluntary and Not Obligatory

Although all of the nurses in this study had voluntarily participated in the care of patients with COVID-19, they nonetheless believed that nurses should not be forced to provide care for COVID-19 patients. They highlighted that nurses could have personal or social factors that placed them and their families at risk. For example, some female nurses could be pregnant, which would place them at high risk, and other nurses could have at-risk family members, such as children or elders. One nurse stated:

"Some nurses might have serious circumstances that could prevent them from taking care of patients with COVID-19. For example, some nurses might be pregnant, whilst others might have family members with low immunity, and if nurses contract the virus, they might pass it on to their family members. Also, some nurses might have children" (NH3).

Another participant reported:

"First, I try to assess the situation and find out why the nurse is refusing to work with COVID-19 patients and whether the reasons are logical or illogical. The nurse might have a logical reason, such as certain family circumstances or psychological or pathological conditions. In these situations, we may accept the nurse's refusal to work" (NH10).

Caring for COVID-19 Patients Is a Community and Professional Commitment

Some of the participating nurses believed that they had a commitment toward their country and their profession to take care of patients with COVID-19. They emphasized that as nurses, they had no choice but to agree to work with COVID-19 patients. One nurse stated:

"As a nurse, you do not have a choice of whether to work or not …. regardless of whether the disease is infectious or not … stable or not … These are patients and you need to take care of them.… I am a nurse and this is what my job requires" (NK4).

Another nurse reported:

"I am one of those nurses who would never say no… I feel that this is a community duty …I was asked, so I went for it" (NK5).

The nurses in this study found it very difficult to refuse taking care of patients with COVID-19, and they indicated that even if they were to be asked again to take care of COVID-19 patients, they would still say yes. One nurse stated:

"Even if I were to be asked again, I would not say no. I don't know …I feel it's my professional obligation to not refuse any work …I as [name of participant] *am not here to be selective in my work and to work only with stable, noninfectious cases…In the end, you as a nurse should provide care not only to stable patients but to all patients, whether they have H1N1 or COVID-19 or AIDS"* (NH10).

Nurses Are Responsible for Protecting Themselves

As frontline healthcare providers, the participating nurses believed that they needed to protect themselves so as to not contract the virus. Thus, they believed that they were obligated to have sufficient knowledge and to protect themselves appropriately. They considered this to be part of their accountability as nurses. One nurse stated:

"You have some people in the community who wouldn't forgive you if you caught the virus… They would say that healthcare providers are the ones responsible for the spread of the virus … I am cautious

when treating patients and follow precautions . . . so that I won't be accountable and won't be asked by people" (NH2).

Some of the interviewed nurses expressed their fear of contracting the virus, as this is perceived as a social stigma. One nurse reported:

"You know, if I were to get infected, this would be a stigma. . . People would say that I am responsible for spreading the disease to the world (laugh). Seriously, I felt scared, so I isolated myself. But even so, people wouldn't forgive me if they found out that I had the virus" (NK5).

Another participant emphasized:

"At the beginning, we had a few members of healthcare staff who got infected and transmitted the disease to their families. Thus, people are considering them responsible and blame them as if they're the reason [for the spread of the disease]*"* (NH4).

DISCUSSION

Nurses are frontline workers providing care for patients, and they struggle with many ethical challenges when providing patient care. Nurses are often faced with everyday ethical decisions in nursing practice that may seem insignificant but which may be stressful for nurses, as they must face the question of what is right and what is wrong (15). This is particularly the case during these times, given the outbreak of the COVID-19 pandemic around the globe. The present study aimed to explore nurses' ethics in the care of patients with COVID-19, considering the fact that it may become particularly difficult for nurses to offer their care and help during a pandemic like the COVID-19 pandemic.

Nursing practice is guided by a professional code of ethics, which is applicable wherever and whenever nurses are working. The code allows nurses to identify ethical issues and provides guidance on how to take ethical decisions and actions when providing care. In certain circumstances, nurses are allowed to choose not to provide patient care. The safety of nurses and other frontline healthcare workers is a pressing ethical concern, as they are often asked to work under conditions that pose substantial and inadequately understood risks to their overall health and well-being. In addition, nurses may choose not to provide patient care if they lack the support they need to meet their personal and family needs or if they are also worried about the moral, professional, and legal protection when providing nursing care.

During emergencies such as pandemics, nurses may prioritize other aspects of emergencies, such as mitigation, preparedness, response, and recovery, over human rights. However, they can only do so after presenting logical reasons, obtaining consent from concerned authorities, and meeting international standards. Nonetheless, even in such situations, it is the duty of nurses to promote patient health and follow proper protocols to prevent all those involved from oppression (16).

The nurses in the current study reported that it was their duty to care for patients regardless of their medical condition or diagnoses. They expressed that this was part of their professional ethics, which are framed by standards of human rights. Since the nurses were aware that their profession is directed toward the care of patients and the community, they believed that they had a national/community commitment to not refuse to provide care for any patient. In addition, the most common ethical issues among the majority of the nurses in the current study were related to the protection of patients' rights, since this is one of the founding principles of nursing practice. The value of beneficence, professional advocacy, and serving the best interests of patients is emphasized by both national and international nursing standards of ethical behavior.

Patients who suffer from any disease feel anxious and uncertain (17), and this is especially the case with COVID-19, a disease with unclear prognosis and treatment. Such diseases, which are often contagious, may be stigmatized by society, and patients may therefore require support and care. It is mostly nurses who are expected to provide this care and support, regardless of the patient's diagnosis.

The nurses in the current study also shed light on the challenges faced by nurses when the COVID-19 patient is also a family member. It is a challenging experience being a nurse, and caregiver, and taking care of relatives. Nurse family careers actively engage in possibilities to maintain a sense of engaged involvement in the everyday caring for their relatives (18).

Support at the organizational level is of great significance for registered nurses. Nurses should be actively involved in the development and implementation of policies related to the quality of care, especially during exceptional circumstances such as the COVID-19 pandemic. Thus, effective communication between registered nurses and their organizations' management teams is essential. Nurses' capabilities of providing patient care should be acknowledged at all organizational levels, and their concerns should be heard and addressed.

The nurses in the current study had volunteered to work with patients with COVID-19, as they believed that it is part of nurses' responsibility to take care of patients regardless of their diagnoses. Nonetheless, the participating nurses expressed that working with COVID-19 patients should not be obligatory, as some nurses may be incapable of providing the required care in unexpected and unclear circumstances such as the COVID-19 pandemic. For example, some nurses may be sick or may have social obligations such as caring for children or elderly family members. The participating nurses felt that it is the obligation of employers to foster work environments wherein the health and well-being of healthcare professionals are ensured. This may include the provision of immunizations and adequate personal protective equipment, in addition to other operational protocols. Moreover, it is impossible to follow the ethical requirements of clinical practice without adequate staffing. Understaffing and other systematic challenges could impede nurses from performing many of their primary duties, such as maintaining the needs of particular patients and families, alleviating pain, and maintaining their own honesty.

While investigating the reasons behind the event of loss of numerous lives by the breakout of severe acute respiratory syndrome (SARS) in 2003, the researchers working at the University of Toronto Joint Center for Bioethics reported that

the healthcare teams were not fully equipped with the knowledge to deal with emergencies and pandemics (19). It was therefore suggested that healthcare institutes should specify beforehand clear guidelines related to dealing with the outbreak of any contagious disease. The researchers also suggested that measures be taken to improve the existing methods of creating awareness among healthcare workers regarding their duties and roles during the outbreak of contagious diseases (19).

A main question that arises during pandemics, such as the COVID-19 pandemic, is whether nurses can refuse to provide patient care in order to protect themselves. Nurses may refuse to provide patient care when this is in the best interest of their personal safety and well-being, as well as their families' (20). In such contexts, the basic right of nurses to protect themselves and their families cannot be overlooked or denied (21–23). On the other hand, there is the view that nurses are professionally responsible for caring for patients regardless of the personal consequences. Therefore, in times such as the COVID-19 pandemic, nurses may find themselves faced with the ethical dilemma of whether to refuse to provide patient care in order to protect themselves or to provide patient care regardless of the consequences this may entail.

The study has a few limitations. A small sample size ($n = 10$) may not represent all nurses working with COVID-19 patients, but this number is sufficient for no new themes to emerge. Also, there was repetition in the information provided and reached saturation. Another limitation of this qualitative study's findings is not intended to be generalized but rather to be used to gain an understanding of the experiences of nurses working with COVID-19 patients.

CONCLUSION

Healthcare providers, including nurses, play a significant role during pandemics and other emergencies in facilitating the provision of healthcare and reducing the damage caused by such disasters. Sympathy has been indicated as a nursing ethical value with traits of understanding the needs of patients and their families and providing care based on moral and ethical standards. The standards of practice and ethical codes to be followed by nurses in the provision of healthcare during pandemics or disasters are specified by current laws and agreements. Working in the healthcare sector entails that nurses should think about their ethical responsibilities, challenging duties, and professional and personal values prior to the occurrence of emergencies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by This Study was conducted after obtaining the approval of the Institutional Review Board at the Jordan University of Science and Technology. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This paper was funded by the Faculty of Scientific Research and Jordan University of Science and Technology.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

REVIEW
published: 12 May 2021
doi: 10.3389/fpubh.2021.560405

DNR and COVID-19: The Ethical Dilemma and Suggested Solutions

Hala Sultan[1†], *Razan Mansour*[2†], *Omar Shamieh*[3], *Amal Al-Tabba'*[4] *and Maysa Al-Hussaini*[5*]

[1] School of Medicine, University of Jordan, Amman, Jordan, [2] Outcomes and Implementation Research Unit, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, MO, United States, [3] Department of Palliative Care, King Hussein Cancer Center, Amman, Jordan, [4] Independent Researcher, Amman, Jordan, [5] Human Research Protection Program, King Hussein Cancer Center, Amman, Jordan

Ethics are considered a basic aptitude in healthcare, and the capacity to handle ethical dilemmas in tough times calls for an adequate, responsible, and blame-free environment. While do-not-resuscitate (DNR) decisions are made in advance in certain medical situations, in particular in the setting of poor prognosis like in advanced oncology, the discussion of DNR in relation to acute medical conditions, the COVID-19 pandemic in this example, might impose ethical dilemmas to the patient and family, healthcare providers (HCPs) including physicians and nurses, and to the institution. The literature on DNR decisions in the more recent pandemics and outbreaks is scarce. DNR was only discussed amid the H1N1 influenza pandemic in 2009, with clear global recommendations. The unprecedented condition of the COVID-19 pandemic leaves healthcare systems worldwide confronting tough decisions. DNR has been implemented in some countries where the healthcare system is limited in capacity to admit, and thus intubating and resuscitating patients when needed is jeopardized. Some countries were forced to adopt a unilateral DNR policy for certain patient groups. Younger age was used as a discriminator in some, while general medical condition with anticipated good outcome was used in others. The ethical challenge of how to balance patient autonomy vs. beneficence, equality vs. equity, is a pressing concern. In the current difficult situation, when cases top 100 million globally and the death toll surges past 2.7 million, difficult decisions are to be made. Societal rather than individual benefits might prevail. Pre-hospital triaging of cases, engagement of other sectors including mental health specialists and religious scholars to support patients, families, and HCPs in the frontline might help in addressing the psychological stress these groups might encounter in addressing DNR in the current situation.

Keywords: COVID-19, do not resuscitate, ethics, healthcare, Pandemic

OPEN ACCESS

Edited by:
Delia Boccia,
University of London, United Kingdom

Reviewed by:
David Hunter,
University of Adelaide, Australia
Paul Russell Ward,
Flinders University, Australia

***Correspondence:**
Maysa Al-Hussaini
mhussaini@khcc.jo

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health

Received: *11 May 2020*
Accepted: *19 March 2021*
Published: *12 May 2021*

Citation:
Sultan H, Mansour R, Shamieh O, Al-Tabba' A and Al-Hussaini M (2021) DNR and COVID-19: The Ethical Dilemma and Suggested Solutions. Front. Public Health 9:560405. doi: 10.3389/fpubh.2021.560405

INTRODUCTION

Cardiopulmonary resuscitation (CPR) was first devised in 1530 (1). However, it was only in 1956 that CPR was reinvented and refined into the currently known and performed technique (2). Do-not-resuscitate (DNR) is defined when neither basic (heart compressions and ventilation) nor advanced (defibrillator or medicines) CPR should be performed. Terminally ill patients for which further medical intervention is considered futile, when quality of life is deemed poor, or

who are expected to be permanently dependent on ventilators are the cases in which DNR is considered a plausible decision. The DNR decision is usually made based on a combination of the medical decisions and the patient's wishes and values. Interestingly though, the legal status of DNR varies between countries; from allowing it to a complete prohibition with legal consequences (personal communication). A link between ethics and DNR became a heated topic and the subject of published literature in 1979 (3), and later on addressed in further publications (4–8). Many linked religious and psychosocial conditions (9), and spirituality (10), as well as ethnicity (11) to the acceptance of the DNR order. Other features like chronic illness and old age may also impact the DNR decision (12–14), although a patient as young as 40 years old might succumb to the DNR order in the face of certain medical conditions (15). Children with DNR orders serve yet another example where physicians might encounter hardship as parents/ guardians have to make difficult decisions (9, 16). Also, more acute conditions within the setting of an intensive care unit (ICU) for example can elicit a DNR order (17). In the setting of lower-respiratory tract infection/pneumonia for example, DNR orders resulted in lower hospitalization and hospital-based mortality incidences suggesting that even in the absence of outbreaks and pandemics, planning and implementing DNR would save resources which can then be re-directed (18, 19).

Resources can become especially scarce during a pandemic. The World Health Organization (WHO) defines a pandemic as "the worldwide spread of a new disease" (20) where the R0, a term that reflects "how infectious a disease is," is >1 (21). In the more recent era, the world had witnessed many disease outbreaks, some of which were declared worldwide pandemics. These include, but are not limited to, the Asian flu in 1957, Severe acute respiratory syndrome (SARS) in 2002, Ebola in 2014, and lastly Zika in 2015 (22).

A thorough search affirmed that the closest recent pandemic to the current COVID-19 pandemic is H1N1 influenza (R0 = 1.4 −1.6). Back in 2009, the UK's Resuscitation Council established guidelines regarding CPR and the H1N1 influenza pandemic (22). It affirmed that DNR patients should be identified early on so that no CPR is attempted. However, in the case of commencement with CPR, only chest compressions should be started; mouth-to-mouth ventilation should be avoided. Recently, an article on the American Heart Associations' guidance for CPR amid the COVID-19 pandemic reiterated the aforementioned H1N1 guidelines, and also emphasized the use of airborne infection isolation rooms especially when there is a risk of dissemination of virus droplets, such as endoscopies, and bronchoscopy procedures, as well as respiratory protection; most importantly an N95 mask (23). More importantly, physicians are recommended to intubate patients with respiratory failure owing to the COVID-19 virus to reduce the risk of aerosol generation (24). The current pandemic, owing to the pervasive COVID-19 virus, with up to 100 million cases worldwide and 2,170,000 deaths (January 27, 2021), advocates for upfront implementation of the DNR order to COVID-19 infected patients; especially the elderly or those deemed associated with poor prognosis as per the physician's assessment (25). The inquiry here is multifaceted. How ethical is it to consider unilateral (i.e., without prior consent of patient) DNR orders for COVID-19 infected patients in the face of limited resources? What are the potential consequences for other patients suffering from acute heart conditions, respiratory conditions, or road traffic accidents who might be competing with COVID-19 infected patients for the limited ventilators? Can we deny pre-planned treatment management to certain groups of patients (like for example new and on-treatment cancer patients) to preserve needed ICU rooms and ventilators if unilateral DNR orders for COVID-19 infected cases could not be made? And essentially, what are the moral consequences for the healthcare providers (HCPs) making these tough decisions? How might these measures interject with the four major principles of medical ethics; autonomy, beneficence, non-maleficence, and justice? What would be a plausible approach to this ethical dilemma?

To address these questions, an exhaustive literature review using PubMed, Medline, Science Direct, and online news sites was undertaken to gather evidence and summarize the local, regional, and international recommendations.

How ethical is it to consider unilateral DNR orders for COVID-19 patients in the face of limited resources?

The answer to this question might not be straight forward. Given COVID-19's very high R0 as well as the relatively low success rate of CPR among ICU patients in general and the scarcity of personal protective equipment (PPE), many "hospitals on the frontline of the pandemic are attempting to weigh the costs of exposing doctors and nurses to the coronavirus" (26). On a global level, the issue is; what happens if HCPs who are at the frontline in our battle against COVID-19 get infected with the virus in an attempt to resuscitate a patient with a very low probability of survival, i.e., older people with preexisting comorbidities; including cardiac, respiratory, and other chronic health disorders (27)? It is also important to recall that the possibility of discharging an ICU patient after using CPR is around 17% (28), and that CPR is only effective in the first 4 to 7 min of cardiopulmonary arrest; by the time physicians reach the patient, especially if they had to wear PPE, they might have already run out of time. On the other hand, rushing to respond to CPR situations can increase the probability of PPE breach, putting HCPs at risk of infection (26). Moreover, most patients who are successfully resuscitated will need a ventilator, further contributing to the scarcity of resources amidst the COVID-19 pandemic, and possibly depriving other patients with a greater probability of survival from using these resources. In light of these debatable questions, DNR seems to be an immensely valid option.

An article by Curtis et al. (27), "Decisions About Do-Not-Resuscitate Orders During COVID-19," emphasizes the dangers of COVID-19 and that its spread has led to the development of so-called "unilateral DNR." This term was coined to "reduce the risk of medically futile CPR to patients, families, and healthcare workers." This is especially when CPR will unlikely allow successful return to an acceptable quality of life. It also saves ICU resources to allow for the accommodation of patients with a better chance of recovery. In the case that such protocols

are implemented, all patients and family members should be knowledgeable about and adhere to the healthcare unit's wishes.

One such example is in New Jersey and some hospitals in New York; as of March 27, 2020, all "COVID-19 patients [will be placed] on a DNR-B resuscitation status." In DNR-B, all patients continue to receive their treatment for all medical conditions except in the event of a cardiac arrest (29), "No code blue will be called on any COVID-19 patients." (30) Other states in the United States, as well as other countries, are yet to decide.

A study in 2016 that addressed the ethicality of allocating scarce medical resources by HCPs explored the views of general practitioner (GP), medical students, and lay people (31). In one of the scenarios addressed (Scenario-B), allocation of scarce beds in hospitals amid an imaginary flu epidemic, lay personnel ranked the "sickest" patient as the priority in the limited bed allocation, while "prognosis" was top rated by the GP, medical students, and other HCPs. This clearly addressed the potential controversy that might arise among HCPs and patients during health crises like pandemics and that should be addressed in anticipation of any.

Whether patients infected with COVID-19 can be considered as a vulnerable population (people in need of special care, support, or protection because of age, disability, or risk of abuse or neglect) warrants further consideration while addressing the issue of DNR. Age was among the discriminator to triage patients; patients older than 80 years were offered DNR because of the futility of treatment and co-morbidities (25). Patients and families of patients diagnosed with COVID-19 disease have been stigmatized in some communities, which further adds to the vulnerability of COVID-19 patients (personal communication).

What are the potential consequences for other patients suffering from acute heart conditions, respiratory conditions, or road traffic accidents who might be competing with COVID-19 patients for the limited resources?

Triaging patients including COVID-19 patients, those with acute conditions like cardiopulmonary cases, those with emergency surgical intervention as well as cancer patients planned for elective surgeries which can be postponed for a maximum of a few weeks, but no longer, would be an important ethical consideration when addressing the potential of limited resources should ICUs and ventilators be needed. In Italy, around 50% of hospital beds in a 1,000-bed hospital in Northern Italy were occupied by COVID-19 patients (32), leaving the other half to deal with the rest of the other medical conditions, which might be sub-optimal to say the least. As a consequence, elective surgeries have been canceled, semi-elective procedures postponed, and operating rooms turned into makeshift ICUs (32).

The practice of dealing with DNR is sub-optimal even in the luxury of the routine practice outside pandemics. Within the setting of oncology practice in particular, Pettersson et al. reported that almost half of the nurses and physicians surveyed on the issue of DNR reported that "it is not likely that the patient would be involved in the decision on DNR," 21% believed that it is irrelevant to inform patients of the DNR decision, and 57% reported that providing information to the patient was important, although only 21% stated that this was likely to happen (33). Importantly, Bovman argues that reversing a DNR code if elective surgery is warranted is associated with a dismal 30-day mortality (34). One important limitation is that patients treated for other conditions might end up infected with COVID-19 once admitted to the hospital (32).

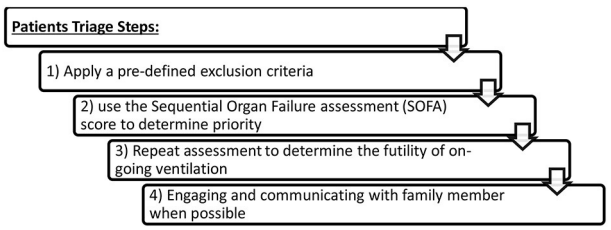

FIGURE 1 | Patient triage steps.

At King Hussein Cancer Center (KHCC), the only stand-alone cancer center in Jordan, difficult decisions had to be made as well (35). During the months of March, April, and May, all elective surgeries, clinical appointments, and procedures were canceled, and chemotherapy and radiotherapy were canceled for the first two weeks and then started to build up gradually during the third week in anticipation of a potential surge of COVID-19 infected cases. In addition, patients were instructed to call a designated hotline if needed instead of in-person arrival to KHCC. A fully prepared ward was assigned to quarantine confirmed COVID-19 patients. All non-frontline employees were asked to stay at home, and a minimal number of HCPs were scheduled to cover the needs. Although this could compromise the small windows cancer patients might have, difficult decisions are made in anticipation of the worst (Ethical Considerations for Treating Cancer Patients during the SARS-COV-2 Virus Crisis: To Treat or Not to Treat? A Cancer Center in Low-Middle Income Country).

What Are the Consequences for HCPs Taking These Tough Decisions?

In harmony with the Hippocratic Oath, every medical physician swears to "apply, for the benefit of the sick, all measures [that] are required" (36). This regards not only to day-to-day practice, but also, and more importantly, for when they are needed most, such as in times of outbreaks. Accordingly, the consequences for the HCPs can be divided into physical/physiological and psychological/moral injuries.

To HCPs, and in accordance with what their degrees encompass, universal DNR to COVID-19 infected patients does not seem to be an option, adding to the ethical dilemma, self-blame, and burnout of the frontline decision makers. In some countries like the US, hospitals should apply for a so-called 1135 waiver, that waiver temporarily lifts Centers for Medicare & Medicaid Services requirements in times of a national emergency, because failing to do so is considered "in violation of patient rights"(37). In a study that addressed frontline vs. non-frontline nurses dealing with COVID-19 patients, a significant difference in both physiology and psychology between both groups was in favor of frontline nurses (38).

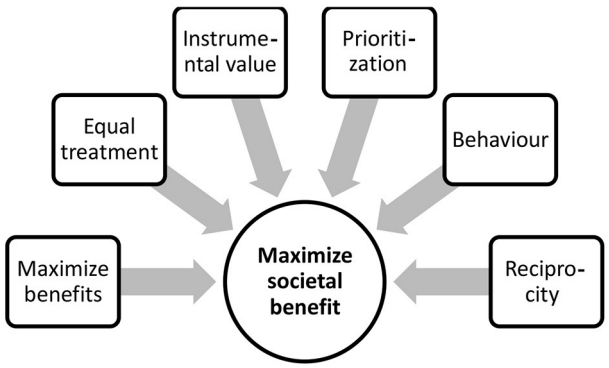

FIGURE 2 | A multi-value ethical framework to maximize societal benefit.

As for the psychological/moral consequences, in this particular setting of the COVID-19 pandemic, initiating or terminating a life supporting ventilator might be among the most difficult acts a physician can make during his/her career (39). Italian physicians were reported to weep in hospital hallways because of the difficult decisions they had to make (40).

It would be of interest to investigate if the HCPs in the current pandemic understand the burden of approving a DNR for patients infected by COVID-19. While this might be unreachable in the current condition, to understand the impact of the one-way tough decisions made by the physicians should be the subject of further research.

How Might These Measures Interject With the Four Major Principles of Medical Ethics; Autonomy, Beneficence, Non-maleficence, and Justice?

The dispute here is whether DNR codes, especially the unilateral DNR code, and resuscitation guidelines respect the four core medical ethics principles: autonomy, beneficence, non-maleficence, and justice (41).

Autonomy

Autonomy and non-maleficence were reported by nurses and physicians, respectively, as the most important ethical values when dealing with the DNR status (42). Deciding on DNR on behalf of patients, i.e., unilateral DNR to save others with a higher probability of survival and to protect HCPs may serve the principles of equity and not equality, and seems to violate the principle of autonomy, which honors the patients' preference and wishes regarding any decision for their medical care. Fostering autonomy would dictate the discussion of all care-related options including the DNR code and do-not-operate (DNO) code with the patient and/or family so that they can make an informed decision (43–45). An informed consent form signed by the patient or a surrogate might, however, falsely re-assure the HCPs of the patient's understanding and thus volunteerism and autonomy (46). Also, making decisions on behalf of a competent patient exemplifies a paternalistic and professional nihilism that contradicts autonomy (47). Additionally, weighing the risk-to-benefit ratio and prioritizing societal over individual benefit is another issue when considering DNR, especially amid the COVID-19 pandemic.

Justice

The principle of justice entails "fair adjudication between conflicting claims," as well as treating patients with fairness, and to do so equally and equitably (48). Concerning the COVID-19 pandemic and DNR, the term "distributive justice" resurfaces, which considers fair allocation of resources, treatments, and benefits during a time of medical resource scarcity. Physicians started treating patients equitably but not equally, and other factors entered the equation when it came to providing care, as patients with the best chance of recovery were prioritized over others (49). Moreover, due to prolonged exposure, close contact, and lack of PPE, healthcare workers are at a significantly increased risk of acquiring infection (50), and should be prioritized when providing critical care when it comes to advanced life support.

What medical and ethical decision should be made when all patients are equal in need and predicted outcome, but the resources are barely enough? One study proposed a central "lottery" system as a solution for the distribution of resources to these patients. Patients' characteristics were suggested to be entered into the system and a supervised random selection process should then take place to ensure fair and equity of distribution (51). This could also apply to patients who are predicted to need CPR. However, the controversy will still be an issue, and there will be no single "best" answer.

Beneficence and Non-maleficence

Beneficence is defined as "an act of charity, mercy, and kindness with a strong connotation of doing good to others including moral obligation" (52). In healthcare, beneficence encompasses the idea that a physician's actions, decisions, and skills must always advocate for what is best for the patient. Physicians must apply the principle of beneficence while causing no harm to patients, a term referred to as non-maleficence ("above all do no harm"). In this instance, CPR is advised to be performed on patients if apparent benefit was the expected result. However, some argue that CPR should not be performed if it is not expected to result in benefit to patients, or if it may prolong their suffering, and the physicians should accordingly write a unilateral DNR order (53). The ethical and medical decision depends upon weighing therapeutic benefits against risks.

What Would Be a Plausible Approach to the Ethical Dilemma?

In a more conscious evaluation of the objective indications of DNR, Lipsky identified four core elements that can be assessed when deciding on DNR; futility of treatment, poor quality of life, patient refusal, and cost (54). If these same elements are applied into the current condition, where societal benefit prevails over self-benefit, it would be logical to consider any of the aforementioned four elements as a justification for the universal or unilateral DNR code adopted by the health sector

in some nations. Along the same lines, Edwards B.S., argues that a small but significant number of ICU DNR-coded patients consume the already scarce resources including HCPs; nurses in this particular case within normal circumstances (55), let alone the current COVID-19 pandemic and the strain on limited resources. Calls for a just allocation for the use of the already limited resources are in place despite potential adverse effects on patient's autonomy and beneficence. Additionally, an important argument would be that an early DNR code would save the patient and family futile interventions (13). Triaging patients can be a multi-step and dynamic process that consists of three steps including (1) the application of exclusion criteria, (2) using the Sequential Organ Failure Assessment (SOFA) score to determine priority, and (3) repeated assessments to determine the futility of on-going ventilation (39). We would suggest a fourth point for engaging and communicating with family members when possible (**Figure 1**).

Curtis et al. shared an algorithm on how to address advanced care planning, the goals of care, and informed assent with a patient or surrogate family. This should proceed stepwise so that the patient and/or family surrogate can affirm understanding or are otherwise allowed to object (27). Since not one single ethical consideration might be able to address how to allocate scarce resources, a multi-value ethical framework, where more than one factor is considered, might seem more ethical (25). Maximizing benefits, i.e., saving the most lives and treating those with better prognosis, equal treatment to people, i.e., selection among people with similar prognosis, instrumental value, i.e., benefits to others, and priority to the sickest or the youngest when it aligns with maximizing benefits, should all be combined to maximize societal benefit. Additional factors that we suggest based on this literature review to help align scarce resources include behavioral status; priority to those who did not engage in risky behaviors that caused their condition or affected it negatively, and reciprocity; priority to those who have voluntarily provided societal services in the past (**Figure 2**).

Deployment of the medical workforce in areas in most need is an effective modality to support healthcare systems. This has been an effective strategy in Wuhan, China, where attempts to contain the spread of the pandemic was a wise decision (38). In the US, due to the likelihood of a shortage of HCPs, many retired physicians and medical students volunteered to aid in the crisis. Dr. Judy Salerno, a retired physician in her 60s declared that "if (she) can use (her) skills in some way that will be helpful, (she) will step up" (56). Medical students have also aided, taking basic histories over phone calls and babysitting for HCPs overwhelmed in hospitals and other facilities. In Jordan, medical students were heavily engaged with surveillance activity for potentially infected persons, as well as volunteering to deliver prescribed drugs to patients (personal communications).

The psychological impact on HCPs is of paramount importance (57), and should be accounted for when nationwide decisions are put in place (38). It is of value to note that whether or not a physician or hospital desires to commence with the unilateral DNR protocol, this decision should not be left entirely up to them; "providers, administrators, attorneys, clergy, and compliance" should be called to discuss the specifics (20). Proper training and education of the HCPs, especially junior staff, should be in place to help alleviate misconception on the timing of, and inclusion/exclusion criteria of the DNR code (58, 59). In addition, DNR needs to be disclosed by the more experienced members in the caring team (60). Many hospitals would triage CPR/DNR patients in the hand of a committee, none of the members of which are involved in patient treatment (39). One suggestion is to create a "triage committee" composed of senior and respected members of the medical community who volunteer to sit in on these committees, thus preventing first-line HCPs from making tough decisions that may impact their well-being. KHCC has adopted a similar approach, where the decision on unilateral DNR has to be made by a committee composed of the primary physician and two other physicians for terminally ill patients if a shortage in ventilators occurs in the future in Jordan (35).

An often overlooked facet is the role religious scholars can play when a DNR order is made. Religious scholars for different theistic groups should be made part of the clinical ethics committees in the hospitals, and in the case of the COVID-19 pandemic, national committees that address the DNR issue in acutely diseased and admitted infected patients (61). Providing support to the patient and/or family should also be extended after discussing the DNR. The presence of ethics-trained religious scholars can be of utmost importance especially when confronting national crises to ensure patient dignity, coping strategies for the family, and relief of the HCPs, with an ultimate goal to support family members as well as HCPs. Of interest, the European Islamic Jurisdiction Council clearly addressed the social impact on larger communities associated with the COVID-19 pandemic. Driven by the larger societal benefit, DNR orders were endorsed if deemed necessary by a compatible physician (62).

CONCLUSION

Despite the ethicality of this matter, and as a result of the rapid evolution and progress of the COVID-19 pandemic, as well as the anticipated shortage of resources, some hospitals have already made decisions. Public trust and confidence in the medical decision should not, however, be overlooked. Transparency of the medical sector, along with public engagement should help in alleviating the ethical burden of applying the unilateral DNR to COVID-19 infected patients and maintaining public trust. Practical approaches are suggested to address the potential sequelae. All in all, the question facing HCPs here may not precisely be how ethical, but rather: what choice do you make when 7.8 billion people's lives are at risk?

AUTHOR CONTRIBUTIONS

HS: literature review, writing the first draft, and review and final approval. RM: literature review, reviewing the first draft, and final review and approval. OS: literature review, critical review of the draft manuscript, and final review and approval. AA-T: literature review, reviewing the first draft, and final review and approval. MA-H: inception of the idea, literature review, critical review of the first draft, and final review and approval. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

METHODS
published: 21 May 2021
doi: 10.3389/fmed.2021.619978

iOntoBioethics: A Framework for the Agile Development of Bioethics Ontologies in Pandemics, Applied to COVID-19

Mohammed Odeh[1,2], Faten F. Kharbat[3], Rana Yousef[4], Yousra Odeh[5], Dina Tbaishat[6], Nancy Hakooz[7], Rana Dajani[8,9] and Asem Mansour[1]*

[1] Cancer Care Informatics Programme, King Hussein Cancer Center (KHCC), Amman, Jordan, [2] Faculty of Environment and Technology, University of the West of England, Bristol, United Kingdom, [3] Software Engineering and Computer Science Department, College of Engineering, Al Ain University, Abu Dhabi, United Arab Emirates, [4] Computer Information Systems Department, King Abdullah II School for Information Technology (KASIT), The University of Jordan, Amman, Jordan, [5] Software Engineering Department, Faculty of Information Technology (FIT), Applied Science Private University, Amman, Jordan, [6] Library and Information Science Department, University of Jordan, Amman, Jordan, [7] Department of Biopharmaceutics and Clinical Pharmacy, School of Pharmacy, University of Jordan, Amman, Jordan, [8] Department of Biology and Biotechnology, Hashemite University, Zarqa, Jordan, [9] Jepson School of Leadership, University of Richmond, Richmond, VA, United States

OPEN ACCESS

Edited by:
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Domenico Criscuolo, Italian Society of Pharmaceutical Medicine, Italy

***Correspondence:**
Mohammed Odeh
Mohammed.Odeh@sky.com

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *21 October 2020*
Accepted: *29 March 2021*
Published: *21 May 2021*

Citation:
Odeh M, Kharbat FF, Yousef R, Odeh Y, Tbaishat D, Hakooz N, Dajani R and Mansour A (2021) iOntoBioethics: A Framework for the Agile Development of Bioethics Ontologies in Pandemics, Applied to COVID-19. Front. Med. 8:619978. doi: 10.3389/fmed.2021.619978

Background: Few ontological attempts have been reported for conceptualizing the bioethics domain. In addition to limited scope representativeness and lack of robust methodological approaches in driving research design and evaluation of bioethics ontologies, no bioethics ontologies exist for pandemics and COVID-19. This research attempted to investigate whether studying the bioethics research literature, from the inception of bioethics research publications, facilitates developing highly agile, and representative computational bioethics ontology as a foundation for the automatic governance of bioethics processes in general and the COVID-19 pandemic in particular.

Research Design: The iOntoBioethics agile research framework adopted the Design Science Research Methodology. Using systematic literature mapping, the search space resulted in 26,170 Scopus indexed bioethics articles, published since 1971. iOntoBioethics underwent two distinctive stages: (1) Manually Constructing Bioethics (MCB) ontology from selected bioethics sources, and (2) Automatically generating bioethics ontological topic models with all 26,170 sources and using special-purpose developed Text Mining and Machine-Learning (TM&ML) engine. Bioethics domain experts validated these ontologies, and further extended to construct and validate the Bioethics COVID-19 Pandemic Ontology.

Results: Cross-validation of the MCB and TM&ML bioethics ontologies confirmed that the latter provided higher-level abstraction for bioethics entities with well-structured bioethics ontology class hierarchy compared to the MCB ontology. However, both bioethics ontologies were found to complement each other forming a highly comprehensive Bioethics Ontology with around 700 concepts and associations COVID-19 inclusive.

Conclusion: *The iOntoBioethics framework yielded the first* agile, semi-automatically generated, literature-based, and domain experts validated *General Bioethics* and *Bioethics Pandemic Ontologies Operable in COVID-19 context with readiness for automatic governance of bioethics processes*. These ontologies will be regularly and semi-automatically enriched as iOntoBioethics is proposed as an open platform for scientific and healthcare communities, in their infancy COVID-19 learning stage. iOntoBioethics not only it contributes to better understanding of bioethics processes, but also serves as a bridge linking these processes to healthcare systems. Such big data analytics platform has the potential to automatically inform bioethics governance adherence given the plethora of developing bioethics and COVID-19 pandemic knowledge. Finally, iOntoBioethics contributes toward setting the first building block for forming the field of *"Bioethics Informatics".*

Keywords: bioethics, COVID-19, pandemic, bioethics ontology, bioethics informatics, iOntoBioethics, agile framework, design science research methodology

INTRODUCTION

One of the key rationales behind developing machine interpretable ontologies is to resolve semantic heterogeneities between key concepts in a particular domain. Such an approach will facilitate common understanding and communication language between both humans and machine leading to better analysis and reusing of the underlying domain knowledge, along with the explicit representation and automatic reasoning based on related conceptual domain assumptions. In healthcare, for instance, context-aware systems must adapt to their changing dynamic environment. Ontology concepts are elicited and implemented in various healthcare computing systems (1). For example, ontology has been employed in the medical field to: enhance the functionality of complex medical data, provide informed medical prescriptions, and reduce errors in diagnosis (1). In addition, ontologies contribute to developing a global mental health ethics to serve the need of having autonomy-driven bioethics in non-western cultures (2). Furthermore, with the emergence of IoT and viable 5G networks, technology has been revolutionizing communication among healthcare systems. Therefore, the role of ontologies is considered a major building block in resolving semantic heterogeneities between healthcare systems in a global context (1).

The bioethics literature reports on few limited ontological attempts to conceptualize the bioethics domain with limited scope representativeness (3). In addition to a lack of a robust methodological approach in driving the research design and evaluation of resultant bioethics ontologies, the literature does not report on the existence of bioethics ontologies in pandemics and more specifically for COVID-19. Therefore, this research aims to develop an agile, highly representative, and robust ontological model within the domain of bioethics in general, and amidst pandemics in particular such as COVID-19. This is anticipated to achieve a better understanding of bioethics processes and automatic governance of these processes when linked to the respective information systems operating in healthcare centers, research and development institutions, civil society organizations, and businesses affected by bioethics.

Our main research hypothesis states that "investigating the bioethics research literature, from the inception of bioethics research publications, leads to identifying a highly agile representative set of bioethics conceptual entities, and governance relationships of bioethics processes". A methodological research framework (iOntoBioethics) has been fit-for-purpose developed to prove this research hypothesis guided by the Design Science Research Methodology (DSRM) (4) and utilizing the systematic literature mapping method. The search space utilized more than 26,000 Scopus-indexed articles with emphasis on bioethics processes in order to inform whether a semi-automatically generated bioethics ontology is comparable to a manually developed generalized bioethics ontology developed also during the course of this research. The sufficiency and representativeness of the automatically generated bioethics ontology have been assessed by domain experts in general, and for pandemic bioethics with reference to COVID-19.

BACKGROUND

Ensuring that bioethics and the principles of ethics are positioned at the forefront and central to all day to day processes, related activities and actions, and intersecting sectors during pandemics is of paramount impact for many reasons. *Firstly,* it is well-known that vulnerable communities are most susceptible to the impact of a pandemic across sectors, including economy, health, education etc. Therefore, inequality of deployment of resources results in the suffering of these sectors and their communities. *Secondly,* during pandemics health personnel and scientists are actively developing therapies and preventive measures such as vaccines. Hence, it is more than often the case that vulnerable communities are taking advantage of to test new therapies and vaccines. For example, the history of clinical trials in Africa

caused notable harm to people (5). Big pharma has a history of taking advantage of the lack of local policies and regulations to protect local citizens in many developing countries to come in and conduct vaccine and drug trials under the auspices of legal procedures. *Thirdly,* because of the development of technology and tracking systems to reduce the spread of a pandemic, people's privacy is being violated. Vulnerable communities—who do not have a voice or legal representation—are the ones who usually suffer the most.

Safeguard recommendations were introduced recently (6) such as data and privacy protection, where new technologies are used for surveillance in response to the COVID-19 pandemic. However, such technologies "may cause discrimination, be intrusive and infringe on privacy, or may be deployed against people or groups for purposes going far beyond the pandemic response" (6). Therefore, for these reasons collectively, bioethics principles and processes ought to be placed central to all governmental and civic society processes and sectors in response to pandemic operational spheres. In healthcare systems and society, McGuire et al. (7) discussed several ethical challenges in relation to healthcare systems and society such as informed consent and prioritization of healthcare workers. They found that multiple factors such as changing circumstances, experience, and patterns of illness play a role in reshaping ethical policy and reassessing ethical principles. They stress that learning from the COVID-19 experience is important for the next pandemic. On the same track, Saha et al. (8) indicated that professionals must be aware of the rapid change in the allocation of resources and evaluating healthcare standards. They also reflected on the technological impact in pandemics and stressed on the role of ethics to handle conflicts of interests and allocation of resources.

Bioethics in a Process Context

Aksoy and Tenik (9) indicated that Bioethics is "a quasi-social science that offers solutions to the moral conflicts that arise in medical and biological science practice". It is a systematic study of human conduct, which is interdisciplinary in nature within life sciences and healthcare, insofar as this conduct is examined in light of moral values and principles (10). The four principles of bioethics are: (1) "respect to autonomy," (2) "non-maleficence," (3) "beneficence," and (4) "justice" (11). These principles govern the ethical conduct in almost every society. Bioethics links all healthcare professionals in an attempt to resolve ethical considerations for healthcare systems arising during patient care (12).

Healthcare systems comprise actors, processes, and activities in complex and dynamic environments with massive served and serving systems of systems interactions. However, these healthcare professionals require input from "multiple different disciplines, considering more than one perspective on the same phenomenon" (13). The adoption of a process centric approach in bioethics is of paramount importance in how information is gathered, and how relationships are managed between different stakeholders and systems involved (14).

It is observed that new directions have been emerging for theorizing about ethical decision-making and practice in healthcare contexts by drawing attention to new ethical actors, changing organizational settings with both broader ethical challenges and conceptualization of gate-keeping processes (15). Such emerging directions are becoming more orthogonal to healthcare services; and accordingly ethical review processes (16) will be in timely demand of data consumed and produced during the different activities of bioethics and healthcare processes. Such a requirement that necessitates building the ontology of the domain of bioethics.

Bioethics in Ontological Context

One of the earliest definitions of ontology from a computing point of view is Gruber's definition "Ontology is a specification of a conceptualization" (17). A further more operationalized definition for ontology was provided by Noy and McGuinness (18) as "formal explicit description of concepts in a domain of discourse [classes (sometimes called concepts)], properties of each concept describing various features and attributes of the concept [slots (sometimes called roles or properties)], and restrictions on slots (facets (sometimes called role restrictions))."

Several efforts have been put into integrating bioethics with ontologies. Koepsell et al. (19) developed the Biomedical Ethics Ontology (BMEO) as a methodology to guide the creation of "a powerful information tool". The attempt was considered as "proof of concept". However, DuBois (20) argued that such a framework was "ill-suited" for the entities related to regulatory definitions and ethical concepts. In addition, Wasilewska (21) evaluated the proposed BMEO framework to generate biomedical ethics ontology. He concluded that BMEO "might face unbeatable obstacles and the domain of moral consideration might not, at the same time, be an appropriate realm to be standardized by ontology tools".

Recently Romanyshyn (3) attempted to show the importance of the ontological classifications and their relation to healthcare rationing. In general, his work set the common ground for the necessity of rationing especially with limited resources to ensure fairness between different parties from the same domain. However, he pointed out the need of relaxed range for accepting concepts "that would err on the side of generosity not facing hard choices". He justified the importance of ontological classification in understanding psychological disorders. One of the main limitations of previous literature is the inability to produce a tangible ontology that can be used in practice. Also, no theoretical grounds for the concepts of bioethics (without any implementation), apparent comprehensive methodological research framework, and governing bioethics processes were observed.

Bioethics processes are heavily engaged in ensuring appropriate ethical conduct in relation to the associated healthcare systems and processes. Such ethical processes have data and information consumed and produced in relation to bioethics entities. Therefore, semantic heterogeneities are likely to emerge and new relationships are likely to proliferate between different entities, systems, standards, protocols, etc.,

that will dictate a complex governance requirement for the underlying bioethics processes. Consequently, this becomes very challenging in highly desperate context aware situations and with the massively changing context of dynamic environments such as the COVID-19 pandemic. Thus, in such complex and extremely timely demanding pandemic environments, ontologies are highly appropriate for resolving semantic heterogeneities at different levels of abstraction of bioethics and healthcare processes and systems.

In this research, we define "Bioethics Ontology" as *the structured and formal shared specification of bioethics concepts at different levels of abstraction along with the properties of these bioethics concepts, and the rules that govern the integrity of the relationships between them such that the specified principles and processes of bioethics are adhered to.*

THE iOntoBioethics RESEARCH FRAMEWORK DESIGN

In order to gain a comprehensive coverage of bioethics concepts and their evolution since they first appeared in the literature in 1971, we have developed a novel agile framework to mine the substantially impactful and well-indexed literature. This agile framework is empowered by fit-for-purpose Text Mining and Machine-Learning (TM&ML) engine that automatically identifies bioethics topics and their associated concepts. Such a framework needs to be agile to evolve with new changes or new topics and concepts emerging as new research, policies, legislations, quality and ethical requirements, etc., are published. Such intelligently generated bioethics topics and concepts are the key building blocks for our novel framework in its agility to evolve the construction and evolution of a universal bioethics domain ontology.

Furthermore, the iOntoBioethics framework adopts the Design Science Research Methodology (DSRM) (4) which enacts a problem-based solving paradigm for understanding, conducting, evaluating, and publishing this work. Given that the nature of the iOntoBioethics framework being a software engineering and information systems artifact, the DSRM methodological approach and its process are fit-for-purpose compared to other research methodological approaches that are more suited to laboratory or humanities research projects. The DSRM approach has been widely used and reported in the literature over the past years with notable examples (22, 23). Following the inception phases of problem formulation and objectives' definition, the DSRM process iteratively implements whole increments of design, development and evaluation activities during the whole life cycle of the research framework development before the final phase of communicating research project outcomes. This means that researchers can revisit and re-evaluate the developed framework as duly needed in order to tune the phased and final outcome in meeting the research aim and objectives (24).

In this research, the systematic literature mapping method has been adopted to address our research aim through the development of the iOntoBioethics research framework utilizing the DSRM. The DSRM fit-for-purpose process was devised with the incremental and iterative phases of design, implementation and evaluation before communicating outcomes in the final phase.

The development of the iOntoBioethics framework has been carried out over five increments as shown in **Figure 1**. Although **Figure 1** depicts linear stages of the iOntoBioethics DSRM process, some iterations and interleaving occur between this process increments from design to evaluation. Besides publishing this article and developing an open platform as a research outcome, as per developments published on the www.iOntoBioethics.org website. The website aims to involve the scientific community of researchers from different disciplines that are interested in collaborating their bioethics and/or ontology-related work in relation to this proposed agile framework.

Phase 1: Defining the Research Problem—The Research Gap Analysis

In this phase, the research problem and rationale are identified. Based on the literature, a notable absence of a generic conceptualization model of bioethics domain is recognized, and in particular the absence of a model that operates in pandemics time.

Phase 2: Define Aim and Objectives of the iOntoBioethics Ontology

The iOntoBioethics framework is agile and evolves with emerging research, policies, legislations, quality and ethical requirements, standards, etc. Therefore, this research aims to develop an agile, highly representative, and robust ontological model of the domain of bioethics in general, and amidst pandemics in particular such as COVID-19. This aim will be achieved when it assists in resolving semantic heterogeneities in the domain of bioethics that may arise because of the different uses of terms, processes, or standards. Therefore, the iOntoBioethics ontology becomes the central body that facilitates a standardized communication language in order to achieve better understanding of bioethics processes and in the automatic governance of these processes when linked to the respective information systems operating in healthcare centers, research and development institutions, civil society organizations, and businesses impacting or affected by bioethics. This phase was led by domain experts in the bioethics domain. Finally, the agility dimension of this framework is driven by a number of factors such as responding to agile changes to the domain of bioethics in relation to bioethics processes, standards, national legislations, technology evolution, etc.

Consequently, the iOntoBioethics research design has been orchestrated based on the following main research hypothesis "investigating the bioethics research literature, from the inception of bioethics research publications, leads to identifying a highly agile representative set of bioethics conceptual entities, and governance relationships of bioethics processes". To assist in proving this hypothesis, the following two research questions were formulated:

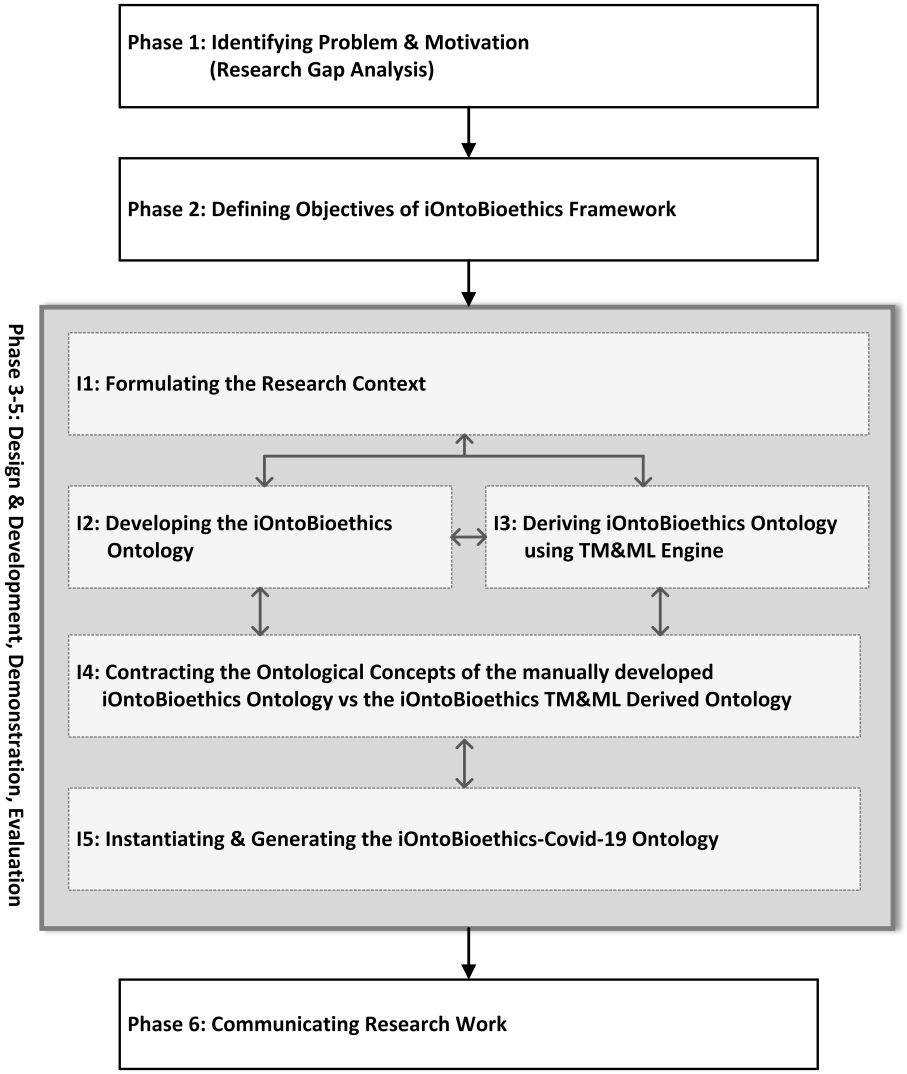

FIGURE 1 | The iOntoBioethics research framework design.

RQ1. How to capture bioethics ontological concepts highly holistically and align them with the COVID-19 pandemic in an agile form?
RQ2. How to evaluate the representativeness of these captured ontological concepts and their relationships within a bioethics COVID-19 ontology?

Phases 3–5: Design and Development, Demonstration, and Evaluation

This part of the iOntoBioethics framework was accomplished in five distinctive increments iterating over the three stages of the DSRM process: design and development, demonstration, and evaluation as depicted in **Figure 1**. Throughout these three phases, bioethics domain experts input and validation were taken. Each of these five increments yielded a significant part or artifact of the iOntoBioethics framework.

The First Increment: Development of the Selection Process of Bioethics Research Sources

The systematic literature mapping method (25, 26) has been employed to guide the bioethics literature classification scheme and the bioethics research contents selection. Upon the formation of the research questions in DSRM phase 2, the well-known Scopus database was selected as the source of studies extracted. Scopus enabled the automatic importing of bibliographic data from scientific publications via the Scopus Database Application Programming Interface (API) (27). In addition, Scopus provides a more accurate representation compared to other databases in the area of bioethics and sciences (28).

The "bioethics" keyword was used as the search term to select the maximum set of bibliographic sources in relation

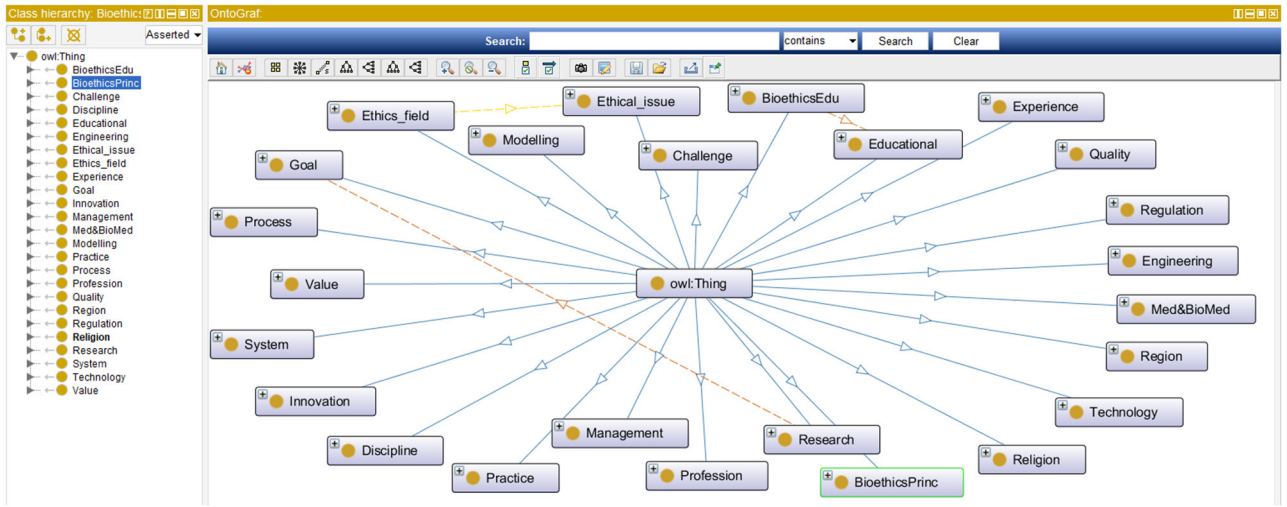

FIGURE 2 | The top-level bioethics classes and the class hierarchy.

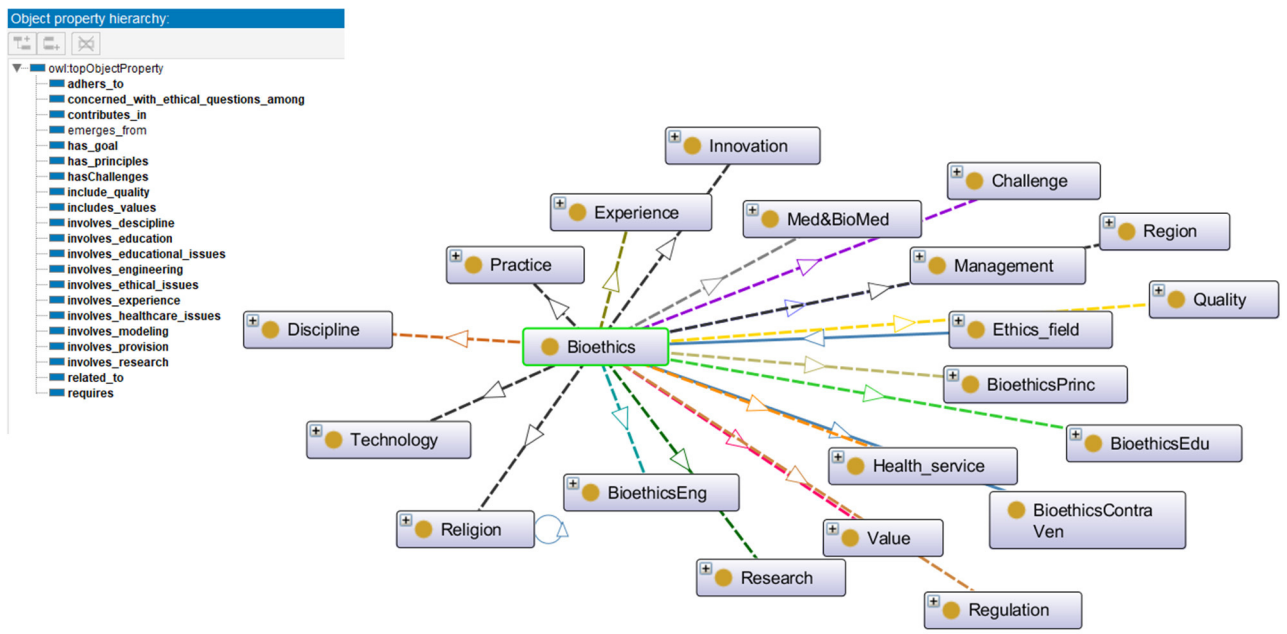

FIGURE 3 | The properties for the Bioethics object, and the relationships between "Bioethics" class and other classes in the iOntoBioethics ontology.

to the field of study in this research without any time restriction. The search process was conducted in June 2020 using the Scopus API to ensure automation and accuracy, which resulted in 26,170 articles distributed over 5,045 sources originating since 1971. These articles established the base to drive advanced analysis of the bioethics literature in order to feed into the development of the iOntoBioethics ontology in two independent strands or increments: second increment and third increment, where the former is associated with the manual construction of the iOntoBioethics ontology and the latter adopting an automated special-purpose text mining and machine learning engine.

For the purpose of manually constructing the iOntoBioethics ontology in strand 2 or the second increment, further filtering and analysis of the 26,170 articles was carried out in order to arrive at a reasonable set of bioethics sources that can be rich enough to inform the identification of representative bioethics ontological elements. The formulated aim and objectives of these literature sources were used to manually drive bioethics ontological concepts. The selection process for this purpose

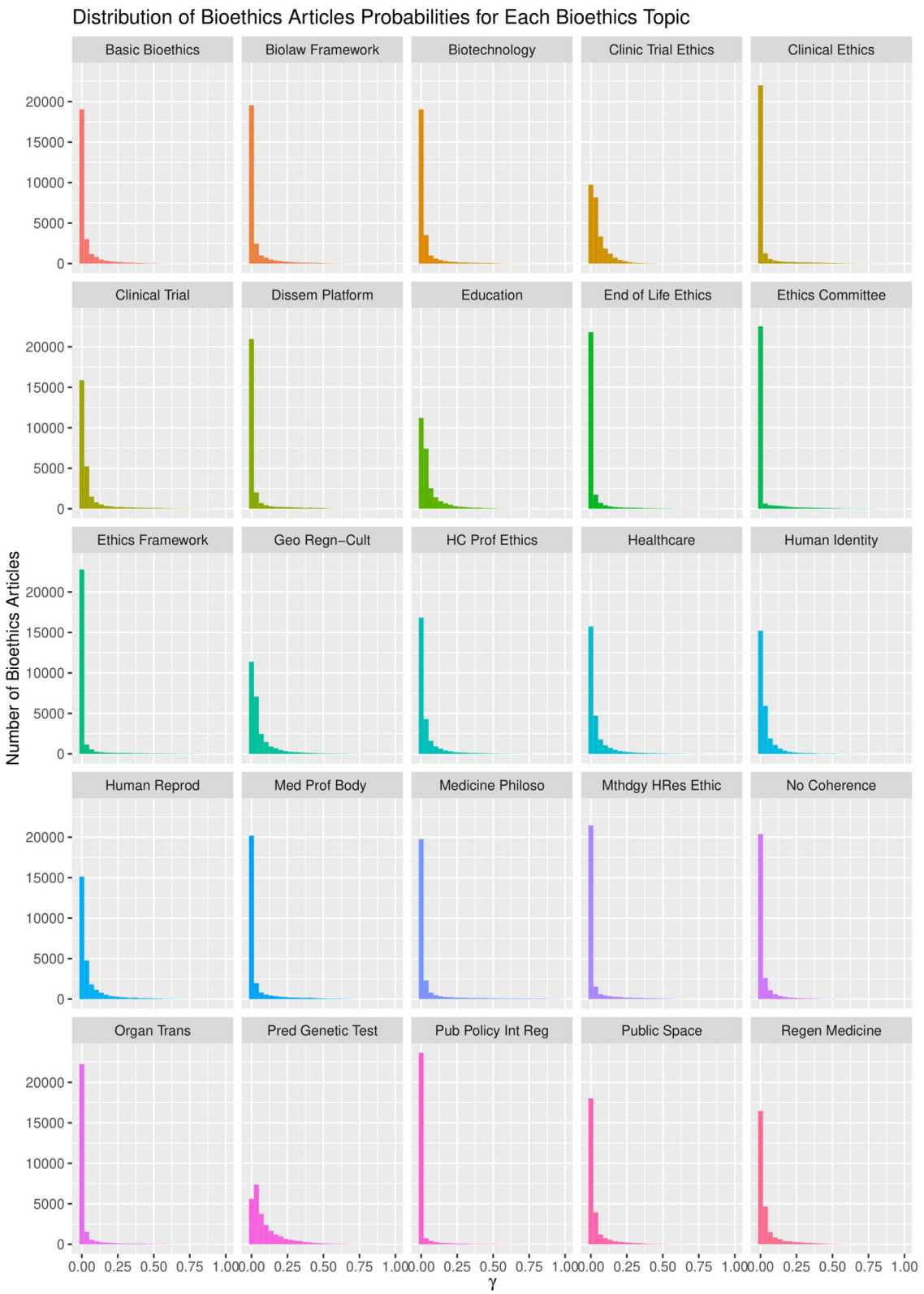

FIGURE 4 | The 25 topics model and their associated information.

implemented the following criteria and was carried out by the researchers and in conjunctions with the bioethics domain specialists:

(1) The source journals are Scopus indexed journals with maximum published number of articles related to "bioethics";
(2) Involve the three-bioethics domain experts in an iterative process to identify the first 20 journals with the highest volume of articles related to bioethics;
(3) If the Scopus indexed journal is not in the list of the "top 100 bioethics journals" (29) and the 2019 Google List (30), other journals were screened manually by three domain experts and were added to the set of literature sources utilized in the manual construction of the iOntoBioethics ontology. Should the bioethics domain experts decide to remove any journal, they replaced it with journals that are common to both the Google Scholar 2019 list and the Hakkarinen list of 2015; and
(4) To gain better coverage of the bioethics domain, the research bioethics domain experts screened other journals related to the bioethics field and added them to the filtered set of literature sources. These were found to be rich with concepts related to bioethics and crossing over to pandemic bioethics.

The execution of the above criteria involved both machine and humans with quantitative and qualitative measurements. The machine provided fast retrieval of outputs that were then assessed with quality-based measurement by domain-experts to identify the journals that were missed by the automated search. As a result, the selected journals comprised nearly 25% of the total number of articles identified that were related to bioethics.

For the automatic generation of the ontological bioethics topic models and associated subjects, the full set of the 26,170 articles titles and abstracts were text mined and machine learned as explained in section The iOntoBioethics Research Framework Design and with the results in section results.

The Second Increment: The Manual Construction of the iOntoBioethics Ontology

This increment is concerned with the manual construction of the iOntoBioethics ontology based on the filtered set of literature sources using the process and selection criteria described in phase one. First, the concepts that signify the scope of each journal are manually extracted and listed for the domain ontology modeler to utilize. Then, a preliminary concept map is generated and reviewed through a brainstorming activity with domain experts. Groups of related terms are arranged into top level classes then, incrementally, more classes are classified and arranged into a hierarchy. These ontological classes and the relationships between them are specified using the Ontology Web Language-Description Logic (OWL-DL) (31), First Order Logic decidable fragment (32). Using OWL-DL classifications are automatically computed, and any inconsistencies are detected. Protégé (33) has been used in this research as the ontology software development environment, which is an open ontology editor software developed by Stanford University. It supports OWL-DL, allows managing and reasoning the created hierarchies, and facilitates ontology graphical design and automatic validation. This paved the grounds for sharing bioethics common understandable knowledge representation agreed upon by bioethics stakeholders to reuse, and integrated with other domain ontologies as generally noted in Horrocks (32) and Kumar et al. (34). Bioethics domain experts evaluated the resultant manually constructed bioethics (MCB) ontology using the walkthrough approach of all the manually derived ontological concepts and their relationships.

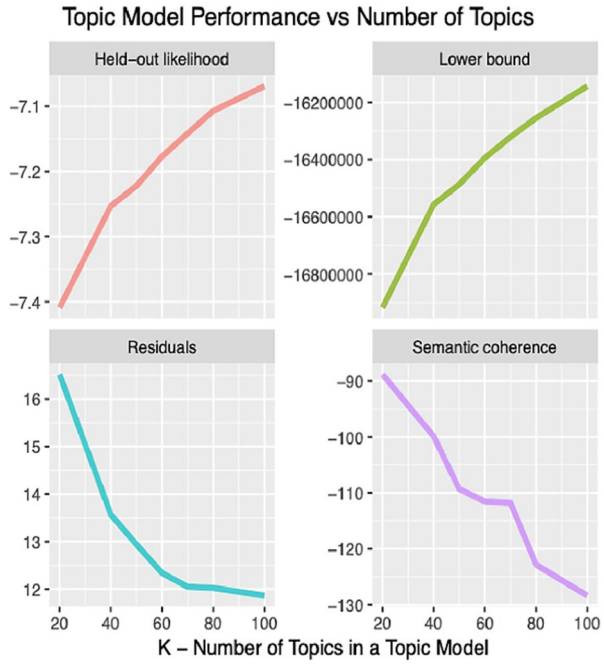

FIGURE 5 | Topic model performance vs. numbers of topics.

The Third Increment: The Automated Generation of the iOntoBioethics Ontology Using Text Mining and Machine Learning

The aim of this increment is to develop a special-purpose Text Mining and Machine Learning (TM&ML) engine that can be utilized to automatically discover bioethics ontological topics and related concepts using the titles and abstracts of the 26,170 bioethics research articles and the COVID-19 recent textbook of Kamp and Hoffmann (35). This textbook has been considered in this research for being a recent and highly comprehensive accumulation of the COVID-19 pandemic covered in the full chapters of *Epidemiology, Transmission, Virology, Immunology, Prevention, Diagnostic Tests and Procedures, Clinical Presentation, Treatment, Severe COVID, Comorbidities, Pediatrics, and Timeline.* Correlations between topics and their related concepts were observed and evaluated by the research bioethics domain experts. The output of this increment is composed of three artifacts: (1) the special

purpose TM&ML bioethics engine, (2) agile, automatically generated, and evaluated topic/concepts generalized bioethics models enacting a generalized and automatically generated bioethics ontology, and (3) agile, automatically generated, and evaluated topics/concepts generalized COVID-19 models enacting a generalized and automatically generated COVID-19 ontology. Both of these enacted ontologies are further utilized in extending the generalized bioethics ontology to become the iOntoBioethics COVID-19 Ontology as the outcome of the fifth research framework increment.

The Fourth Increment: Contrasting the Manually Constructed Bioethics Ontological Concepts to the Automatically Generated Ones Using the iOntoBioethics TM&ML Engine

This increment is aimed at contrasting the MCB ontological model to the TM&ML developed one, to inform agreement on common ontological entities, disagreements and which ontological elements have been missed in one and not in the other, along with domain experts consensus to yield the first validated iOntoBioethics ontology. Hence, the resultant bioethics ontological entities are assessed by both domain specialists and the ontology modelers *to inform the representativeness of the bioethics ontological entities including ontological entities for the governance of bioethics processes.*

The Fifth Increment: Extending the Bioethics Ontology to Derive the iOntoBioethics COVID-19 Ontology

In this increment, the COVID-19 ontology generated in the second increment was utilized to extend the fully validated iOntoBioethics ontology in the fourth increment to become the finally constructed and validated Bioethics COVID-19 ontology, namely the iOntoBioethics first COVID-19 ontology. This final research artifact (or deliverable) marked the conclusion of the iOntoBioethics research framework implementation.

Phase 6: Communication

The agile design and development of the iOntoBioethics ontology, and results from the cycles of phases 2–5 are incrementally communicated to selected bioethics domain experts and for publication in key healthcare and bioethics journals. In addition, it is aimed to publish the iOntoBioethics framework and its ontologies as an open platform to be utilized by informatics driven bioethics researchers, communities and healthcare centers and industrial platforms.

RESULTS

This section reports on the results of implementing the iOntoBioethics research framework with the incremental outcomes of developing the first agile, semi-automatically generated, literature-based, generalized, and domain experts validated two novel ontologies: (1) *bioethics ontology*, (2) *bioethics pandemic ontology in COVID-19 context*.

The Manually Constructed iOntoBioethics Ontology (Second DSRM Increment)

The knowledge engineering methodology proposed by Noy, McGuinness and others (18) was adopted to manually develop the iOntoBioethics ontology. Though this methodology has been in existence since 2001, it naturally fits with the simple intuitive progression in ontology development whether machine interpreted or not. It is also one of the most commonly used methodologies for building research ontologies. It consists of seven iterative steps and suits small-scale ontologies. The work undertaken in each of these steps to manually construct the iOntoBioethics ontology is detailed below:

Step 1: The first task in this step is to decide the bioethics ontology's scope and boundaries. This depends on the domain of the ontology and the purpose for its use. As mentioned in section The iOntoBioethics Research Framework Design, the iOntoBioethics ontology aims to provide a general conceptualization model for bioethics that can be specialized for certain bioethics' spheres that may emerge and require special actions. Accordingly, the iOntoBioethics ontology's scope is determined to include all ethical issues related to medicine (and healthcare) and biology. In addition, disciplines, management activities, experiences, educational issues and religious issues related to bioethics have been included in the search space for bioethics ontological elements and associated relationships.

Step 2: This step recommends reusing existing ontologies instead of developing them from scratch. Therefore, ontologies can be imported and extended depending on the purpose for using them. In addition, ontologies can be imported and merged with other ontologies. A number of libraries of reusable ontologies are available on the web for these purposes. Reviewing the literature, it has been concluded that limited work is available concerning bioethics ontological conceptualization, specifically for generic ontological models that are capable of being instantiated for new situations such as the emergence of COVID19. Hence, the iOntoBioethics ontology was developed without any reuse of existing ontologies in order to fulfill this gap in the bioethics domain.

Step 3: In this step, key terms in the bioethics domain are enumerated. These bioethics terms were obtained from the scope of filtered set of journals following the systematic mapping literature review and the selection criteria detailed in section Phases 3–5: Design and Development, Demonstration, and Evaluation. These terms were enumerated in a list to eliminate redundancy. This process resulted in about 430 terms concerning bioethics, which formed the basis for the iOntoBioethics ontological conceptualization. Examples of such terms are: ethics, legal aspects, legislation, bioethics education, bioethics research, clinical practice, medical aspect, genetics, healthcare system, decision-making, etc.

Step 4: In this step bioethics classes (or entities) are specified along with their bioethics class hierarchy. This step is intertwined with the previous one. While bioethics terms were collected, they

were classified into meaningful bioethics groups to generate a bioethics concept map. Each group contained related concepts and was semantically linked to other bioethics groups. Class hierarchies can be developed either top-down, bottom-up, or a combination of both. Our approach in developing the bioethics class hierarchy for the iOntoBioethics ontology combined both top-down and bottom-up approaches. Each time a new bioethics term was encountered, it was placed either in one of the available bioethics groups if it was found appropriate; otherwise a new bioethics group was created, and then the concerned bioethics terms were either specialized or generalized according to the remaining available terms. For example, the terms "Aging," "Animal human hybrids," "Care," "Cell topic," "Clinical matter," etc., can all be grouped into the top level class "Medical and Biomedical issue". These terms can have more specific terms, for example all types of "Care" such as "Home care," "Long term care," "Community care," "Complex care" etc., are added as subclasses to the "Care" class. The resultant bioethics class hierarchy consists of 25 top-level classes, and the remaining classes were in the middle and lower levels. **Figure 2** shows the top-level bioethics classes and depicts part of the bioethics class hierarchy, both specified in OWL-DL and generated using Protégé (31).

Step 5: In this step the properties of the bioethics classes are identified and specified using the OWL-DL language. There are different types of properties: intrinsic, extrinsic, parts, and relationships to other individuals. According to the purpose of the iOntoBioethics ontology development, the aim is to represent the terms used in bioethics to assist in resolving semantic heterogeneities when interoperable in healthcare sector and especially *when interacting with related healthcare systems and Institution Review Board Systems* (36). Hence, the relationships between the bioethics classes need to be defined, and more specifically, the relationships between individuals of the class "bioethics" with all related top-level classes. With the domain experts' collaboration and guidance, 21 object properties were identified and specified as shown in **Figure 3**. For example, the property "adheres to" is defined to relate individuals of class "Bioethics" with those of class "Regulation and Legislation".

Step 6: This is associated with defining features for the object properties, such as properties' domains and ranges, cardinalities, value types, etc. For each object property defined in the previous step for the iOntoBioethics ontology, the domain and range were specified. Class "Bioethics" is specified as the domain for most of the defined properties, such as "adheres to," "has challenges," "has principle," "includes quality," etc., and the ranges for the defined properties are specified, for example, the domain of the property "adheres to" is the class "Bioethics" and the range is the class "Regulation and Legislation". **Figure 3** shows the relationships between the "Bioethics" class and other classes in the ontology.

Step 7: This is the final step and is concerned with creating instances of bioethics classes. The iOntoBioethics ontology is a general and abstract ontological model that is used to conceptualize bioethics terms and set semantic relationships between them. This ontology can be instantiated for certain topics where individuals or instances can be created accordingly and operationalized for particular healthcare institutions and their systems, and now has the readiness for interacting with IRB systems and stakeholders.

The Automatically Derived iOntoBioethics Ontology Using the TM&ML Engine (Third DSRM Increment)

One of the key motivations behind this research is that the bioethics research portfolio is rich in articles dating back to 1971. Thus, much of the hidden bioethics terms and relationships between them exist. Bioethics researchers, bioethicists, bioethics informaticians, and healthcare organizations can benefit from an automatically generated global or universal ontology of bioethics that can resolve semantic heterogeneities between bioethics concepts, terms, and associated. Such ontological construction facilitates interfacing to IRB healthcare systems and for developing bioethics semantic web applications with global software services that can be instantiated to inform adherence to bioethics processes governance in particular contexts, languages, cultures, legislations, etc.

Accordingly, the researchers hypothesized that an automatic generative process needs to be employed to generate ontological bioethics topics from the incrementally developing bioethics publications. These publications embed a hidden structure of bioethics topics that can agilely evolve with emerging publications added to the repository of bioethics publications. Hence, the goal of this automatic generative process is to discover these hidden bioethics topics and their underlying concepts from a repository of given bioethics publications. These underlying bioethics concepts relate to their certain bioethics topics with varying levels of statistical significance; and therefore, these bioethics topics relate to each of the bioethics publications with some statistical significance.

Accordingly, each of the given bioethics publications relates to the discovered bioethics topics but with varying proportions. It can be easily observed that we have two types of structures: observed and hidden. The observed structure is the bioethics publications, while the hidden structure relating to three key elements: (a) bioethics topics, (b) bioethics topics distribution per document, and (c) bioethics concepts assignment per bioethics topic in a bioethics publication. Consequently, such characterization fits with the motivation behind the Latent Dirichlet Allocation (LDA) (37, 38) algorithm in the field of machine learning. Hence, a *reverse engineering approach* is observed here, as we aim to discover the hidden structure (the bioethics topics and their associated concepts) from the observed structure (represented by the bioethics publications) in order to automatically discover our iOntoBioethics ontological elements and their associated concepts' relationships with varying statistical significance.

The agility of the iOntoBioethics framework stems from the unsupervised machine learning approach exhibited in our TM&ML engine that can dynamically reconfigure the bioethics topics vs. bioethics concepts vs. bioethics publications when implementing the LDA topic-modeling algorithm. However, the LDA algorithm requires as a precondition the known number of topics in the search and assignment

space for topics vs. concepts. In this research, bioethics domain experts have been involved at the completion of this reverse engineering generative process, to characterize these LDA numbered topics with bioethics literal topics as discussed below.

However, before applying the LDA topic-modeling algorithm to the repository of bioethics publications, text mining had to be applied to the bioethics publications with a set of pre-processing steps applied to each of the collective text of these publications. The following process summarizes the implementation process of the fit-for-purpose TM&ML engine developed using R (39). This process was also reused for the automatic generation of ontological topic model of COVID-19 as discussed further on in this section:

1. *Studying the Bioethics Publications:*
   Following the completion of the first DSRM increment with the selection of the bioethics publications, the quality of the meta-data of these publications were checked for any anomalies such as duplication of entries, null values in their data attributes, etc. Notable examples were observed, for instance some of the publications did not have full abstracts included in the Scopus database;
2. *Consolidating the Bioethics Publications for Text Mining* (40)*:*
   In order to maximize the richness of the resultant bioethics' topic model, the textual volume of each of the publications is maximized to include publication title and abstracts to be text mined and machine learned using the LDA algorithm. This collective text for all bioethics publications is referred to as the *Bioethics Publications Texting Mining Database* (BPTM_db);
3. *Standardizing the BPTM_db Text Characteristics with reliance on R's TM (Text Mining) package* (40) *as follows:*
   a. Convert all upper case characters to lowercase characters, so that all words in the text of each bioethics publication are in lower case.
   b. Remove all stop words such as "the," "on," etc.
   c. Remove all white spaces.
   d. Remove all numbers.
   e. Remove improper punctuations.
4. *Generate the Document Term Matrix (DTM) and apply the TF-IDF* (41, 42) *algorithm to normalize words or concepts occurrences amongst the bioethics publications in the BPTM_db:*
   a. Perform the tokenization process, where each word in each of the BPTM_db publications becomes a token.
   b. Construct the DTM and then TF-IDF matrix where the rows of the matrix represent the bioethics publication ids and the columns represent the tokens or words. Each row-column intersection provides the normalized count of the number of times a particular token or word has occurred in a particular publication.

Now, the DTM/TF-IDF matrix over the BPTM_db DTM is constructed for the bioethics publications. The LDA algorithm is applied to calculate the probabilities of the topics and their associated concepts or terms (words or tokens above) using Equation (1) from Blei et al. (37) and Blei (38):

$$p(\beta_{1:k}, \theta_{1:D}, Z_{1:D}, \mathcal{W}_{1:D}) = \prod_{i=1}^{k} p(\beta_i) \prod_{d=1}^{D} p(\theta_d) \left(\prod_{n=1}^{N} p\left(Z_{d,n}|\theta_d\right) p(\mathcal{W}_{d,n}|\beta_{1:k}, Z_{d,n}) \right) \quad (1)$$

where $\beta_{1:k}$ represents the set of pre-input bioethics k number of topics, where $1 \leq i \leq$ k, and k is a pre-determined value, and each β_i is a distribution over words or concept in DTM, q_d is the bioethics topic proportions for publication d, $q_{d,k}$ denotes the bioethics topic proportion the k^{th} topic in publication d, Z_d for the d^{th} publication topic assignments, $Z_{d,n}$ denoting the n^{th} word topic assignment of publication d, *and* the observed words structure for each publication d is w_d, such that $w_{d,n}$ is the n^{th} word of publication d.

The generative process for LDA corresponds to the following joint distribution of the hidden and observed variables, The conditional distribution of the hidden bioethics publications topics structure (and with associated terms or concepts) is called the LDA posterior probability computation adapted from Blei et al. (37) and Blei (38):

$$p(\beta_{1:k}, \theta_{1:D}, Z_{1:D}|\mathcal{W}_{1:D}) = \frac{p(\beta_{1:k}, \theta_{1:D}, Z_{1:D}, \mathcal{W}_{1:D})}{p(\mathcal{W}_{1:D})} \quad (2)$$

The joint distribution of the hidden bioethics topics structure is computed in the numerator of Equation (2), whereas denominator computes the probability of the observed structure of publications under a given bioethics topic structure.

The LDA algorithm topics model performance experimented with 20–100 bioethics topics. It was found that with the 40 topics model, the semantic coherence, holdout likelihood, lower bound, and residuals (43) had common performance measures as can be observed in **Figure 4**. However, it was found that after 25 topics, the concepts under these topics and the topics' themselves started to be redundant. In addition, this was found relatively coinciding with the number of core ontological bioethics classes of the MCB ontology in the second DSRM increment discussed in section The Manually Constructed iOntoBioethics Ontology (Second DSRM Increment). **Figure 5** depicts the distribution of the bioethics publications for each bioethics topic, where similar probability distribution of bioethics across all the 25 topics is shown.

It is worth noting that the LDA algorithm does not name the topics discovered, but it assigns them random numbers within the range of the pre-defined number of topics. Therefore, we involved three bioethics domain specialists to study independently the 25 topic structures, arriving at a consensus of naming these 25 topics as depicted in **Figure 6**, with the concepts below each ontological topic with varying levels of statistical significance. These 25 topics represent the most significant topics automatically discovered using the LDA topic modeling with unsupervised learning in the first stage and then human-in-the-learning loop was deployed

through these three bioethics domain specialists to arrive at this 25-topics model of the domain of bioethics along with the most significant 20 concepts per each of these topics. This 25-topics ontological model of bioethics was put forward for domain specialists to contrast against the MCB ontology as discussed in section The iOntoBioethics General Ontology—Domain Expert Validated (Fourth DSRM Increment).

The same TM&ML process applied to the bioethics publications was reused to generate the ontological topic model of the COVID-19 pandemic using the recent COVID-19 textbook of Kamp and Hoffmann (35) as discussed in section Phases 3-5: Design and Development, Demonstration, and Evaluation. Likewise, the bioethics ontology construction stages discussed above were re-adapted to apply the LDA topic-modeling algorithm to the full chapters of this textbook in order to automatically construct the COVID-19 ontology. Although the LDA topic-modeling performance was observed to saturate with semantic coherence around 40 topics, it was not found without redundancy after 20 topics, and hence the three domain specialists agreed on the naming of these automatically discovered as depicted in **Figure 7**. This LDA COVID-19 topics ontology has been used to link the iOntoBioethics merged and validated ontology in section The iOntoBioethics General Ontology—Domain Expert Validated (Fourth DSRM Increment) to yield the iOntoBioethics COVID-19 ontology, as discussed in section The iOntoBioethics COVID-19 Pandemic Ontology—Domain Expert Validated (Fifth DSRM Increment).

The iOntoBioethics General Ontology—Domain Expert Validated (Fourth DSRM Increment)

In this section, the process for contrasting the MCB ontology and the TM&ML automatically generated one is described, followed by the outcomes of the finally agreed iOntoBioethics ontology. In general, the notable observation is that the TM&ML driven approach leads to deriving concepts at a higher level of abstraction and less specialization compared to the MCB one. For example, the topic "Ethics framework" that was generated from the TM&ML engine, is defined at a higher level of abstraction and at a lower level of specialization than the one generated from MCB. As shown in **Figure 8**, the detailed concepts from the MCB ontology reveals a different structure starting with the "Ethics" upper concept, which includes bioethics, model of ethics, and ethical issues as sub-concepts. The similarity of the main concepts exists in both ontologies with different structures as shown in **Figure 8**.

After investigating all the generated concepts from the TM&ML engine, eight topics were found to have similarities with the MCB ontology. The topics are: (1) *ethics framework, (2) medical professional bodies involved in human ethical issues, (3) education, (4) human identity, (5) geographical region, (6) predictive genetic testing, (7) platforms and channels for dissemination of ethical guidelines, and (8) Ethics of end of life*. Few topics (or classes) were unique to MCB, for example "animal ethics". This distinguishes the MCB approach from the corresponding TM&ML approach. Few MCB topics (classes) were found to be more holistic than the corresponding concepts in the TM&ML ontology, such as the "Geographical Region" topic.

In addition, some TM&ML driven topics matched with the MCB topics (classes). These are: *(1) human reproduction, (2) human research ethics methodology, (3) human identity, (4) organ transplantation, and (5) clinical trials.* This is an indication of the substantial common ontological topics or classes that both the MCB and the TM&ML have been consistently in agreement with at a higher level of abstraction, and that the MCB approach yielded additional ontological; topics (or classes) at lower levels of abstraction such as *"clinical ethics," "regenerative medicine," "biotechnology," and "professional healthcare ethics"*.

In addition, few topic concepts were found similar at their levels of abstraction in both approaches, yet having different details of the underlying classes such as the topic *"Public policies and international regulations"*. Also, it was observed that comparing topics and associated concepts, or properties of both the MCB and TM&ML bioethics ontologies did not always result in straightforward similarity between the topics and related concepts, for example 5 topics were similar and 19 others required subject interpretation to inform similarity consensus. Finally, one topic *"Clinical trials ethics"* of the TM&ML generated ontology matched a corresponding similar ontological topic in the MCB ontology.

Examining the TM&ML 25 generated ontology topics with the bioethics domains experts confirmed that the TM&ML approach provided a higher level of abstraction related to bioethics yielding a well-organized and structured bioethics ontology class hierarchy compared to the MCB bioethics ontology. However, the MCB based ontology provided more detailed and specific classifications of bioethics terms at lower levels of abstraction but with less structured class hierarchy.

Accordingly, both the MCB and TM&ML approaches complemented each other and that the MCB approach confirmed the findings and the ontological topics or classes and their related concepts and/or properties which resulted in a higher order unified and comprehensive bioethics ontology that can evolve with the incremental emergence of new bioethics literature. This higher order unified iOntoBioethics ontology contains 44 classes, 7 object class properties, and 697 SubClassOf class axioms with demonstration in **Table 1**. Considering the TM&ML 25 automatically generated topics (at higher level of abstraction) and the 20 concepts (at lower level of abstraction) as depicted in **Figure 6** below each of these topics, it may be concluded that with these possible 25 × 20 (topic × concepts) relationships, variations between the MCB and TM&ML bioethics ontologies will continue to be the case, but most importantly the bioethics domain specialists confirmed the representativeness of the MCB and TM&ML ontologies in covering bioethics concepts and their associated relationships. **Figure 9** depicts a snapshot of the iOntoBioethics ontology class hierarchy.

FIGURE 6 | Each ontological topic with varying levels of statistical significance.

FIGURE 7 | The highest 20 topics mined from the COVID-19 book.

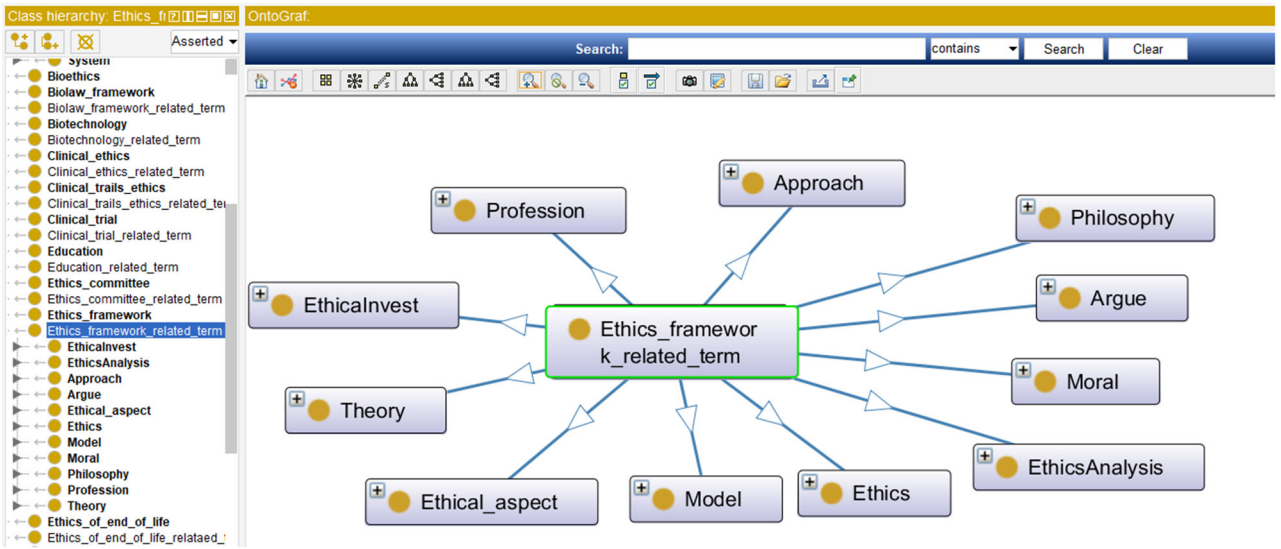

FIGURE 8 | A sample ontological topics from MCB ontology.

The resulting iOntoBioethics ontology provides the concepts and semantic relationships that help achieve a better understanding of bioethics processes. In addition, it can be used to manage automatic governance of bioethics processes when linked to healthcare systems and research institutions. This can be seen from the representation of the four main governance quality attributes (44) highlighted in **Figure 10** where the concepts: *policy, standard, process, and qua*lity are all specified and related in the iOntoBioethics ontology.

The iOntoBioethics COVID-19 Pandemic Ontology—Domain Expert Validated (Fifth DSRM Increment)

The iOntoBioethics framework has been designed as a generic framework that when instantiated at any particular time using state of the art literature in bioethics, will semi-automatically generate a generalized bioethics ontology with validation by bioethics domain specialists. A first version of this generalized bioethics ontology was delivered by the completion of the fourth DSRM increment in section The iOntoBioethics COVID-19 Pandemic Ontology—Domain Expert Validated (Fifth DSRM Increment). In the fifth DSRM increment, this first version iOntoBioethics is utilized in a process centric approach to yield the iOntoBioethics COVID-19 pandemic ontology. This process is composed of the following steps:

(1) Create the iOntoBioethics COVID-19 Ontology as an empty container;
(2) Instantiate the iOntoBioethics ontology validated in section The iOntoBioethics General Ontology—Domain Expert Validated (Fourth DSRM Increment) to the iOntoBioethics COVDI-19 ontology container.
(3) Add a new ontology class named "Pandemic".
(4) Create "COVID19" as a subclass of the "Pandemic" class.
(5) Walkthrough through the automatically generated COVID-19 topics using the special-purpose TM&ML engine in section The Manually Constructed iOntoBioethics Ontology (Second DSRM Increment). The bioethics domain specialists examined each of these 20 COVID-19 topics to inform its association with the bioethics domain. If a COVID-19 topic relates to the domain of bioethics, then it is added as a subclass of the COVID-19 class, otherwise this topic is ignored.

This process resulted in 19 classes integrated with the original iOntoBioethics ontology and jointly validated by the bioethics domain specialists to form the first unified novel Bioethics COVID-19 ontology as depicted in **Figure 11** and detailed in **Table 2**. The primary linkages between the TM&ML COVID-19 topic model classes and the iOntoBioethics ontology are "*COVID19*" and the Bioethics classes, respectively. This "COVID19" class is linked to the top-level class "*COVID19 related topic*" through the "*involves topic*" class object property, and linked to the "*Bioethics*" class in the iOntoBioethics ontology through the "requires" object property. Finally, each COVID19 related topics' class was linked to the iOntoBioethics ontology's classes using their associated relationships. **Algorithm 1** describes the above Bioethics COVID-19 process in general.

iOntoBioethics Ontology Quantitative Evaluation

For ontology evaluation purposes, the metric-based ontology quality analysis OntoQA (45) was adapted. It is a feature-based method that utilizes the knowledge represented in the ontology to measure its quality. The features are divided into two groups to describe different aspects of the ontology: schema metrics and knowledgebase (instance) metrics.

TABLE 1 | The detailed MCB ontology classes that contributed to interfacing to the TM&ML ontology resulting with the iOntoBioethics unified bioethics ontology.

Classes in the MCB ontology	Actions taken in the TM&ML ontology
Bioethical principle	*Covered*—No action is needed
Bioethics education	*Class is added* (with all its subclasses) as a subclass of "Education"
Challenge	*Subclasses were added* to "Challenge" class under "Basic bioethics related term"
Discipline	*Subclasses are either covered or are irrelevant*—No Action needed
Educational issue	*Class is added* as subclass to "Education related term" with relationship "Education has some Educational issues"
Engineering	*Class is added* (with all its subclasses) as subclass of "Basic bioethics related term" with relationship "Basic bioethics involves some Engineering"
Ethical issue	*Subclasses were added* to "Ethics_framework_related_term" with relationships "involves some"
Ethics	*All subclasses are either covered in the derived ontology or are irrelevant*—No Action needed
Experience	*Class is added* (with all its subclasses) as a subclass of "Basic bioethics related term" with the relationship "Basic bioethics involves some Experience"
Goal	*Class is added* (with all its subclasses) as a subclass of "Basic bioethics related term" with the relationship "Basic bioethics includes some Goal"
Innovation	*Class is added* (with all its subclasses) as a subclass of "Basic bioethics related term" with the relationship "Basic bioethics related to some innovation"
Management activity	*Class is added* (with all its subclasses) as subclass of "Ethics committee related term" with relationship "Ethics committee involves some Management activity"
Medical_and_Biomedical_issue	*Most subclasses are either covered or are irrelevant*—no action is needed Subclasses of "Care" are added under "clinical ethics related term" "Cell topic" and its subclasses are added under "Regenerative medicine related term" with relationship "Regenerative medicine involves some Cell topic" "Drug issue" and its subclasses are added under "Clinical trial related term" with the relationship "Clinical trial involves some Drug issue." "Gene related issue" and its subclasses are added under "Predictive_Genetic_testing_related_term" with the relationship "Predictive Genetic testing involves some Gene related issue." "Health issue" and its subclasses are added under "Healthcare related term" with the relationship "Healthcare involves some Health issue." "Healthcare issue" and its subclasses are added under "Healthcare related term" with the relationship "Healthcare involves some Healthcare issue." "Illness" and its subclasses are added as a top level class with "concerned with" relationship to "Bioethics"
Modeling	*Subclasses were added* to "Model" class under "Ethics framework related term" class
Practice	*Subclasses were added* to "Practice" class under "Basic bioethics related term"
Process	*Subclasses were added* to "Process" class under "Basic bioethics related term"
Profession	*Class is added* (with all its subclasses) as a subclass of "Ethics framework related term" class with "involves" relationship to "Bioethics" class
Quality	*Class is added* (with all its subclasses) as subclass of "Basic Bioethics related term with the relationship "Basic Bioethics related to some Quality"
Region	*Subclasses were added* to "Geographical region" class
Regulation and legislation	*Subclasses were added* to "Public_Policies_and_international_regulations_related_term" class with "involves" relationship
Religion related issue	*Subclasses were added* to "Ethics of end of life related term" and with the relationship "includes"
Research	*Subclasses were added* to "Research" class under " Clinical_trails_ethics_related_term" class
System	*Class is added* (with all its subclasses) as subclass of "Basic Bioethics related term" with the relationship "Basic Bioethics involves some System"
Technology	*Subclasses were added* to "Technology" class under " Biotechnology related term" class
Value	*Subclasses were added* to "Value" class under " Healthcare professional ethics related term" class

Schema metrics evaluate the ontology design. They include relationship, inheritance, and attribute richness (AR). Relationship Richness (RR) shows the diversity of the relationships in the ontology, calculated as the percentage of the number of non-inheritance relations to the total number of relations, the higher the percentage is, the higher is the relationship richness. Inheritance richness (IR) indicates how good classes are grouped into categories; it is defined as the average number of subclasses per class, high IR means a horizontal ontology that covers wide range of knowledge with less details, while low IR indicates vertical ontology that covers only a specific knowledge area, but with more details. Attribute Richness (AR) is defined as the average number of attributes per class; this measure indicates the amount of information related to instances.

Knowledgebase metrics reflect the way data is placed in an ontology. These include class richness, class connectivity, class importance, cohesion, and relationship richness. Since our main research product is the abstract iOntoBioethics ontology—which is intended to be instantiated for specific bioethics domains—we

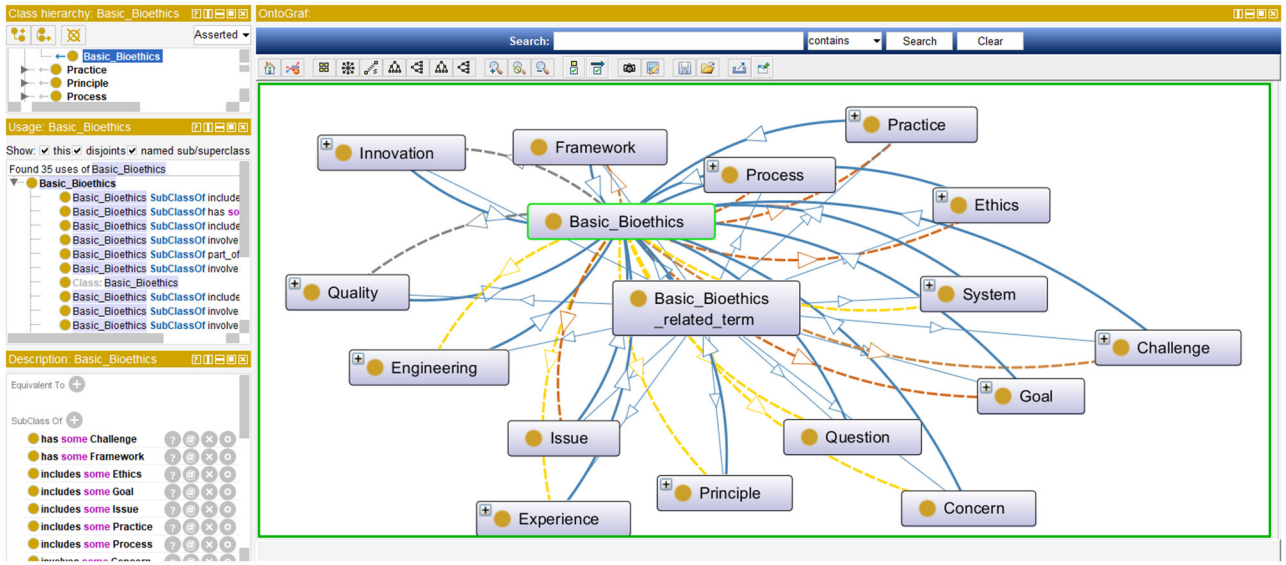

FIGURE 9 | Part of the final bioethics ontology's class hierarchy.

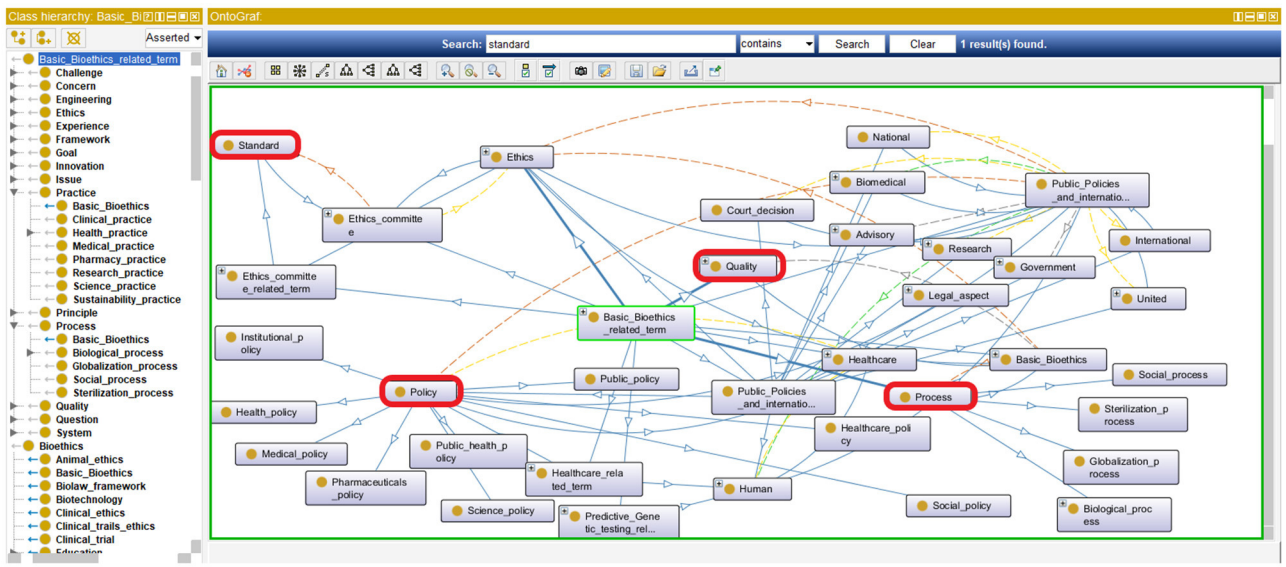

FIGURE 10 | A Representation of the main governance quality attributes in the iOntoBioethics ontology.

only consider the schema metrics for evaluation purposes. **Table 3** shows the results of evaluating the iOntoBioethics ontology as well as the two bioethics ontologies that were generated by the manual construction of concepts and by the TM&ML engine.

As can be seen from **Table 3**, the average number of non-inheritance relationships per class in the MCB ontology was 0.1, while it was 0.52 using the TM&ML engine. As the iOntoBioethics ontology is an integrated composition of both ontologies (manually and TM&ML constructed), it was not surprising to have the highest relationship richness. Inheritance richness shows that the manually constructed ontology concepts appeared highly horizontal in the inheritance hierarchy, whereas the TM&ML-based ontology concepts are richer. However, the final iOntoBioethics ontology is the deeper ontology compared to the manually and TM&ML constructed ontologies. This reflects on the higher level of semantic enrichments that the integrated approach the iOntoBioethics ontology provides compared to either the manually and TM&ML based construction of ontologies. Finally, the AR metric shows poor

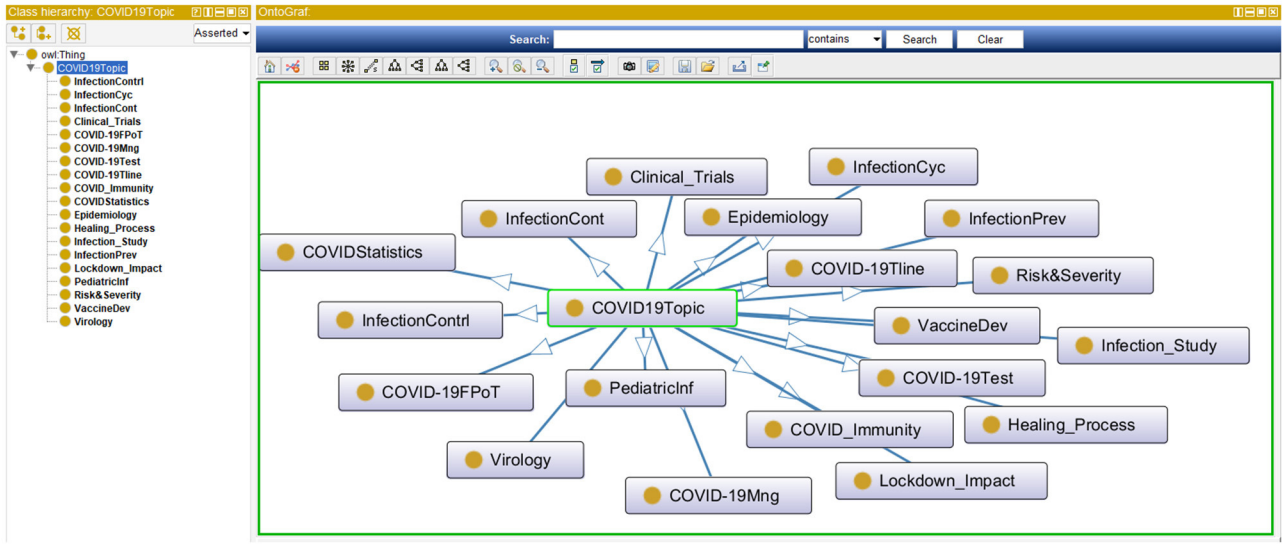

FIGURE 11 | The COVID-19 ontological class model.

Algorithm 1: Constructing the iOntoBioethics COVID-19 Ontology.

 # k: is the number of COVID-19 topics as can be traced to ***Figure 6****, which is 20 topics*
 # l: is the number of COVID-19 topic concepts as can be traced to ***Figure 6****, which is 20 concepts,*
 # for example the Cycle of Infection COVID-19 topic has 20 concepts such as day, test, respiratory, etc
#
iOntoBioethics COVID-19 Ontology <– iOntoBioethics Topics_Ontology
For each $topic_i$ *in the TM&ML COVID-19 Topic Model* $(1 \leq i \leq k)$*,* $k =$ *no of topics*
if $topic_i$ *does not exist in iOntoBioethics Topics_Ontology, then*
add $topic_i$ *as an ontology class to the iOntoBioethics COVID-19 Ontology*
endif
for $concept_j$ *in topic i* $((1 \leq i \leq l)$*,* $l =$ *no of concepts in topic i)*
if $concept_j$ *does not exist in iOntoBioethics Topics_Ontology, then*
add $concept_j$ *to the iOntoBioethics COVID-19 Ontology as an ontology class*
endif
link $concept_j$ *to* $topic_i$ *in the iOntoBioethics COVID-19 Ontology*
endfor $concept_j$
endfor $topic_i$

number of attributes per class in the manually constructed ontology, richer in the TM&ML based ontology and neutral in the merged one, due to including more classes in the iOntoBioethics ontology.

DISCUSSION

In this section, we discuss the research we have conducted to prove the iOntoBioethics research hypothesis and its associated research questions bottom-up. This implies answering the two iOntoBioethics research questions first, and then reflectively concluding evidence to support the research hypothesis. In addition, we reflect on the effectiveness of the research design and the DSRM process adaptation in the development of the iOntoBioethics research framework design in achieving the main aim of this research. Finally, we conclude this section with reflections on the impact this framework is conjectured to have on the formal development of the new discipline we propose as *"Bioethics Informatics"* with reference to both agility, automation of governing bioethics processes in healthcare organizations, and the underlying software technology implications.

Addressing the Research Hypothesis and Associated Research Questions

The hypothesis of this research states that *"investigating the bioethics and COVID-19 research literature, from the inception of bioethics research publications, leads to identifying a highly agile representative set of bioethics conceptual entities, and governance relationships of bioethics processes in general and COVID-19 in particular"*. In order to prove or disprove the hypothesis, the following research questions, RQ1 and RQ2 are answered first:

RQ1: *How to capture bioethics ontological concepts highly holistically and align them with the COVID-19 pandemic in an agile form?*

The iOntoBioethics research framework has been designed with dedicated stages. First, well attributed and indexed bioethics research literature since 1971 until today have been

TABLE 2 | COVID-19 TM&ML topic classes extending the iOntoBioethics ontology in forming the iOntoBioethics COVID19 ontology.

TM&ML COVID19 topic classes	*Actions taken to build the* iOntoBioethics COVID19 ontology
Cycle of COVID-19 infection	*A new class is created with the relationship:* Part of "Predictive Genetic testing"
Healing process	*A new class is created as a subclass of* "Process" under "Basic Bioethics"
COVID statistics	*A new class is created as a subclass of* "Subject" under "Clinical trials ethics" and with the *relationship* part of "Research" under "Clinical trials ethics"
COVID immunity	*A new class is created with the relationship:* Part of "Research" under "Clinical trials ethics"
Lockdown impact	*A new class is created as a subclass of* "Challenge" under "Basic Bioethics"
COVID-19 management	*A new class is created as a subclass of* "Management" under "Ethics committee"
Vaccine development	*A new class is created as a subclass of* "Process" under "Basic Bioethics"
COVID-19 focal point of transmission	*A new class is created with the relationship: part of* "Process" class under "Basic Bioethics"
Infection prevention mechanism	*A new class is created with relationship:* Part of "Research" under "Clinical trials ethics"
Infection study	*A new class is created as a subclass of* "Subject" under "Clinical trials ethics"
COVID-19 testing method	*A new class is created with the relationship:* Part of Research
Infection containment	A new class is created as a *subclass of* "Process" under "Basic Bioethics"
Epidemiology	A new class is created as a *subclass of* "Subject" under "Clinical trials ethics"
Infection	A new class is created as a *subclass of* Illness
Risk and severity factor	*A new class is created for Severity Factor as a subclass of "Challenge" under "Basic Bioethics" (Risk is already covered)*
Infection control	*A new class is created as a subclass of "Goal" under "Basic Bioethics"*
Virology	*A new class is created as a subclass of "Subject" under "Clinical trials ethics"*
Clinical trial	*class is already covered*
COVID-19 timeline	*A new class is created with the relationship: Part of "Process" class under "Basic Bioethics"*

TABLE 3 | Schema metrics results.

Schema metric	Bioethics ontology (manual concept construction)	Bioethics ontology (TM&ML concept construction)	iOntoBioethics ontology
Relationship richness	0.10	0.52	0.61
Inheritance richness	0.87	0.76	0.57
Attribute richness	0.06	10.7	0.6

captured through an automated open gateway (or API) to the Scopus (46) indexed literature database while applying the systematic literature mapping method (26) with domain expert validation of the automatically identified literature sources using a designated fit-for-purpose selection criteria as discussed in section The iOntoBioethics Research Framework Design. Therefore, the highly holistic (or comprehensive) dimension in RQ1 appears to have been well attended to with the resultant 26,170 literature sources.

In addition, the agility dimension has been attended to through the special-purpose TM&ML engine that demonstrated effectiveness and representativeness in the automatic capturing of a set of bioethics topics (high level ontological classes) and their associated concepts (as either subclasses or associated ontological relationships) as briefly introduced in section The iOntoBioethics Research Framework Design and critically demonstrated in section Results using the LDA topic modeling machine learning algorithm (47). Also, a rich bioethics ontology has been manually constructed based on the literature selection criteria detailed in section The iOntoBioethics Research Framework Design and through applying ontology development methodology (31).

RQ2: *How to evaluate the representativeness of these captured ontological concepts and their relationships within a bioethics COVID-19 ontology?*

Three bioethics domain specialists have been incrementally engaged in the evaluation of the iOntoBioethics research framework artifacts (or products) as per the designated DSRM increments 2–4 detailed in section The iOntoBioethics Research Framework Design. First, the representativeness of the MCB ontology was manually assessed using the walkthrough software engineering validation technique (48) to validate the manually identified ontology classes and their relationships as discussed in section The Manually Constructed iOntoBioethics Ontology (Second DSRM Increment). This resulted in the first version of a manually bioethics ontology constructed from the scope of existing authenticated literature. This validated ontology has been cross-checked against the automatically generated TM&ML bioethics ontology using the research designated 26,170-bioethics literature sources. These two ontologies, the manually constructed and the automatically generated TM&ML ontologies were found to complement each other. Few bioethics ontological classes at higher level of abstraction were uniquely observed in the latter than in the former ontology. In addition, semantic heterogeneities between ontology terms, classes, associations have been resolved through the OWL-DL ontology language capabilities.

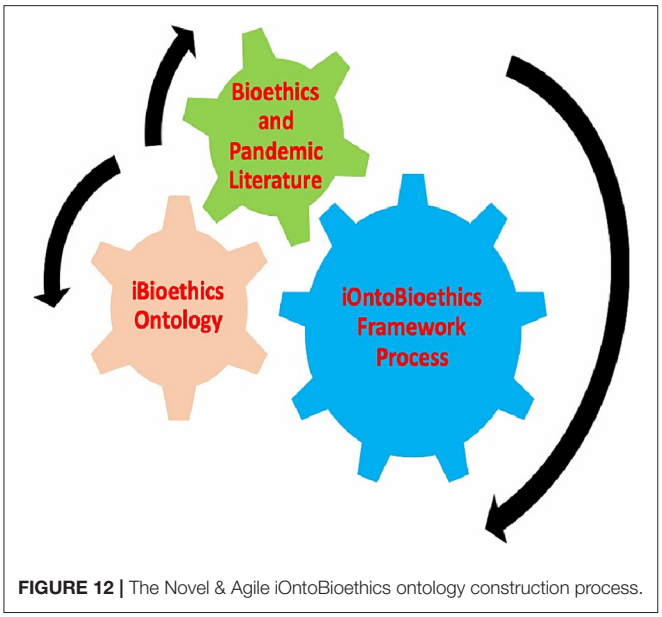

FIGURE 12 | The Novel & Agile iOntoBioethics ontology construction process.

Both of these two bioethics ontologies have been cross-linked and cross-validated yielding the iOntoBioethics Ontology, *as the first enriched general bioethics ontology, agile-developed based on a profile of evolving authenticated and indexed literature.* Furthermore, COVID-19 ontological concepts have been automatically inferred through a designated recently published COVID-19 full textbook using the same TM&ML engine that has yielded automatically generated and generalized COVID-19 topics and their associated concepts. *These have been integrated to form the first semi-automatically generated, text-mined and machine learned Bioethics COVID-19 ontology using an agile process that can be re-instantiated to enrich the iOntoBioethics ontology as per the emergence of new bioethics and COVID-19 publications.*

Furthermore, cross-validating the linking of the iOntoBioethic generalized ontology and the COVID-19 ontological topic models by the designated bioethics domain experts was achieved through visiting every COVDI-19 ontological topic and its associated concepts, and assessing their proper association with the generalized iOntoBioethics ontology. *This has culminated in constructing the* first *Bioethics COVID-19 ontology within our framework that we have named the iOntoBioethics COVID-19 Ontology.* This will serve as an open universal platform to implement a full machine learning cycle, where the current bioethics publications served as the training data set, the newly emerging literature in bioethics and pandemics will be used as the testing dataset, to improve on and evolve the current state of the iOntoBioethics-Pandemic ontology.

The above attempt to answering the two research questions, RQ1 and RQ2, suggests that the research hypothesis has been answered with the following attributions:

(1) A highly generalized bioethics ontology has been constructed whose agility stems from the research framework design based on the special-purpose developed text-mining and machine learning engine that can be enriched, as per the evolution of availed authenticated and indexed bioethics and pandemic or COVID-19 literature;
(2) The iOntoBioethics generalized ontology (as per the last revised version of the evolving iOntoBioethics ontology) is proposed as a universal baseline to extend and specialize the bioethics domain within any potential healthcare challenges, illnesses, scientific revolution, or pandemics; and
(3) Consequently, related and specialized governance processes continue to be enriched as per the associated inner domain processes, quality requirements, standards, and policies as reflected on in section The Manually Constructed iOntoBioethics Ontology (Second DSRM Increment), contributing to the manifestation of these four aspects of governance.

The Research Design Framework and the Impact of Adopting the DSRM Process

Adopting the DSRM process in the iOntoBioethics research framework design impacted the efficient undertaking and delivery of the research components and efficiently manage this research project with increased parallelism between project increments or tasks. For example, while the bioethics literature sources were being assessed by the bioethics domain experts, the development of the third DSRM increment of the "TM&ML engine" was taking place while the bioethics and COVID literature were availed. Also, the second and third framework DSRM increments continued in parallel in developing the manually constructed and automatic TM&ML bioethics ontologies. Such parallelism allowed some form of synchronization for the cross validation by the bioethics domain experts in the fourth and fifth DSRM increments, when both the iOntoBioethics general and the iOntoBioethics-Pandemic or COVID-19 ontologies were fully validated, respectively.

The "Bioethics Informatics" Discipline and the Underlying Evolving Software Technology Implications

As ontologies play an important role in empowering Semantic Web Technologies (SWT) (32) and Internet of Things (IoT) (49), and hence they can be utilized to resolve semantic heterogeneities while exchanging knowledge for operating, managing, and governing bioethics operational and decision-making processes. As iOntoBioethics ontologies are developed using OWL-DL, and hence they are W3C's (32) Semantic Web compliant. Therefore, iOntoBioethics establishes an open platform for bioethics processes sharing new development in policies, regulations, legislations, e-consenting, standards, etc, to benefit big data analytics software services with enriched versions of multi-language and multi-culture support.

CONCLUSION

This research has been orchestrated with the aim to inform whether the current state of the bioethics and COVID-19 literature can be utilized for the agile development of a generic "Bioethics Ontology" that can be extended to a "Bioethics COVID-19" ontology aiding the automatic governance of bioethics processes in pandemics. The iOntoBioethics research framework has been developed adopting the Design Research Methodology with five fit-for-purpose cycles or increments that demonstrated both effectiveness and efficiency in achieving the research aim and objectives. This has resulted with the following four key novel artifacts (or products) for the bioethics research community and healthcare organizations:

(1) A generalized agile Bioethics Ontology, to serve as a common denominator to utilize and extend in particular healthcare contexts and settings;
(2) A generalized agile Bioethics COVID-19 Pandemic Ontology;
(3) The iOntoBioethics research framework with its agile process (depicted in **Figure 12**) that evolves with developing knowledge and literature in the field of bioethics and emerging pandemics or illnesses.; and
(4) An open platform for the (a) iOntoBioethics and (b) the iOntoBioethics COVID-19 Ontologies that is being hosted on the website for this research project with the URL: http://www.iOntoBioethics.org.

Furthermore, *the iOntoBioethics COVID-19 ontology has now emerged as the first publicized Bioethics Pandemic Ontology given the shared characterization of the COVID-19 ontology classes (or topics and associated concepts) with the generalized conceptualization of pandemics*. However, the scientific, healthcare and R&D communities, civic society and related organizations are still in their infancy stage of learning about COVID-19. Therefore, this first Bioethics Ontology will undergo a significant evolutionary wave, where the iOntoBioethics framework can agilely and semi-automatically evolve this ontology as per the process depicted in **Figure 12**.

Moreover, the iOntoBioethics ontologies can be extended to embed ontological conceptualization of specific metrics to assess *legal, social, ethical, and professional* adherence in healthcare organizations, regionally, etc. Finally, the iOntoBioethics framework establishes a foundation to linking bioethics processes and related healthcare systems to empower bioethics big data analytics.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author and to https://www.iontobioethics.org.

AUTHOR CONTRIBUTIONS

Authors had various inputs such research framework design, sections writing with different levels of interest and expertise. MO research project leadership, research framework design, development of text mining and machine learning engine, domain and topic modeling validation, paper workflow, writing/co-writing sections of the paper, cross validation of ontologies, and final version review. FK research framework design, bioethics and ontologies review, contrasting of MCB and TM&ML ontologies, paper referencing, consolidation of sections, and final version preparation. RY research framework design, MCB ontology modeling, and extending to COVID-19. YO research framework design, ontologies cross validation, and referencing. DT research framework design, ontologies cross validation, and bioethics review. NH research framework design, ontologies cross validation, and bioethics review, bioethics from domain expert view. RD framework design, ontologies cross validation, and bioethics review, bioethics from domain expert view, and paper review. AM research framework, bioethics views, research project direction, and final paper review. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 01 June 2021
doi: 10.3389/fpsyt.2021.664808

Psychological Distress, Social Support, Coping Style, and Perceived Stress Among Medical Staff and Medical Students in the Early Stages of the COVID-19 Epidemic in China

Zhe Li[1,2†], Xin Yi[3†], Mengting Zhong[4], Zhixiong Li[5], Weiyi Xiang[6], Shuang Wu[4] and Zhenzhen Xiong[4*]*

[1] Mental Health Center, West China Hospital, Sichuan University, Chengdu, China, [2] Sichuan Clinical Medical Research Center for Mental Disorders, Chengdu, China, [3] School of Nursing, Chengdu University, Chengdu, China, [4] School of Nursing, Chengdu Medical College, Chengdu, China, [5] The Third Department of Clinical Psychology, Karamay Municipal People's Hospital, Karamay, China, [6] The West China College of Medicine, Sichuan University, Chengdu, China

OPEN ACCESS

Edited by:
Thalia A. Arawi,
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University of Lahore, Pakistan

***Correspondence:**
Zhenzhen Xiong
xzz62308631@163.com
Shuang Wu
ws910902@163.com

[†] These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Public Mental Health, a section of the journal Frontiers in Psychiatry

Received: 06 February 2021
Accepted: 28 April 2021
Published: 01 June 2021

Citation:
Li Z, Yi X, Zhong M, Li Z, Xiang W, Wu S and Xiong Z (2021) Psychological Distress, Social Support, Coping Style, and Perceived Stress Among Medical Staff and Medical Students in the Early Stages of the COVID-19 Epidemic in China. Front. Psychiatry 12:664808. doi: 10.3389/fpsyt.2021.664808

Background: The COVID-19 pandemic has had impact that may contribute to a rise in mental health problems. The present study was aimed to better understand psychological status among medical staff and medical students during the early epidemic and to explore the influence factors of psychological distress.

Methods: A cross-sectional survey was conducted online from February 2–14, 2020. We collected general information related to the COVID-19 outbreak. Respondents were assessed using the Kessler-6 Psychological Distress Scale (K6), Social Support Rating Scale (SSRS), Perceived Stress Scale (PSS) and Simplified Coping Style Questionnaire (SCSQ). Stepwise multiple linear regression was performed to identify factors influencing psychological distress.

Results: Five hundred and twenty-eight respondents returned valid questionnaires. Medical staff and Medical students scored averages of 6.77 ± 5.04, 15.48 ± 8.66 on the K6, 37.22 ± 11.39, 22.62 ± 11.25 on the SSRS and 18.52 ± 7.54, 28.49 ± 11.17 on the PSS, respectively. Most medical staff (279, 91.77%) and 148 medical students (66.07%) showed a positive coping style. Social support, perceived stress, hours spent watching epidemic-related information per day and frequency of epidemic-related dreams were identified as factors influencing psychological distress among medical staff and medical students. Coping style emerged as a determinant of psychological distress among medical staff.

Conclusions: In the early stages of the COVID-19 epidemic in China, medical staff and medical students were at moderate to high risk of psychological distress. Our results suggest that psychological interventions designed to strengthen social support, reduce perceived stress and adopt a positive coping style may be effective at improving the mental health of medical staff and medical students.

Keywords: COVID-19, psychological distress, social support, coping style, stress, medical staff, medical students

INTRODUCTION

After being declared an international public health emergency and then an epidemic within <2 months (1, 2), the novel coronavirus disease (COVID-19) epidemic has caused worldwide panic as the numbers of patients, suspected cases and affected regions have increased. As of September 7, 2020, data from the World Health Organization continue to show strong increases in new COVID-19 cases and deaths during the previous week; however, no effective treatment or targeted vaccine is yet available (3).

Many countries have implemented strict control measures in an unprecedented effort to contain the epidemic. Schools and businesses have closed, people have isolated themselves, and personal protective equipment has become scarce, contributing to a global atmosphere of fear, anxiety and depression (4). Overwhelming, sensationalist media coverage has intensified the psychological impact on the public, and may be causing more serious consequences than COVID-19 itself (5). The National Health Commission in China has mandated mental health strategies for patients, medical workers, and people in medical isolation in order to combat the psychological impact of the epidemic (6).

Medical staff, as front-line warriors in epidemic control and prevention, are at high risk of being infected and are continuously exposed to the stresses of providing clinical care under resource-limited conditions. When a new infectious disease outbreak, medical personnel are often at the highest risk of exposure. In the early stages of the epidemic in China, more than 3,000 medical staff in Hubei Province were infected, 40% of which occurred in hospitals (7). Overwork and worry about being infected may increase the risk of psychological distress among medical staff. The prevalence of various negative conditions was higher among medical health workers than among non-medical health workers, including insomnia (38.4 vs. 30.5%), anxiety (13.0 vs. 8.5%), depression (12.2 vs. 9.5%), somatization (1.6 vs. 0.4%), and obsessive-compulsive symptoms (5.3 vs. 2.2%) (8).

Medical students are an important force in the fight against the epidemic in the future, so their mental state when dealing with the epidemic also deserves attention. Studies have confirmed that medical students, in particular because of their professional background, pay close attention to the epidemic, leading them to experience excessive stress and concern (9). For example, in a study at Changzhi Medical College in China, 0.9% of students reported severe anxiety; 2.7%, moderate anxiety; and 21.3%, mild anxiety (9). Studies conducted during epidemics of Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Ebola also identified varying degrees of psychological problems among medical staff and students (10–12). Although medical students have some medical training, it is still difficult and stressful for them to make decisions during epidemics due to their lack of clinical experience, particularly during emergency situations (13–15). Therefore, investigating their psychological status during an epidemic may help us better understand and train medical students in the future.

When faced with emerging outbreaks of infectious disease or traumatic experiences, people may respond differently according to their coping style, level of social support or perceived level of stress. This can lead to stronger or weaker psychological distress. Coping strategies refer to the specific efforts, both behavioral and psychological, that people employ to master, tolerate, reduce, or minimize stressful events (16). Coping styles in a disease outbreak are significantly correlated with mental state: positive coping can generate positive emotions and behaviors that lead to improved outcomes, while negative coping styles may be associated with serious psychological distress such as post-traumatic stress disorder (PTSD) (17–19). Among Chinese physicians, coping styles appear to mediate 23–30% of overall psychological distress and its three dimensions (depression, anxiety, reduced self-affirmation) (20). Similarly, negative coping among front-line nurses positively correlates with psychological distress during the COVID-19 epidemic (21). Nevertheless, another study found that negative coping styles may have beneficial effects on relieving stress and temporarily coping with setbacks, suggesting that the difference between the two coping styles may be quantitative (22). It indicates the need to investigate whether these coping styles increase or reduce psychological distress among medical staff and medical students during the COVID-19 epidemic.

The definition of social support is a series of support measures accessible to an individual through their social relationships with other individuals, groups, and the larger community. Social support can be divided into three components: subjective support, objective support, and the utilization of support (23). Social support can influence mental and physical health through two possible mechanisms. One is through main effects: social support is salutary for all individuals independent of the extent of stress that they are currently facing. The other mechanism is a stress-buffering model, in which the social support of others may have an ameliorating effect on life stressors, particularly for individuals under greater stress (24). Effective social support can relieve negative emotions caused by stressors as well as improve self-efficacy, which can increase confidence and courage in fighting against crises such as the COVID-19 epidemic (23). Among Chinese medical workers, lack of support from society and patients was identified as an important factor in the workers' psychological burden (25). However, social support is not always beneficial, as one study indicated that Asians are more likely to benefit from implicit social support (social networking), whereas, Caucasians are more likely to benefit from explicit social support (event-specific advice) (26). The potentially complex effect of social support on psychological distress among medical staff and medical students during the COVID-19 epidemic needs to be investigated.

In the early stage of the COVID-19 epidemic, when little was known about the virus and the disease, the individuals may have suffered psychological stress about becoming infected or spreading the virus to their families, friends, or colleagues (27). Perceived psychological stress may increase risk of mental conditions such as depression, anxiety and PTSD (28, 29). Excessive levels of stress can also affect the work environment and produce long-term psychological consequences, especially during an emergency (30). Therefore, studies of people's coping styles, social support and perceived stress during the

present epidemic may help guide psychological screening and intervention.

Despite widespread calls for such research, few epidemiological studies have examined psychological distress among medical staff and students, which might serve as the basis for strategies against current and future mental health challenges. The present study aimed to investigate the psychological status and analyzed risk and protective factors of psychological distress among medical staff and medical students in the early stages of the COVID-19 epidemic. We hypothesized that an active coping style and social support were protective factors against psychological distress. We further hypothesized that perceived stress was risk factor against psychological distress among medical staff and medical students. The goal is to provide a scientific basis for psychological interventions and for targeted training programs to strengthen mental health status when facing the epidemic.

METHODS

Medical staff and medical students in China were invited by snowball sampling to participate in this study. All invitees completed the questionnaire online using Questionnaire Star (www.wjx.cn). The initial set of invitees (10 medical staff and 10 medical students) was chosen to ensure broad representation of sex, age, education level, academic or medical specialty, medical or academic institution, and city. Then the questionnaire was forwarded by this set of invitees to 10 colleagues and 10 classmates whom they considered suitable for the survey, and this second set forwarded the questionnaire in the same way, and so on (31).

Inclusion criteria for medical staff were: (1) current engagement in clinical work, (2) possession of a valid medical license, and (3) written informed consent. Inclusion criteria for medical students were: (1) current enrollment in a university or medical institution at any educational level, and (2) written informed consent. Respondents would be excluded if they reported ever having been diagnosed with any disorder listed in the Diagnostic and Statistical Manual of Mental Disorders (4th edition).

Given our desire to assess ∼20 factors that might influence psychological distress in our sample, we aimed to recruit at least 10 times as many respondents in order to ensure adequate statistical power (32). We increased this number by 20% to allow for drop-outs, giving a minimal sample size of 220.

Data Collection

A cross-sectional, Internet-based survey was conducted during February 2–14, 2020. The study was approved by the Ethics Committee of West China Hospital, Sichuan University (No. 2020–178). The complete description of this survey and informed consent form were set prior to questionnaires. After the participants chose "Yes," the data collection can be continued. Surveys were prepared and administered using Questionnaire Star.

The following validated surveys were administered to all subjects. In addition, they filled out a custom-made questionnaire, designed based on the literature and expert consultation, that collected data on demographics (gender, age, education state, marriage status), place of residence, quality of family relationships, suspected infection of respondents, suspected infection of their family members, hours per day spent watching media coverage of the epidemic, history of visiting Wuhan or contacting with people from Wuhan in recent month and frequency of epidemic-related dreams.

Psychological Distress Assessment

The 6-item Kessler Psychological Distress Scale (K6) was used to assess the psychological distress of respondents. It asks about six psychological symptoms during the previous 30 days, including feeling "nervous," "hopeless," "restless or fidgety," "depressed," "everything is an effort," and "worthless" (33, 34). Responses on a 5-point Likert scale were scored with "0" (none of the time), "1" (seldom), "2" (some of the time), "3" (most of the time), or "4" (all the time). The total score ranges from 0 to 24 (35). Participants in the present study were categorized as being at low risk of psychological distress (total score of 0–12) or high risk of psychological distress (total score of 13 or more) (36). The scale has proven to show cross-cultural reliability and validity (37, 38). The Chinese version of the K6 has shown moderate to high reliability and validity, with the test-retest reliability was 0.79, Cronbach's alpha was 0.84, split-half coefficient was 0.84, and the correlation between K6 and K10 was 0.961 (39–41).

Social Support Assessment

Social support was assessed using the Social Support Rating Scale (SSRS) (42), which consists of 10 items. The scale includes three dimensions: objective support, subjective support and availability of support. The total score is the sum of the scores on each dimension; higher scores reflect more social support. The scale has shown high validity and reliability among Chinese, with a Cronbach's alpha of 0.949 (43).

Perceived Stress Assessment

Perceived stress among medical staff and medical students was assessed using the Perceived Stress Scale (44), which measures extent of self-aware stress and the belief that one's life has been overloaded, unpredictable, or uncontrollable during the previous 30 days. The survey includes two dimensions of loss of control and tension, and the 10 items are answered on a 5-point Likert scale. The total score from 0 to 40 is the sum of the scores on the two dimensions; a higher score indicates greater mental stress. The scale has shown high validity and reliability among Chinese (45), with a Cronbach's alpha of 0.82 (46).

Coping Style Assessment

Coping style was measured using the Chinese version of the Simplified Coping Style Questionnaire (SCSQ) (22). The 20-item scale consists of two dimensions, positive and negative coping. The first 12 items cover positive coping, and the latter 8 items cover negative coping. The score is based on a 4-point Likert scale (0 = never, 1 = occasionally, 2 = often, 3 = always), with higher scores representing greater positive

TABLE 1 | Univariate analysis of factors associated with psychological distress among medical staff and medical students.

Characteristics	Psychological distress of medical staff	*t/F*	*P*-value	Psychological distress of medical students	*t/F*	*P*-value
Gender						
Male	94 (30.92%)	−0.007	0.994	70 (31.25%)	1.737	0.084
Female	210 (69.08%)			154 (68.75%)		
Education state						
Under bachelor's degree	51 (16.77%)	0.783	0.458	43 (19.19%)	14.048	<0.001**
Bachelor's degree	187 (61.51%)			161 (71.88%)		
Graduate degree	66 (21.72%)			20 (8.93%)		
Marriage						
Yes	78 (25.66%)	2.935	0.004**	7 (3.13%)	−0.292	0.771
No	226 (74.34%)			217 (96.87%)		
Place of residence						
Non-Hubei province	274 (90.13%)	−3.320	0.001**	167 (74.55%)	−6.251	<0.001**
Hubei province	30 (9.87%)			57 (25.45%)		
Family relationship						
Good	281 (92.43%)	2.817	0.039*	214 (95.54%)	19.216	<0.001**
General	21 (6.91%)			10 (4.46%)		
Bad	2 (0.66%)			0 (0.00%)		
Suspected infection of the respondent						
Yes	29 (9.54%)	−4.617	<0.001**	144 (64.29%)	−54.476	<0.001**
No	275 (90.46%)			80 (35.71%)		
Suspected infection of their family members						
Yes	15 (4.93%)	−6.708	<0.001**	144 (64.29%)	−54.476	<0.001**
No	289 (95.07%)			80 (35.71%)		
Spent hours watching outbreaks per day						
Little (<2 h)	13 (4.28%)	22.095	<0.001**	7 (3.10%)	158.636	<0.001**
Moderate (2–4 h)	101 (33.22%)			45 (20.10%)		
Much (>4 h)	190 (62.50%)			172 (76.80%)		
History of visiting Wuhan or contacting with people from Wuhan in recent month						
Yes	56 (18.42%)	1.927	0.055	148 (66.07%)	38.848	<0.001**
No	248 (81.58%)			76 (33.93%)		
Frequency of epidemic-related dreams						
Almost never	199 (65.46%)	29.420	<0.001**	76 (33.93%)	71.410	<0.001**
Sometimes	57 (18.75%)			4 (1.78%)		
Frequent	48 (15.79%)			144 (64.29%)		
SCSQ						
Positive coping	279 (91.77%)	−11.904	<0.001**	148 (66.07%)	−8.080	<0.001**
Negative coping	25 (8.23%)			76 (33.93%)		

*$P < 0.05$; **$P < 0.01$. *M*, mean; *SD*, standard deviation; *K6*, the 6-item Kessler Psychological Distress Scale; *SCSQ*, Simplified Coping Style Questionnaire.

or negative coping. In the present study, we determined each respondent's coping style based on the difference between the Z-converted standard score for positive coping and the Z-converted standard score for negative coping. If the difference was higher than 0, we considered that the respondent generally adopted a positive coping strategy; otherwise, we considered that the respondent tended to show a negative coping style (47). The scale has shown high reliability and validity among Chinese, with Cronbach's alpha of 0.916 for positive coping and 0.808 for negative coping (22).

Statistical Analysis

All data were analyzed using SPSS 23.0 (IBM, Chicago, IL, USA). Categorical data were reported as frequencies; continuous data, as mean values. Differences in psychological distress (K6 score) among individuals with different categorical data were assessed for significance using an independent two-samples *t*-test and analysis of variance, while differences in K6 score among individuals with different continuous data were assessed using linear correlation analysis. Stepwise multiple linear regression was performed to identify correlations of psychological distress

TABLE 2 | Correlation analysis between factors and psychological distress among medical staff and medical students.

Characteristics	Psychological distress of medical staff	*r*	*P*-value	Psychological distress of medical students	*r*	*P*-value
Age	37.15 ± 9.75	−0.156	0.006**	20.34 ± 2.41	−0.236	<0.001**
SSRS	37.22 ± 11.39	−0.640	<0.001**	22.62 ± 11.25	−0.909	<0.001**
PSS	18.52 ± 7.54	0.719	<0.001**	28.49 ± 11.17	0.946	<0.001**

***P < 0.01. SSRS, Social Support Rating Scale; PSS, Perceived Stress Scale.*

with demographic characteristics, epidemic-related variables, social support, perceived stress and coping style. Differences associated with $P < 0.05$ were considered statistically significant. All statistical tests were two-tailed.

Quality Control

The same IP address could be used only once to complete the questionnaire. The survey did not collect any personal information such as names, in order to ensure anonymity and honest responses.

RESULTS

Sample Characteristics

A total of 331 medical staff and 249 medical students began completing the surveys. After excluding 27 medical staff and 25 medical students who did not complete them, 304 (91.84%) medical staff and 224 (89.96%) students were included in the final analysis.

Among all medical staff, 210 (69.08%) were women and 94 (30.92%) were men. Ages ranged from 21 to 69 years (mean, 37.15; SD, 9.75), and more than half (74.34%) were unmarried. Among all staff, suspected infection of respondents and their family members were 9.54 and 4.93%, respectively. Fifty-six (18.42%) had a history of visiting Wuhan or being in contact with people from Wuhan in recent months, 9.87% lived in Hubei province, 0.66% reported poor family relationships, 15.79% reported frequent epidemic-related dreams, and 13 (4.28%) spent just a few hours per day watching media coverage of the epidemic.

Among all medical students, 134 (66.67%) were women. Ages ranged from 18 to 32 years (mean, 20.34; SD, 2.41), 95.54% reported good family relationship, suspected infection of respondents and their family members were 64.29% for both. and 148 (66.07%) had a history of visiting Wuhan or being in contact with people from Wuhan in recent months, while 27.86% lived in Hubei province, 144 (64.29%) had frequent epidemic-related dreams, and 7 (3.10%) spent just a few hours each day watching media coverage of the epidemic (**Table 1**).

Psychological Distress, Social Support, Perceived Stress, and Coping Style Among Medical Staff and Medical Students

Medical staff scored a median of 6.77 on the K6, and individuals who scored higher were more likely to develop psychological distress. Average SSRS score was 37.22 ± 11.39, and average PSS score was 18.52 ± 7.54 (**Table 2**). Most staff (279, 91.77%) showed a positive coping style. Factor values are listed in **Table 3**. Multivariate analysis identified the following factors as significantly associated with psychological distress among medical staff (**Table 4**): hours per day spent watching media coverage of the epidemic ($\beta = 1.003$, $P = 0.003$), frequent epidemic-related dreams ($\beta = 0.575$, $P = 0.032$), social support ($\beta = -0.104$, $P < 0.001$), perceived stress ($\beta = 0.285$, $P < 0.001$) and coping style ($\beta = 2.520$, $P = 0.004$).

TABLE 3 | Variables assessed in the analysis of risk factors for psychological distress among medical staff and medical students.

Variable	Value
Age	Original value
Gender	0 = male, 1 = female
Education state	0 = under bachelor, 1 = bachelor, 2 = graduate
Marriage	0 = No, 1 = Yes
Family relationship	0 = Good, 1 = Average, 2 = Poor
Spent hours watching outbreaks per day	0 = Little, 1 = Moderate, 2 = Much
History of visiting Wuhan or contacting with people from Wuhan in recent month	0 = No, 1 = Yes
Frequency of recent epidemic-related dreams	0 = Almost never, 1 = Sometimes, 2 = Frequent
SSRS	Original value
PSS	Original value
SCSQ	0 = Positive, 1 = Negative

SSRS, Social Support Rating Scale; PSS, Perceived Stress Scale; SCSQ, Simplified Coping Style Questionnaire.

Medical students scored a mean of 15.48 on the K6; their average SSRS score was 22.62 ± 11.25, and their average PSS score was 28.49 ± 11.17 (**Table 2**). A small majority (148, 66.07%) showed a positive coping style. Multivariate analysis identified the following factors as significantly associated with psychological distress among students (**Table 5**): hours per day spent watching media coverage of the epidemic ($\beta = 1.679$, $P < 0.001$), frequent epidemic-related dreams ($\beta = 3.745$, $P < 0.001$), social support ($\beta = -0.135$, $P < 0.001$), and perceived stress ($\beta = 0.256$, $P < 0.001$).

TABLE 4 | Analysis of independent risk factors for psychological distress among medical staff.

Factors	Unstandardized coefficients		Standardized coefficients beta	*t*	*P*-value	95%CI
	β	SE				
Constant	2.703	1.415	-	1.910	0.057	−0.082–5.487
Spent hours watching outbreaks per day	1.003	0.339	0.114	2.962	0.003**	0.337–1.670
Frequency of recent epidemic-related dreams	0.575	0.267	0.086	2.157	0.032*	0.050–1.100
SSRS	−0.104	0.022	−0.234	−4.708	<0.001**	−0.147 to −0.060
PSS	0.285	0.035	0.426	8.040	<0.001**	0.215–0.355
SCSQ	2.520	0.865	0.138	2.913	0.004**	0.818–4.223

*$P < 0.05$; **$P < 0.01$. SSRS, Social Support Rating Scale; PSS, Perceived Stress Scale; SCSQ, Simplified Coping Style Questionnaire.*

TABLE 5 | Analysis of independent risk factors for psychological distress among medical students.

Factors	Unstandardized coefficients		Standardized coefficients beta	*t*	*P*-value	95%CI
	β	SE				
Constant	−0.343	1.736	-	−0.198	0.843	−3.764 to 3.077
Spent hours watching outbreaks per day	1.679	0.436	0.098	3.848	<0.001**	0.819–2.539
Frequency of recent epidemic-related dreams	3.745	0.564	0.409	6.638	<0.001**	2.633–4.857
SSRS	−0.135	−0.175	−0.175	−3.792	<0.001**	−0.204 to −0.065
PSS	0.256	0.330	0.330	5.955	<0.001**	0.171–0.341

**$P < 0.01$. SSRS, Social Support Rating Scale; PSS, Perceived Stress Scale.*

DISCUSSION

The current study assessed the prevalence of psychological distress among Chinese medical workers and medical students during the early stages of the COVID-19 epidemic, and it explored potential correlations of that distress with social support, perceived stress, and coping style. Similar to previous bio-disasters including SARS, Ebola, H1N1 influenza and MERS epidemics, the COVID-19 epidemic appears to have strongly adverse psychological effects on medical staff, such as depression, anxiety and insomnia (48).

Psychological Distress Among Medical Staff and Medical Students

The present results about psychological distress among medical staff are consistent with a previous study among Chinese medical staff (48). The study among healthcare workers in Ireland reflected that 42.6% for depression and 45.1% for both anxiety and stress (49). Also, there were study indicated that during the outbreak, the prevalence of depressive was in 27.5–50.7%, insomnia was in 34–36.1%, and severe anxiety in 45% among Italian healthcare workers (50). However, a study on Singapore healthcare workers revealed a lower prevalence with a proportion of 5.3 on depression and 8.7 on anxiety, 3.8% of them screened for moderate to severe levels of psychological distress during the COVID-19 epidemic (51). The discrepancy of psychological impact of COVID-19 on healthcare workers may reflect the different epidemic situation in different counties in the early stages of COVID-19 outbreak.

The present study further showed that a substantial proportion of medical students also experienced psychological distress during the initial stages of the COVID-19 epidemic. Previous studies found prevalence of anxiety to be 24.9% and prevalence of depression to be 40.5% among medical students during the COVID-19 epidemic (52, 53). These prevalence are much higher than those in the general Chinese population (54). A survey on Australian medical students revealed a mean K10 score of 20.6 indicating moderate psychological distress (55). As reported in a study on Iranian medical students, the prevalence of anxiety was 38.1% and depression was 27.6% (56). Also, a previous study on home-quarantined Bangladeshi students reflected that, 28.5% of them had stress, 33.3% had anxiety and 46.92% had depression from mild to extremely severe (57). These higher prevalence may reflect that, because schools have been closed, medical students tend to receive COVID-19 information more from social media rather than from scientific sources (58), which may lead to inaccurate assessment of the epidemic situation, leading in turn to excessive stress and concern that compromises their ability to gain professional knowledge in school (12).

Our results are consistent with the idea that the COVID-19 epidemic has placed a substantial burden on the mental health of medical staff and medical students in China. Therefore, psychological interventions should be provided urgently not only for medical staff but also for medical students, who are the reserve

forces for medical staff. Such interventions should aim to enhance mental health during the COVID-19 epidemic.

Factors Influencing Psychological Distress Among Medical Staff and Medical Students

Multilinear regression identified social support, perceived stress, hours per day spent watching media coverage of the epidemic, and frequency of recent epidemic-related dreams as factors significantly influencing psychological distress among medical staff and medical students. Coping style was identified as another influencing factor among medical staff.

Social Support

Social support was identified as a factor influencing psychological distress in medical staff and medical students. Individuals who reported more social support were less likely to develop psychological distress. This is consistent with previous studies of Chinese medical workers (42, 59). Several studies have emphasized the role of social support in protecting mental health of various populations, including medical students (52, 60, 61). For example, inadequate support from family and friends has been associated with significantly greater risk of depression among US medical students (61), and a study of Australian medical students found similar results (62). Social support from friends or family can help medical staff reduce anxiety and stress, by reducing the perceived threat and inappropriate behavior that can result from stress events (63, 64). Social support can also improve self-efficacy, leading to more understanding, encouragement, courage, and a sense of professional achievement, resulting in increased confidence and optimism, which improves positive coping when facing stress (65, 66).

Psychological resilience may partially mediate the effects of social support on mental health, as suggested by a study of Chinese health care workers during the peak of the COVID-19 epidemic (59). Resilience has been positively associated with social support during the aftermath of major disasters: a study of adolescent survivors of the Wenchuan earthquake found that resilience can help protect individuals against mental illness (67, 68). This positive correlation has been observed across different populations faced with different disasters (69–72). Therefore, institutions should pay more attention to providing their staff with support that complements the social support they receive from families and healthcare authorities. More importantly, medical schools can embed training in emotional resilience into the curriculum in order to reduce psychological distress among medical students in daily life and emergency events (62).

Perceived Stress

In the present study, a higher level of perceived stress among medical staff or medical students was associated with greater likelihood of developing psychological distress. A study of medical staff in Guangdong, China found that individuals with moderate-to-severe anxiety or depressive symptoms were more likely to perceive higher stress (73), and perceived stress has been shown to predict anxiety among the general Chinese population during COVID-19 (46). A study of women in the US found that stressful life events were significantly associated with depression (74). Our results with medical students are consistent with a previous study suggesting that anxiety and depression among medical students are significantly related to their stress (75). Perceived stress reflects one's psychological experience after the self-interpretation of stressful event (76). A higher score is associated with higher risk of developing mental illness. Psychological stress may weaken immunity, resulting in a higher risk of infection and mental illness (77, 78).

In addition to the social support mentioned above, resilience can also alleviate the adverse effects of stress on medical workers and students (79, 80). For example, resilience negatively correlates with perceived stress among Chinese medical staff during COVID-19 (81). A study of medical staff during the SARS epidemic found that measures to increase resilience reduced perceived stress among medical staff (82). Another study found that resilience among medical students can protect them from stress (83). This protective role of resilience may help guide the design of measures to alleviate the stress of medical workers and medical students during the COVID-19 epidemic as well as during normal professional and personal life (84).

Hours per Day Spent Watching Media Coverage of the Epidemic

Medical staff and medical students in our study who spent more time daily watching media coverage of the epidemic were more likely to develop psychological distress. Similar results were reported in a study of the general Chinese population (85). During the early stage of the epidemic, media reports may have caused intense worry and panic by highlighting the government's efforts to fight against the outbreak, protective interventions, numbers of suspected infections and confirmed cases every day, while also highlighting the lack of effective treatments (85). At the same time, medical staff are concerned about their own health and about the risk of transmitting infection to their families. The more time they spend on searching for information about the epidemic, the more anxiety, stress or fear they report (86–88).

Medical students, in contrast, have tended to depend more on social media rather than scientific sources to obtain information about the epidemic and prevention measures, which may lead to inaccurate assessment of the epidemic situation (58). The frequent mention of the outbreak in the media and excessive attention paid to it may also aggravate their concerns and fears, compromising their ability to learn professionally about it (12, 89). Our results support the idea that medical students' self-confidence in coping with COVID-19 can be increased by giving priority to traditional national media directly connected to trustworthy medical decision-makers (90).

Frequency of Epidemic-Related Dreams

Frequency of epidemic-related dreams was significantly associated with psychological distress among medical staff and medical students in our study. Similar results have been reported in a study of the general Chinese population (54). Sleep problems, especially dreams in which the content relates directly

to the traumatic event, are core symptoms of PTSD (91). This suggests that Chinese medical staff and medical students may have experienced PTSD symptoms in the early stages of the COVID-19 epidemic.

Coping Style

Multivariate analysis also showed that coping style was an important factor influencing psychological distress among the medical staff in our study. Medical staff with a positive coping style were less likely to report psychological distress. Several studies have linked negative coping style with subsequent mental illness, and positive coping style with better mental health (20, 92, 93). Indeed, these results have been reported for the general Chinese population during COVID-19 (54), as well as for Romanian healthcare workers (94). Therefore, appropriate psychological interventions should be urgently provided to medical workers with negative coping styles during COVID-19.

Among medical students in our study, coping style did not emerge from multivariate analysis as significantly associated with psychological distress, although it was significant in single-factor analysis (see **Table 1**). These results suggest that coping style may not be a major determinant of psychological distress among medical students. It is also possible that our sample was too small to detect an association.

Limitations

This study was conducted during the early stages of the COVID-19 epidemic, only a few days after the entire city of Wuhan was placed under quarantine. While it may give a reasonably accurate view of the situation early in the epidemic, our results should be interpreted with caution given several limitations. One is the on-line format, necessary in large part because of the inability for us to interact face-to-face with potential respondents. So it is unclear whether our results can be generalized to people without Internet access. Secondly, the snowball sampling method may cause selection bias which may reduce the generalizability of our study. Thirdly, we did not assess whether and how respondents were engaging in prevention, as preventive behaviors can also play a role in mediating stress levels (95). Fourthly, the influence factors related to COVID-19 epidemic would change and the starting situations were different in different counties. However, our study may benefit to develop targeted training programs to strengthen mental health status of medical staffs and students when facing the similar infectious disease epidemic in the future in different countries. Finally, our cross-sectional study could not capture changes in psychological distress or identify its predictors during the course of the COVID-19 epidemic. Therefore, future studies would be to convey a follow-up for the current situation and engage in a more consistent analysis about the long-term psychological effects of the COVID-19 epidemic among medical staff and medical students. Such work should also further explore the ability of social support and coping strategies to mediate the effects of the COVID-19 epidemic on psychological distress and mental health more generally.

The COVID-19 epidemic in China has substantially affected the mental health of medical staff and medical students. Urgent mental health interventions should be implemented in a timely manner in order to prevent psychological distress and promote recovery. Our study has associated higher social support, lower perceived stress and less time spent daily watching media coverage of the epidemic with lower psychological distress among medical staff and medical students in the early stages of the COVID-19 epidemic. Medical staff with a positive coping style may also have lower psychological distress. Our results have several practical implications. Medical staff and medical students may benefit from being taught positive coping strategies and being encouraged to seek and maintain social support. Such interventions may help protect their mental health not only during the current COVID-19 epidemic but also during future public health emergencies. Most importantly, they should regularly receive comprehensive, systematic training in order to be more resilient to the daily pressures of their work. To benefit medical students, who are the reserve forces supporting medical staff, medical schools should use social media more frequently to disseminate knowledge and develop training plans (53). Medical schools should also consider adding training in mental resilience for emergency events into their curricula (61).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the corresponding authors on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of West China Hospital, Sichuan University and run in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent to participate in this study was obtained from all individual participants included in this study through the Web-based surveys.

AUTHOR CONTRIBUTIONS

ZheL and XY developed concept, study design, and wrote the original paper. MZ, ZhiL, and WX collected and analyzed the data. SW and ZX made critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

FUNDING

This study was sponsored by the Science and Technology project of Health Commission of Sichuan Province (20PJ027, ZheL), Applied Psychology Research Center of Sichuan Province (CSXL-202A08, ZheL), the Department of Human Resources and Social Security of Sichuan Province [(2020) 291-20, ZheL], the special project of Aging Career and Industrial Research Center in 2020, Key Research Base of Social Sciences in Sichuan Province XJLL2020002, ZX).

ACKNOWLEDGMENTS

We thank all the medical staff and medical students participated in the study.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

SYSTEMATIC REVIEW
published: 07 July 2021
doi: 10.3389/fpubh.2021.613321

Depression and Coping Styles of College Students in China During COVID-19 Pandemic: A Systemic Review and Meta-Analysis

Shengyu Guo[1], *Atipatsa Chiwanda Kaminga*[2] *and Jie Xiong*[3]*

[1] Department of Economics and Management, Changsha University, Changsha, China, [2] Department of Mathematics and Statistics, Mzuzu University, Mzuzu, Malawi, [3] Department of Mathematics and Computer Science, Changsha University, Changsha, China

Background: The rapid spread and uncertain outcome of the 2019 novel coronavirus disease (COVID-19) around the world have caused worry, fear, and stress among the general population. Nevertheless, the prevalence of depression among college students in China during lockdown, following the COVID-19 pandemic, and their coping strategies have not been quantitatively assessed.

Objective: We aimed to evaluate the prevalence of depression among college students in China during the lockdown due to the COVID-19 pandemic and assess their coping strategies.

Methods: Systematic review and meta-analysis were conducted to assess the prevalence of depression among college students in China and their coping strategies.

Results: The results indicated that, during lockdown in the COVID-19 pandemic, the prevalence rates of college students in China suffering from mild, moderate, and severe depression were 25% (95% CI = 17–33%), 7% (95% CI = 2–14%), and 2% (95% CI = 1–5%), respectively. Besides, the proportion of college students who use WeChat and Weibo to acquire COVID-19 knowledge was 39% (95% CI = 13–68%), whereas the proportion of college students using mental health application services (APPs) to deal with depression was 59% (95% CI = 41–73%).

Conclusions: The prevalence of depression among college students in China was high during the lockdown in the COVID-19 pandemic. Thus, considering the adverse outcomes of depression, it is imperative to screen college students in China for depression during the CIVID-19 pandemic and provide them with necessary psychological interventions to control and prevent depression. Social media platforms, such as WeChat and Weibo, and mental health APPs could provide an opportunity for psychological health information dissemination for college students. However, their effectiveness in reducing depression will have to be assessed.

Keywords: COVID-19, depression, college students, meta-analysis, mental health apps

OPEN ACCESS

Edited by:
Asem H. Mansour,
King Hussein Cancer Center, Jordan

Reviewed by:
Richa Tripathi,
All India Institute of Medical Sciences Gorakhpur, India
Maysa Al-Hussaini,
King Hussein Cancer Center, Jordan

***Correspondence:**
Jie Xiong
zndxxhl@126.com

Specialty section:
This article was submitted to Public Mental Health, a section of the journal Frontiers in Public Health

Received: *02 October 2020*
Accepted: *17 May 2021*
Published: *07 July 2021*

Citation:
Guo S, Kaminga AC and Xiong J (2021) Depression and Coping Styles of College Students in China During COVID-19 Pandemic: A Systemic Review and Meta-Analysis. Front. Public Health 9:613321. doi: 10.3389/fpubh.2021.613321

INTRODUCTION

Coronavirus disease (COVID-19) started in Wuhan, one of the biggest cities in China, in 2019 and quickly spread to almost every human settlement on the planet. The outbreak has been particularly severe in the United States, India, and Brazil such that each had more than 2 million cases. According to a report of the World Health Organization (WHO), there were nearly 20 million COVID-19 patients all over the world, and about three-quarters of a million people died from this disease. Although millions of patients have recovered from the disease, their quality of life has been severely affected by different side effects (1). Furthermore, public health measures including social restrictions and quarantines have been adopted by countries to control the spread of COVID-19, and these have also seriously affected the lives of billions of people (2). Some studies have indicated that the outbreak of COVID-19 and the social isolation policies adopted by countries could lead to serious mental health problems in the general population (3, 4).

Specifically, college students in China were seriously affected by the outbreak of COVID-19 in that most of them were confined to the same place during lockdowns, and emerging data have suggested that the COVID-19 pandemic has brought unbearable psychological pressure to many people (5), including college students (6). For example, some studies have confirmed that COVID-19 has caused an increase in anxiety and depression among medical staff (7), while other studies have found that socially isolated college students have higher rates of unhealthy behaviors, such as longer cell phone use (8) and smoking and drinking (9, 10). However, these studies did not quantitatively evaluate the mental health problems of college students amidst the COVID-19 pandemic and the related prevention and control measures. Therefore, quantitative studies, such as meta-analysis, that can provide more valuable information for the improvement of mental health services in colleges are warranted.

Clinically, depression can be classified into mild, moderate, and severe according to the symptoms of the patients, and different levels of depression should receive different mental health services (11, 12). Reasonable treatment measures can effectively alleviate the symptoms of depression; otherwise, lack of appropriate treatment may worsen the patient's state (13). In our previous research (14), we found that many Chinese college students did not have an ideal mental health literacy, and these students could not correctly judge depression and were reluctant to seek professional psychological help.

Students with severe depression should receive timely treatment to reduce their depressive symptoms; otherwise, some of them may decide to commit suicide (15). Some recent studies have suggested that the impact of the epidemic are profound and lasting, possibly leading to higher suicide rates among the population (16, 17), and a survey has shown that the suicide intention of the Chinese population is higher than that in normal times; especially, people aged 18–24 years (college students are in this age range) have a much higher suicide intention during the epidemic (18).

Therefore, this study conducted a meta-analysis of the incidence of depression among college students during the COVID-19 pandemic in China. In this regard, the proportions of mild, moderate, and severe depression among college students were calculated to help authorities provide targeted interventions to college students with different degrees of depression. In addition, a quantitative assessment of the coping styles of college students with depression was conducted, and the role of new information platforms, such as Weibo and mobile application services (APPs), in disseminating knowledge about the prevention and control of the COVID-19 pandemic as well as mental health among college students was evaluated.

Abbreviations: COVID-19, 2019 novel coronavirus disease; APPs, application service; PHQ-9, Patient Health Questionnaire 9; SCL-90, Symptom Checklist 90.

METHODS

Search Strategy

Six electronic databases (Web of Science, PubMed, Embase, WanFang, CNKI, and WeiPu) were searched for related studies published not later than July 2020. Furthermore, studies published only in English or Chinese were considered. The search terms included "COVID" OR "COVID19" OR "Coronavirus" OR "SARSCOV2" AND "college students" OR "university students" AND "depression" in the title and/or abstract.

Study Selection

The included studies met the following criteria: (1) they investigated Chinese college students; (2) they were conducted during the COVID-19 outbreak; (3) they examined the emotional or psychological changes in college students; (4) they used valid diagnostic criteria for depression symptoms; (5) they were written in Chinese or English language; (6) they contained the necessary research outcomes needed for this study; (7) depression in this study refers to individuals showing obvious negative emotions such as decreased interest, hopelessness, inferiority, etc. These negative emotions can be evaluated using professional scales.

Data Extraction

The following data from eligible studies were independently extracted by two authors: first author, year of publication, study design, research location, sample size, number of college students with varying degrees of depression, assessment tools for depression, coping styles of depressed college students, number of college students who obtained relevant information through electronic social media platforms, and other information.

Outcome

The main outcome variable for this study was the prevalence of mild, moderate, and severe depression among Chinese college students during the COVID-19 pandemic.

Mild depression was defined as not being interested in many things. In this case, negative emotions do not affect normal work and study. These symptoms last no more than 2 weeks and can be alleviated by talking to family or friends (11, 12).

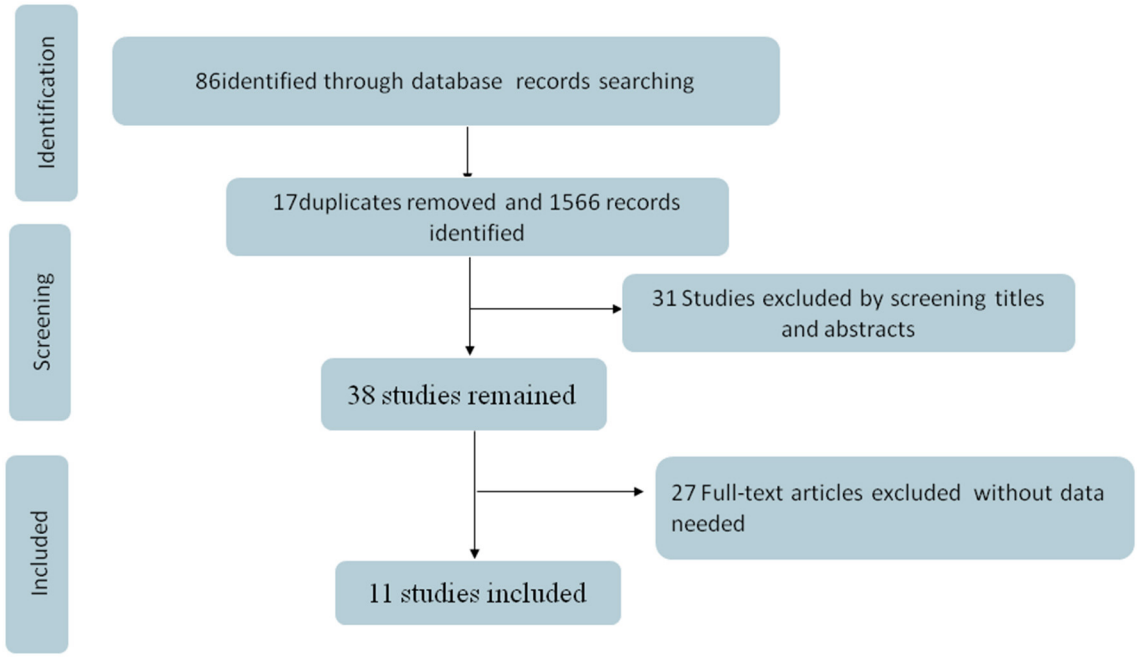

FIGURE 1 | Flowchart presenting the steps of the literature search and selection.

Moderate depression was defined as negative emotions such as pessimism, low productivity, and inability to fully engage in work and study. These symptoms last more than 2 weeks.

Severe depression was defined as a chronic lack of sleep, suicidal tendencies, and inability to work or study properly. For the classification of depression, this study referred to the International Classification of Diseases (ICD-10); relevant literatures were also reviewed, and the classification was consistent (11, 12).

The secondary objective of this study was to assess the role of new information platforms, such as Weibo and mobile APPs, in disseminating knowledge about the prevention and control of the COVID-19 pandemic as well as mental health among college students.

A mobile APP in this study refers to any mental health APP supported by iPhone and Android systems. Weibo is also called as Microblog, which is a platform based on user relationship information sharing, dissemination, and acquisition; users can form personal communities through various clients, such as Web.

Risk of Bias Assessment

The risk of bias was assessed according to the guidelines of the Cochrane reviews (19). Two authors evaluated the following information: representativeness of sample, consistency of the survey tools, and information integrity. The included studies were graded according to the Newcastle Ottawa Scale, with respect to the above information.

Statistical Analysis

The untransformed proportions (PRAW), log transformation (PLN), logit transformation (PLOGIT), arcsine transformation (PAS), and the Freeman–Tukey double arcsine transformation (PFT) were used to evaluate whether the distribution of the main outcome (rate of depression) conforms to a normal distribution (20). The index that was closest to the normal distribution was selected to perform rate merging. The rate of depression and the corresponding 95% confidence intervals (CIs) were calculated. Heterogeneity was assessed using the I^2-test. Accordingly, an $I^2 > 50\%$ indicated the existence of heterogeneity, and in this case a random model was adopted, whereas an $I^2 < 50\%$ implied low heterogeneity and, hence, a fixed model is adopted (21). In addition, publication bias was evaluated by a funnel plot and confirmed using Egger's test. All statistical analyses were conducted using R version 3.4.4 (R Project for Statistical Computing, Vienna, Austria). Statistical tests were considered significant when $P < 0.05$.

RESULTS

Study Selection

We first obtained 86 related studies from six electronic databases (Web of Science, PubMed, Embase, WanFang, CNKI, and WeiPu). Of these, 17 were duplicates and so were removed. After screening the titles and abstracts of the remaining studies, 31 were excluded. Furthermore, among the 38 full-text studies left, 27 were ruled out because they did not have the outcomes of interest for this study. Finally, a total of 11 studies (22–32) with 25,020 Chinese college students were included in the present study. The flowchart is schematically shown in **Figure 1**.

Study Characteristics

Detailed information about the included studies is shown in **Table 1**. Ten of the included studies were published in Chinese journals and one in an English journal. In terms of the diagnostic criteria, six studies used the SCL-90 (Symptom Checklist 90) while four studies used PHQ-9 (Patient Health Questionnaire 9) to assess depression symptoms. Samples were selected from different regions of China. Furthermore, the quality of the included literatures is shown in **Table 1**. In this regard, according to the Newcastle Ottawa Scale, four papers were evaluated to have four points and seven papers have three points.

College Students With Mild Depressive Symptoms

According to the diagnostic criteria for depression, college students with depression during the COVID-19 pandemic were classified as having mild, moderate, and severe depression (11). Additionally, 10 studies provided information on college students who suffered from mild depression during the COVID-19 pandemic, and the normality test indicated that logit conversion of the original rate was the closest to the normal distribution, so logit conversion was performed on the original rate before merging the rates. The result of heterogeneity indicated that there was significant heterogeneity in this result, so the random model was selected. During the COVID-19 pandemic, about 25% (95% CI = 17–33%) of college students suffered from mild depression (**Figure 2**). Based on the information in the included literature, the incidence of depression between the sexes was explored, and the results indicated that there was no significant difference between genders [relative risk (RR) = 0.94, 95% CI = 0.82–1.07]. **Figure 3** shows the details.

College Students With Moderate Depressive Symptoms

Eight included studies described the prevalence of moderate depression among college students during the COVID-19 pandemic, and this involved 5,000 subjects. The combined results, using a random model, showed that the proportion of college students suffering from moderate depression during the COVID-19 pandemic was 7% (95% CI = 2–14%) (**Figure 4**).

College Students With Severe Depression

Furthermore, 10 different studies involving 24,234 college students found that 590 had major depression. The normality test indicated the use of the PFT to perform rate merging; due to significant heterogeneity, the random model was applied. During the COVID-19 pandemic, the combined incidence of severe depression among Chinese college students was 2% (95% CI = 1–5%). **Figure 5** shows the details.

Analysis of Channels Used by College Students to Acquire COVID-19 Knowledge

The proportion of college students who use WeChat and Weibo to acquire COVID-19 knowledge was 39% (95% CI = 13–68%). Social software (including mobile APPs and public accounts) also played an important role in spreading knowledge of the prevention and control of the pandemic. Our research results showed that about 28% (95% CI = 10–51%) of the college students acquired COVID-19 prevention and control knowledge through the foregoing channel. This proportion is slightly lower than that for social platform users, but higher than that for traditional communication channel users (**Figure 6**).

Analysis on the Ways of Seeking Help for Depressed College Students

During the COVID-19 pandemic, college students in China were in social isolation. Research on college students' coping or seeking help for depression during the isolation period is beneficial for improving the quality of the mental health service system. The results indicated that 70% (95% CI = 51–85%) of the college students sought help from family members when they were depressed.

Moreover, 59% (95% CI = 41–73%) of depressed college students often used mobile phone mental health APPs for help in dealing with depression. **Figure 7** shows the details.

Publication Bias

The funnel plot is shown in **Figure 8**. The results of the Eggers test indicated that there was no significant publication bias ($t = 0.51$, $p = 0.616$, bias = 1.56, se.bias = 3.06, slope = 0.51), thus justifying the validity and credibility of this meta-analysis.

DISCUSSION

Principal Findings

College students are in a special period of transition from teenagers to adults and have poor ability to adjust and cope with emergencies. Major public events can have negative effects on the psychology of young people, such as SARS in 2003 (33) and the Wenchuan earthquake in 2008 (34). Recently, the COVID-19 pandemic has lasted longer than the preceding events, and social isolation measures have been stricter than those for SARS in 2003 (35). Public health emergencies are strongly stressful situations for individuals; under such circumstances, people will show a lot of abnormal psychology and behavior, such as anxiety, depression, sleep disorders, and physical discomfort (16). Social supports based on social networks can effectively mitigate the impact of the epidemic on affected people. However, due to the restrictions of relevant policies, the function of social networks has been weakened; thus, during the COVID-19 pandemic, some people may commit suicide because they could not stand the strict social isolation policies or due to other reasons (32). A recent study indicated that people aged 18–24 years may have a higher risk of depression and a higher rate of suicidal thoughts than on normal days (18).

The COVID-19 outbreak in China came at a time when college students were in the Spring Festival holiday, and they had to isolate themselves at home for the next 6 months after the outbreak. Previous studies found that the strict social segregation policy may have a negative impact on children's psychology (36), suggesting that revising the policy so as to include psychological intervention measures was necessary.

TABLE 1 | Basic information and data of all the included studies in the meta-analysis.

References	Region (city)	Sample (total) /M/F	Mil number /M/F	Mil/mod /ser	Study design	Screening questionnaire	Outcomes	Type of college	Newcastle Ottawa scale (points)	Classification of published journals
Zhu and Li (22)	Wuhan	838/344/494	546/231/395	546/66/14	Cross-sectional study	Self-design questionnaire	1	University	3	Authorative journal
Ding and Hu (23)	Fujian	3,055/1,420/1,635	1330/596/734	1,330/1,039/303	Cross-sectional study	National Health Commission questionnaire	1, 3	University	4	Authorative journal
Wei (24)	Guangzhou	6,289/–/–	1,013/–/–	1,013/222/75	Cross-sectional study	PHQ-9	1, 2	University	4	Unauthorative journal
Deng et al. (25)	Wuhan	517/135/382	15/5/10	15/2/1	Cross-sectional study	PHQ-9	1	University	3	Authorative journal
Liu (26)	Haerbing	553/292/261	89/44/45	89/53/44	Cross-sectional study	SCL-90	1	College	3	Authorative journal
Wang et al. (27)	Haerbing	1,111/203/908	279/49/230	279/–/24	Cross-sectional study	SCL-90	1, 3	University	4	Authorative journal
Chang et al. (28)	Guangdong	3,881/1,434/2,447	659/229/430	659/123/39	Cross-sectional study	PHQ-9	1, 2	University	4	Authorative journal
Ma et al. (29)	Shanxi	516/–/–	143/–/–	143/43/5	Cross-sectional study	SCL-90	1	College	3	Authorative journal
Cao et al. (30)	Shanxi	7,143/2,168/4,975	1518/525/993	1518/196/62	Cross-sectional study	SCL-90	1	University	3	Authorative journal
Mo (31)	Anhui	786/–/–	158/–/–	158/–/–	Cross-sectional study	SCL-90	2	University	3	Authorative journal
Zhong and Xiong (32)	Chengdu	331/155/176	95/36/59	95/–/23	Cross-sectional study	SCL-90	1	University	3	Unauthorative journal

For outcomes, 1: there was information about the prevalence of depression; 2: included information about using new information platforms; 3: information about help seeking.
M, male; F, female; mil, mild depression; mod, moderate depression; ser, serious depression.

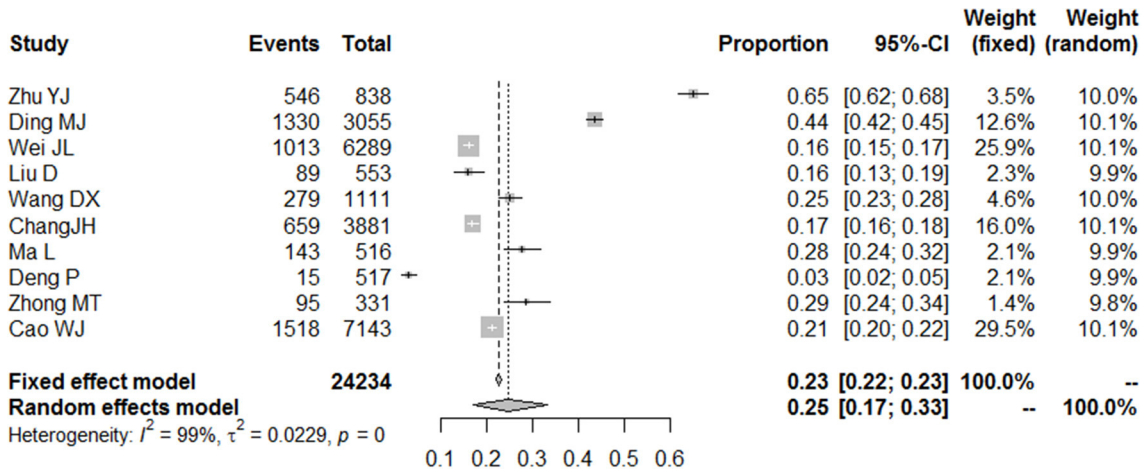

FIGURE 2 | Forest plot of the incidence of mild depression among college students during COVID-19.

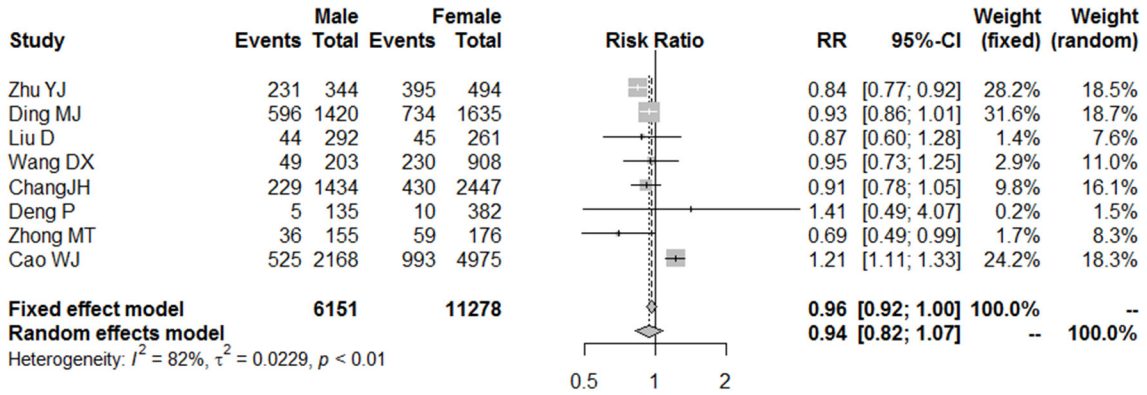

FIGURE 3 | Forest plot of the incidence of mild depression between genders.

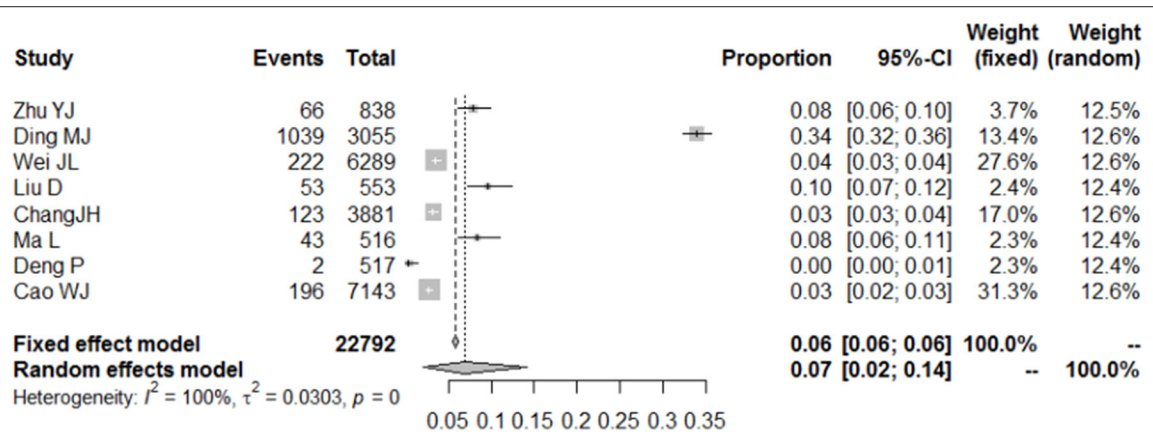

FIGURE 4 | Forest plot of the incidence of mild depression among college students during COVID-19.

This study explored the psychological state of college students during lockdown in the COVID-19 pandemic. The results indicated that college students suffered from depression at a higher rate than in normal circumstances, which was consistent with the concerns of some scholars (34, 37).

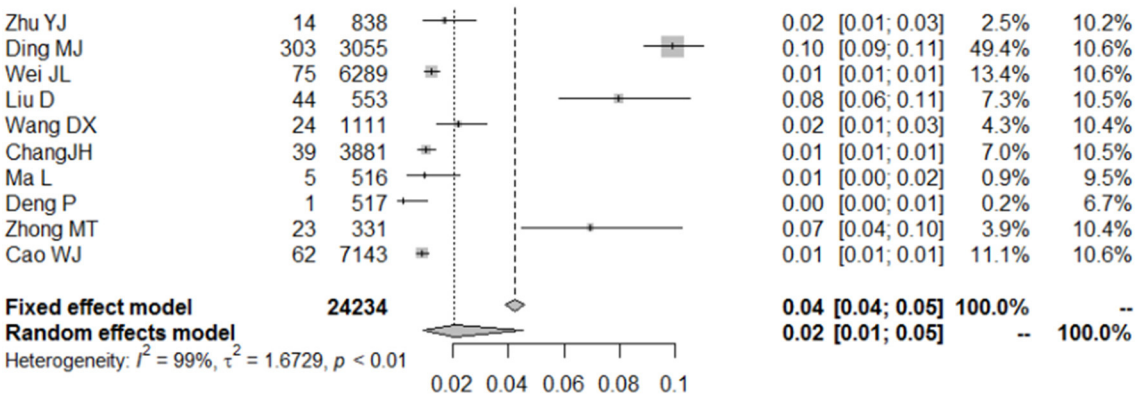

FIGURE 5 | Forest plot of the incidence of mild depression among college students during COVID-19.

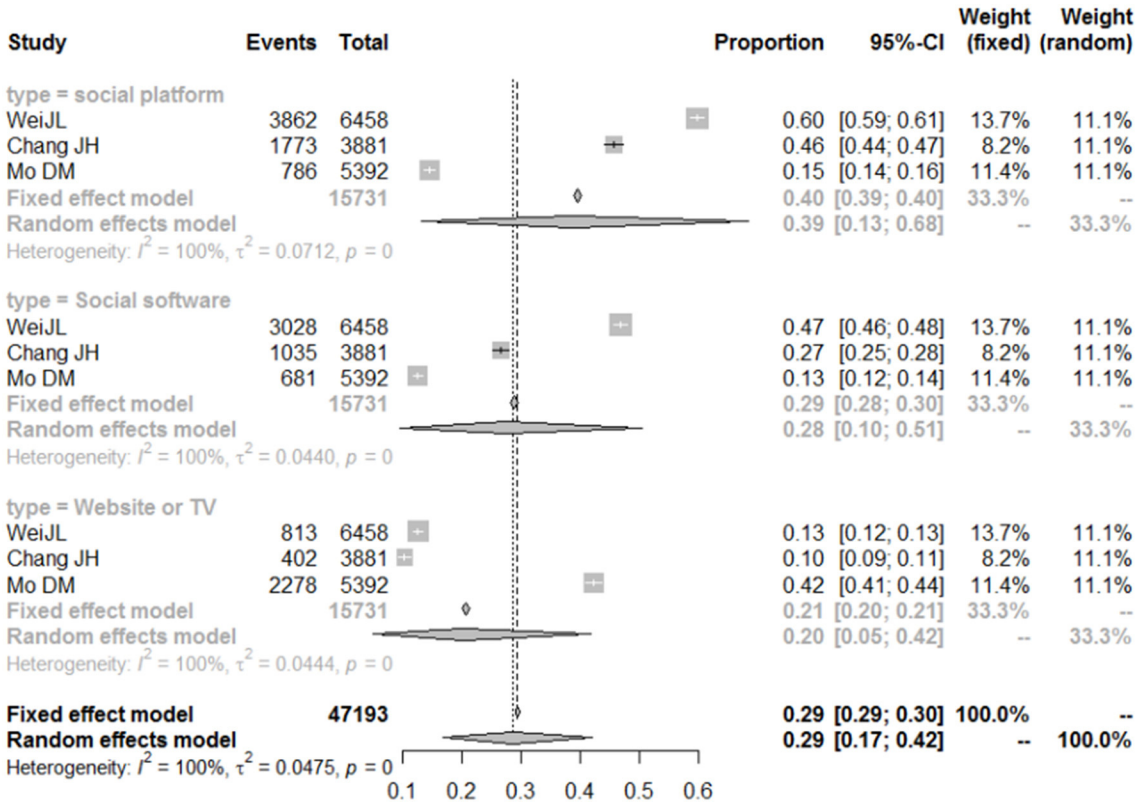

FIGURE 6 | Forest plot of the importance of different information platforms in disseminating COVID-19 knowledge.

Specifically, the results of the meta-analysis showed that the proportion of college students with mild depression was 25% (95% CI = 17–33%), those with moderate depression was 7% (95% CI = 2–14%), and those with severe depression was 2% (95% CI = 1–5%). There was no significant gender difference in the incidence of mild depression (RR = 0.94, 95% CI = 0.82–1.07); however, this result may be related to the samples of the included literatures, in which gender parity was not considered when conducting the surveys.

Due to the non-uniform assessment criteria for depression used in the included literatures (there were four assessment criteria, including two questionnaires and two international

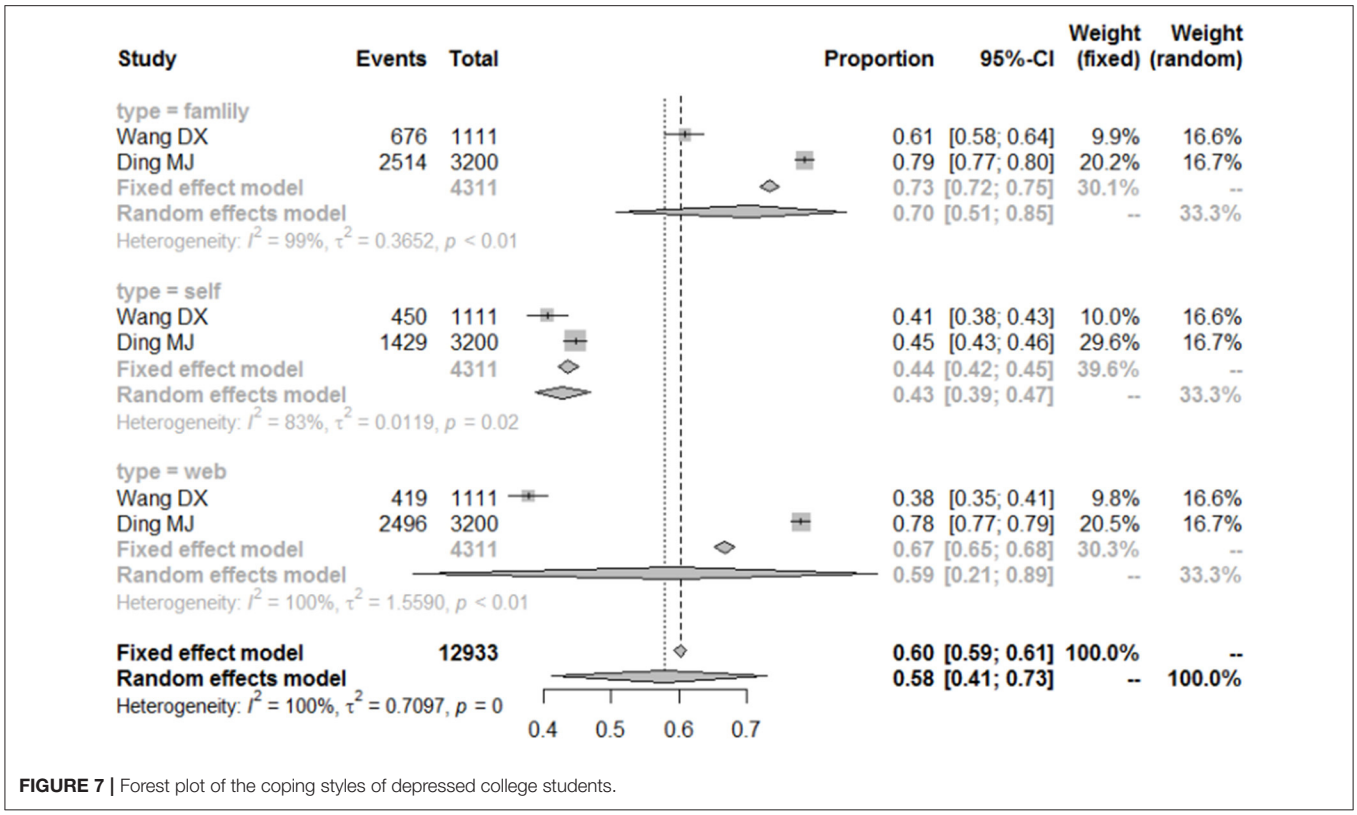

FIGURE 7 | Forest plot of the coping styles of depressed college students.

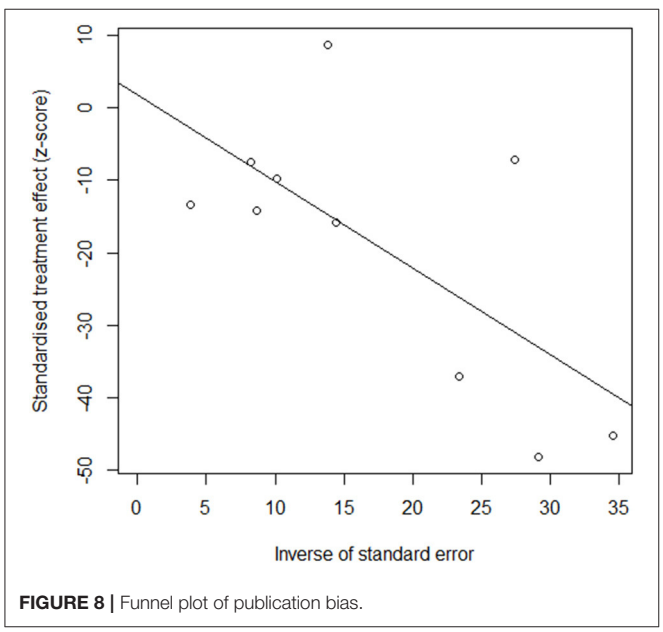

FIGURE 8 | Funnel plot of publication bias.

depression assessment scales), the confidence intervals of the data obtained in this study were relatively wide. However, the results indicated that the COVID-19 pandemic has had a significant negative impact on the mental state of college students. Therefore, in order to reduce the impact of COVID-19 on the mental health of college students, colleges and universities should provide effective mental health services to their students during the COVID-19 pandemic.

Some scholars have conducted studies on the impact of COVID-19 on people's mental state, which recommended that adolescents, including university students, should be provided with effective mental health services to reduce the impact of the epidemic on them (38, 39).

In this study, college students with depression were classified as having mild, moderate, and severe depression according to the diagnostic criteria for depression, suggesting that different interventions should be developed according to the degree of depression in students in order to prevent the aggravation of depressive symptoms.

Thus, although previous studies showed that the COVID-19 pandemic negatively impacted on the healthcare systems in many countries, including mental health services[1], it is imperative for college administrators to pay more attention to the mental health of their students in the same way as they do when protecting them from COVID-19.

With regard to help seeking for depression, the results of this study indicated that most depressed students sought help from their families, suggesting that social support, such as family, can play an important role in alleviating depression. Furthermore, about 59% of the depressed college students used mobile phone APPs of mental health category for help in

[1] Available online at: https://www.who.int/publications/i/item/WHO-2019-nCoV-EHS_continuity-survey-2020.1

dealing with bad emotions, indicating that these APPs also play an important role in helping depressed college students to cope with their bad emotions. However, the antidepressant effects of these mobile phone APPs were not evaluated in this study. Thus, an evaluation of the effectiveness of these mobile phone APPs in providing mental health services to Chinese college students should be conducted precisely because, although previous studies have confirmed that these APPs may play a role in providing mental health services for early depression, they also have some shortfalls (40). For example, some studies found that some psychological intervention APPs have disadvantages such as excessive disclosure of personal privacy, inappropriate use, and lack of professional psychological intervention content (40). Also, a study examining the effectiveness of a smartphone APP in treating depression found that the exact contribution of the APP in decreasing the depression scores was unclear (41).

In addition, concerning the sources of knowledge for the COVID-19 pandemic, this study found that Weibo, official accounts, and other social media platforms were not only the most important sources of knowledge about the COVID-19 pandemic accessed by Chinese college students but they also played an important role in communication. These results are consistent with the results of related previous studies.

Limitations

Some limitations should be noted in this study. Firstly, most of the included studies investigated Chinese college students, which may preclude generalizing these results to other non-Chinese college students. Secondly, symptoms of depression were not a predefined outcome, hence may not have been accurately evaluated. Besides, among the included studies, there were different evaluation scales for depression, including PHQ-9, SCL-90, and the National Health Commission questionnaire, which may account for the heterogeneity in the results. Despite the preceding limitations, the present study provides valuable information for psychological interventions aimed at effectively improving the depression symptoms of college students.

Conclusion

The prevalence of depression among college students in China was high during the lockdown in the COVID-19 pandemic. Thus, considering the adverse outcomes of depression, it is imperative that college administrators frequently screen college students in China for depression during the CIVID-19 pandemic and provide them with necessary psychological interventions to control and prevent depression. Social media platforms, such as WeChat and Weibo, and mental health APPs could provide an opportunity for psychological health information dissemination for college students in China. However, their effectiveness in reducing depression will have to be assessed.

AUTHOR CONTRIBUTIONS

SG and JX conceived and designed the analysis and performed the analysis. SG, JX, and AK wrote the paper. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Education fund of Hunan Province (number: 18B409; http://jyt.hunan.gov.cn/sjyt/xxgk/tzgg/201903/t20190318_5297301.html).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

ORIGINAL RESEARCH
published: 26 July 2021
doi: 10.3389/fpubh.2021.600134

Smartphone Use Among University Students During COVID-19 Quarantine: An Ethical Trigger

Heba Saadeh[1], Reem Q. Al Fayez[2], Assem Al Refaei[3], Nour Shewaikani[3], Hamzah Khawaldah[4], Sobuh Abu-Shanab[5] and Maysa Al-Hussaini[6,7]*

[1] Department of Computer Science, King Abdullah II School of Information Technology Faculty, The University of Jordan, Amman, Jordan, [2] Department of Computer Information System, King Abdullah II School of Information Technology Faculty, The University of Jordan, Amman, Jordan, [3] School of Medicine, The University of Jordan, Amman, Jordan, [4] Department of Geography, School of Arts, The University of Jordan, Amman, Jordan, [5] Psychosocial Program, King Hussein Cancer Center, Amman, Jordan, [6] Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, Amman, Jordan, [7] Human Research Protection Program Office, King Hussein Cancer Center, Amman, Jordan

OPEN ACCESS

Edited by:
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***Correspondence:**
Heba Saadeh
heba.saadeh@ju.edu.jo

Specialty section:
This article was submitted to Public Mental Health, a section of the journal Frontiers in Public Health

Received: *28 August 2020*
Accepted: *30 June 2021*
Published: *26 July 2021*

Citation:
Saadeh H, Al Fayez RQ, Al Refaei A, Shewaikani N, Khawaldah H, Abu-Shanab S and Al-Hussaini M (2021) Smartphone Use Among University Students During COVID-19 Quarantine: An Ethical Trigger. Front. Public Health 9:600134. doi: 10.3389/fpubh.2021.600134

To reduce the spread of COVID-19, Jordan enforced 10 weeks of home quarantine in the spring of 2020. A cross-sectional study was designed to assess this extended quarantine's effect on smartphone addiction levels among undergraduates. A random sample of 6,157 undergraduates completed an online questionnaire (mean age 19.79 ± 1.67 years; males 28.7%). The questionnaire contains different sections to collect socio-demographic, socio-economic, academic, quarantine-related information, and smartphone usage. The smartphone addiction scale-short version was used to assess the degree of addiction during the quarantine. The mean addiction score across the whole sample was 35.66 ± 12.08, while the prevalence of addiction among participants was 62.4% (63.5% in males and 61.9% in females). The majority of the participants (85%) reported that their smartphone usage during the quarantine increased or greatly increased (27.6 and 57.2%, respectively), with some 42% using their smartphones for more than 6 h a day. Nevertheless, three-quarters of the students wished to reduce their smartphone usage. Several demographic and quarantine factors have been assessed, and students' gender, the field of study, parental education, household income in addition to the location of quarantine (urban, rural) and the house specifications (apartment, independent house, with/without a garden) showed statistically significant associations with smartphone addiction during the quarantine. Female students, students studying scientific- and medical-related majors compared to those studying humanity majors, those with higher incomes, those who had been quarantined in an apartment without a garden, and those who lived in urban areas showed significantly higher addiction scores.

Keywords: COVID-19, Jordan, quarantine, short version addiction scale, smartphone addiction, university students

INTRODUCTION

The novel coronavirus 2019 (COVID-19) infected more than 180 million people in 222 countries and killed around 4 million globally (as of 07/07/2021), according to the World Health Organization (1, 2). This disease is a severe acute respiratory syndrome caused by betacoronavirus (SARS-CoV-2), which might disrupt the human body's normal immune response and cause lots of implications (3, 4). Therefore, the vagaries of this pandemic forced many countries to take severe actions to protect their citizens from infection. Jordan applied complete lockdown around mid-March 2020, closing all schools, universities, shops, public and private sectors, borders, and airlines, forbidding any civil movement for several days. A curfew was then applied to restrict all movement, allowing only short walks and for short periods. The majority of the population was under home quarantine for around 10 weeks. These extreme measures helped contain the spread of the virus and controlled the number of casualties and deaths in Jordan in the spring and summer of 2020. Due to the countrywide closure, schools, universities, and companies moved to online platforms for distance learning and remote working. This new lifestyle, enforced by staying at home and under quarantine, has brought new challenges socially, economically, physiologically, and psychologically (5–9).

One significant lifestyle shift is the complete reliance on the internet and smart devices, like tablets, laptops, and mobiles. During the quarantine, with the necessary social/spatial distancing, the usage of these smart devices increased at an increasingly fast pace. Unfortunately, this total dependence has shown to be a form of addiction, i.e., a compulsive physiological need for and use of a habit-forming substance (10). Nowadays, addiction is not only restricted to extensive substance or drug abuse but also extends to the behavioral obsession with a specific activity that disturbs people's healthy daily lives. Recently, internet-based activities, like online gaming, chatting, and communications through the different available applications, have shown similar addiction levels to those of drugs (11–13).

The impact of internet misusage has increased significantly due to its high accessibility through smartphones, especially during the COVID-19 pandemic. Mobile phones are widely used; around 60% of the world's population and 80% of Jordanian households have mobiles (14, 15). In the past year alone, Jordanian mobile phone connections, internet users, and active social media users increased by 1.7, 1.2, and 7.4%, respectively (15). Several studies have identified the prevalence of smartphone addiction risks in different countries, using the smartphone addiction scale-short version (SAS-SV) (16–25). Although a few recent studies have highlighted the different aspects of internet usage related to COVID-19 (26–29), none, to the best of our knowledge, have examined smartphone addiction during the current lockdown and quarantine. This is the first research that presents a large-scale study of thousands of Jordanian undergraduate students to assess the effect of COVID-19 extended home quarantine on smartphone addiction levels. This is assessed by collecting many exposures to cover the demographic, economic, and quarantine-related factors that might worsen the effect of quarantine on smartphone overuse.

METHODS

Participants

Responses to the online questionnaire were submitted by 7,146 undergraduates at the University of Jordan (UJ) during the April and May of 2020. After cleaning the data by removing all duplications, 6,157 unique participants who had fully completed the online questionnaire and participated voluntarily remained for analysis. There was no missing data as all the questions were mandatory. Participants could withdraw at any time by failing to answer any of the questions. The study's purpose and procedures had been approved by the Institutional Review Board and the Research Ethics Committee at UJ.

Participants' ages ranged between 17 and 30 years, with a mean of 19.79 $\pm$ 1.67. 1,769 students were male (28.7%) and 4,388 female (71.3%). Half were studying humanities-related majors and around one-third scientific majors, with the rest studying medical-related majors. Nearly half of the students were in their first year.

Measurements

This study focuses on the association between the new lifestyle forced by home quarantine and smartphone usage, which might even reach the addiction level. The online questionnaire was distributed in Arabic, the Arabic version of the SAS-SV was validated in 2018 (30), targeting all UJ undergraduates and ensuring that all the participants fully understood the questions and the accompanying choices. The questionnaire contains several sections, collecting an extensive list of exposures, like socio-demographic, socio-economic, and quarantine-related information, in addition to the 10 items of the SAS-SV to measure the primary outcome: smartphone addiction level. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for observational cross-sectional studies were used to guide the reporting of this study (31).

Socio-Demographic/Socio-Economic Variables

The study examined the participants' different socio-demographic measures: gender, age, place of residence, class (year at university), academic major (Scientific, Medical, or Humanities), academic performance ranging from acceptable to excellent, and their smoking practices. The study also collected a few socio-economic factors, such as parental education levels, parental employment status, and household income level ranging from <200 JD ($282) to more than 1,500 JD ($2,115).

Quarantine Variables

To assess the association between smartphone addiction and quarantine, 12 questions were listed. Some questions asked about the place of residence during quarantine, whether in a city or a village and the house specifications, like an apartment or a house with or without a garden. The study also asked about the number of people quarantined with each student, ranging from 0 to >10, how many children are among them, and whether they have specific health issues, including chronic diseases. The students were also asked about communication with the family members who lived with them and those who did not. Furthermore,

TABLE 1 | Socio-demographic, socio-economic, and quarantine characteristics of study participants.

Variable	Mean ± SD or *N* (N %)	Variable	Mean ± SD or *N* (N %)
Gender		Age	19.79 ± 1.67
Male	1,769 (28.7%)	**Employment status (parents)**	
Female	4,388 (71.3%)	Both work	1,075 (17.5%)
Major		Only father works	3,762 (61.1%)
Humanities	3,092 (50.2%)	Only mother works	244 (4.0%)
Medical	840 (13.6%)	Neither work	1,076 (17.4%)
Scientific	2,235 (36.2%)	**Household Income Level**	
Class		Less than 200 JD	375 (6.2%)
Year 1	3,003 (48.8%)	200–400 JD	1,225 (19.9%)
Year 2	1,757 (28.5%)	400–600 JD	1,207 (19.6%)
Year 3	793 (12.9%)	600–800 JD	951 (15.4%)
Year 4	481 (7.8%)	800–1,000 JD	955 (15.5%)
> Year 4 (Year 5, Year 6, and more)	123 (2.0%)	1,000–1,200 JD	493 (8.0%)
GPA Level		1,200–1,500 JD	341 (5.5%)
Excellent	655 (10.6%)	More than 1,500 JD	610 (9.9%)
Very good	2,065 (33.5%)	**About to graduate**	
Good	2,057 (33.4%)	Yes	217 (3.5%)
Acceptable	1,380 (22.5%)	No	5,940 (96.5%)
Education level (father)		**Cigarette smoking**	
Post graduates	732 (11.9%)	Yes	1,006 (16.3%)
Bachelor	2,066 (33.6%)	No	5,151 (83.7%)
Diploma	1,126 (18.3%)	**Education level (mother)**	
High School	1,485 (24.1%)	Post Graduates	308 (5.0%)
Others (did not reach high school)	748 (12.1)	Bachelor	1,779 (28.8%)
Location of the house during the quarantine		Diploma	1,543 (25.1%)
Urban areas	5,315 (86.3%)	High School	1,900 (30.9%)
Rural areas	842 (13.7%)	others (did not reach high school)	627 (10.2%)
Home specification		**Household income during the quarantine**	
Apartment with garden	1,176 (19.1%)	Increased	275 (4.5%)
Apartment without a garden	2,174 (35.3%)	Stay the same	2,640 (42.9%)
House with garden	2,210 (35.9%)	Decreased	2,467 (40.1)
House without a garden	597 (9.7%)	Stopped completely	775 (12.5)

Total number of participants: 6,157 students.
SD, Standard Deviation.
Only age is a continuous variable. Thus, it has a mean and standard deviation, while the rest are discrete variables; therefore, they were summarized using percentages.

questions about students' hobbies, including newly practiced ones started during the quarantine, and the household income during quarantine, whether it remained the same, increased, decreased, or stopped altogether, were included.

Smartphone Usage

Smartphone Addiction Scale–Short Version

The original scale consisted of 33 items developed by Kwon et al. (29). The same authors developed the short version (SAS-SV) scale in 2013 (25) to evaluate smartphone addiction's level of risk and its prevalence, based on self-reporting. It has been validated and has greater durable internal consistency than the original version (25). It has 10 items (listed in the results section), each rated on a six-point Likert scale, ranging from strongly disagree (scores 1 point) to strongly agree (scores 6 points). A high score indicates high risk but does not diagnose an addiction. According to Kwon et al. (25), different cut-off values were suggested for each gender: 31 for males and 33 for females. In this study, the short version scale was used to reduce the number of questions the participants needed to answer.

Usage of the Smartphone During Home Quarantine

In addition to the addiction scale, the questionnaire included a few questions regarding the number of hours spent using smartphones per day. Students were also asked about the most frequent smartphone applications (Facebook, YouTube, Twitter, Snapchat, Instagram, and Netflix) used before and during the quarantine, and the level of change in usage was assessed.

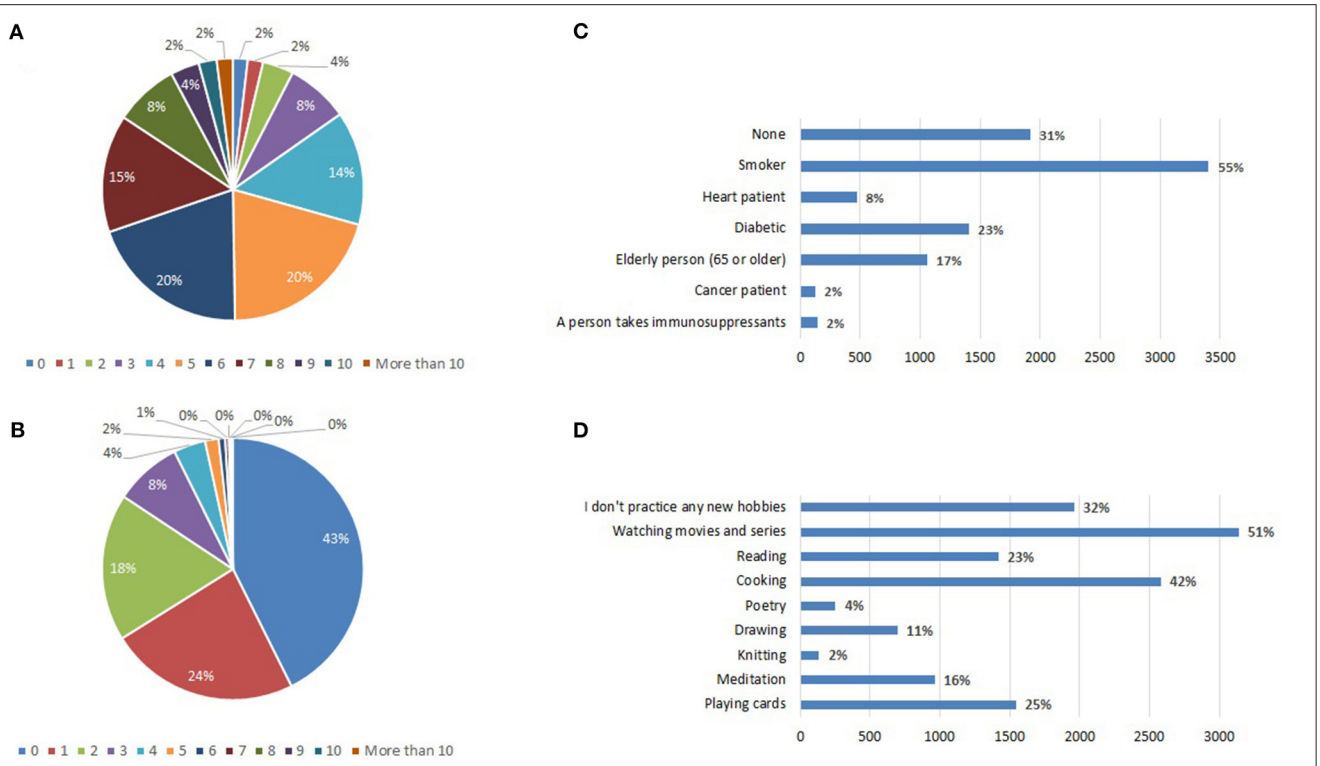

FIGURE 1 | (A) Pie chart for the percentages of people quarantined with each of the study participants ranged from no one (0) to more than 10. **(B)** Similar to **(A)** but for the percentage of the children quarantined with each student. **(C)** Horizontal bar chart for the percentage of the quarantined people (with each student) with specific health issues. **(D)** Similar to **(C)** but for the percentages of the new hobbies that the students started to practice during the quarantine. *X*-axes in **(C)** and in **(D)** shows the frequency of the participants.

Statistical Analysis

Descriptive statistics were performed on the whole sample. Numerical and categorical variables were summarized as mean ± standard deviation and total numbers (percentages), respectively. Binary factors were tested for significance using a two-sample *t*-test, while factors with more than two values were analyzed using a one-way analysis of variance (ANOVA). Tukey Honestly Significance Difference (TukeyHSD) was used as a *post-hoc* analysis to follow up on the significant factors that resulted from the ANOVA to identify the pair of values that had a significant mean difference. The significant factors were further investigated using logistic regression to identify the significant predictors of the addiction state, and to control the potential confounding factors and selection bias. A threshold value of $p = 0.05$ was used to test for significance. All statistical analyses were performed using R version 4.0.0 and RStudio version 1.2.5042.

RESULTS

The original sample consisted of 7,146 submissions, which were then reduced to 6,157 after omitting duplicated responses. Half of the 6,157 undergraduate students were in their first year; the average age was 19.79 ± 1.67. Around 70% ($n = 4,388$) were female, nearly half ($n = 3,092$) were studying humanities-related majors, and about 85% ($n = 5,151$) were non-smokers. The academic performance of the students was categorized into four levels: excellent (10.6%, $n = 655$), very good (33.5%, $n = 2,065$), good (33.4%, $n = 2,057$), and acceptable (22.5%, $n = 1,380$), as declared by the students themselves. The household income level of the participants ranged from <200 JD (1 *JD* = ∼1.4 USD) to more than 1,500 JD; around 45% ($n = 2,807$) had very low to low income (< 600 JD), around 30% ($n = 1,906$) had medium-level (600–1,000 JD), and the rest ($n = 1,444$) had high-level (more than a 1,000 JD) income. The majority of the students (77.2%, $n = 4,751$) lived in the capital city (Amman). **Table 1** summarizes participants' demographics.

Parental employment status showed that for more than half of the students (61.1%, $n = 3,762$) only their father worked and 4%($n = 244$) only their mother; 17.5% ($n = 1,075$) had both parents working, and a similar percentage ($n = 1,076$) neither. For about one-third ($n = 2,066$) of the students, their father was educated to bachelor level, and for a similar proportion ($n = 1,900$) their mother to high school level; only around 12% ($n = 732$) and 5% ($n = 308$) of the students had fathers and mothers educated to postgraduate level, respectively (**Table 1**).

Around one-seventh (n = 842) of the students lived in a village during the quarantine. An equal proportion ($n = 2,174$ and 2,210, ∼35%) lived either in an apartment without a garden or in a house with a garden, with 55% ($n = 3,386$) living in a household with a garden. For nearly 50% ($n = 3,242$) of the students, their

TABLE 2 | Items of smartphone addiction scale–short version.

Item		Mean ± SD
1	Missing planned work due to smartphone use	3.71 ± 1.48
2	Having a hard time concentrating in class, while doing assignments, or while working due to smartphone use	3.68 ± 1.45
3	Feeling pain in the wrists or at the back of the neck while using a smartphone	3.61 ± 1.52
4	Will not be able to stand not having a smartphone	4.02 ± 1.57
5	Feeling impatient and fretful when I am not holding my smartphone	3.32 ± 1.54
6	Having my smartphone in my mind even when I am not using it	3.21 ± 1.53
7	I will never give up using my smartphone even when my daily life is already greatly affected by it.	3.66 ± 1.55
8	Constantly checking my smartphone so as not to miss conversations between other people on Twitter or Facebook	3.54 ± 1.53
9	Using my smartphone longer than I had intended	3.63 ± 1.53
10	The people around me tell me that I use my smartphone too much.	3.28 ± 1.53

SD, standard deviation.
This scale was proposed by Kwon, Kim, Cho and Yang, 2013 (25) as a short version for the original Smartphone Addiction Scale that contained 33 items (32).

household income either decreased or completely stopped during the quarantine, indicating financial difficulties (**Table 1**).

During the quarantine, 77% (n = 4,741) of the students lived with 3–7 family members, and 43% (n = 2,648) were not quarantined with children (**Figures 1A,B**). More than half (n = 3,386) were quarantined with a smoker, about 20% (n = 1,416) with a diabetic patient, around 8% (n = 493) with a cardiac patient, and 17% (n = 1,047) with an elderly member of the family (>65 years) (**Figure 1C**). The majority of the students (89.7%, n = 5,523) increased communication with their families, and about 70% (n = 4,310) communicated more with a distant family member during the quarantine. Around 80% (n = 4,926) spent more time with their families than they normally do.

Nearly 70% (n = 4,310) of the students spent most of their time watching movies/series and/or sleeping and about 50% (n = 3,079) in eating/cooking. Many students (68%, n = 4,187) started new hobbies during quarantine (**Figure 1D**), including watching movies/series (51%, n = 3,140), cooking (42%, n = 2,586), board games (25%, n = 1,539), reading (23%, n = 1,416), meditation (16%, n = 985) and drawing (11%, n = 677).

The primary outcome (addiction level) was assessed by the SAS-SV. The 10 items in the SAS-SV are included in **Table 2**. Mean scores ranged from 3.21 (item 6: **Table 2**) to 4.02 (item 4: **Table 2**). The 10 items had totals ranging between 10 (all items scored 1) and 60 (all items scored 6) with a mean score of 35.66 ± 12.08. The associations between the different demographic and quarantine variables with smartphone addiction levels, i.e., SAS-SV scores, are presented in **Table 3**. The lowest SAS-SV score was 33.51 ± 13.25 (house without a garden: **Table 3**), and the highest 36.83 ± 11.63 (apartment without a garden: **Table 3**). The prevalence of addiction among participants was 62.4% (n = 3,841), representing potential excessive use, with a mean SAS-SV score of 43.18 and a standard deviation of 7.59. However, based on the suggested SAS-SV score threshold of ≥31 for males and ≥33 for females (25), the prevalence of addiction was 63.5% (n = 1,124, total number of males = 1,769) and 61.9% (n = 2,717, total number of females 4,388) with SAS-SV scores of 42.33 ± 7.85 and 43.53 ± 7.45 for males and females, respectively (**Table 4**).

Among the tested binary variables, including the gender, graduation status, smoking habit, and the house location during the quarantine, both the graduation status and smoking habit variables were not significant ($p > 0.05$). Females and quarantine in urban areas were significantly associated with smartphone addiction (**Table 3**). Furthermore, the field of study (major), city, household income, parental education, and the house specifications were found significant (ANOVA $p < 0.05$). The mean difference between the humanities and each of the scientific and medical majors was significant (TukeyHSD p-values: 0.009 and 0.007, respectively), with the scientific and medical majors having a larger SAS-SV mean score than the humanities-related majors (**Table 3**). Although the mother's education had a significant association (ANOVA p-value: 0.030), the TukeyHSD analysis did not find any significant pair-wise comparison between its different values ($p > 0.05$); hence, this factor is not considered significantly associated with smartphone addiction levels. On the other hand, the household income had a significant association (ANOVA p-value: 6.9e-4), and this is mainly due to the difference between <200 JD and higher income levels (TukeyHSD $p < 0.05$). Likewise, the father's education (ANOVA p-value 0.013); only the comparison between a diploma and below high school was significant (TukeyHSD p-value: 0.007), while other education levels showed no significant associations (**Table 3**). Finally, house specifications were found to be significantly associated with addiction levels. Living in a house and not in an apartment, as well as having a garden, had lower SAS-SV scores. Quarantine in an apartment without a garden showed a higher significant association with smartphone addiction and the highest SAS-SV score (**Table 3**).

The six significant factors (ANOVA and TukeyHSD p <0.05) of gender, house location, major, household income, father's education, and the house specifications were further investigated using logistic regression. The aim was to identify which of these factors was a significant potential predictor of the students' addiction state [calculated based on the suggested SAS-SV score thresholds of ≥31 for males and ≥33 for females (25)] (**Table 5**). As expected, quarantine in urban areas and studying health- or science-related majors had a significant positive association with

TABLE 3 | Association between smartphone addiction level (SAS-SV score) and the socio-demographic, socio-economic and quarantine characteristics of the participants.

Variable	SAS-SV score mean ± SD or (*p*-value)	Variable	SAS-SV score mean ± SD or (*p*-value)
Gender	**(1.4e-03[a]*)**	**Age**	35.66 ± 12.08
Male	34.88 ± 12.24	**Employment Status (Parents)**	(0.065[b])
Female	35.98 ± 12.00	Both of them work	36.20 ± 12.13
Major	**(1.1e-03[b]*)**	Only Father works	35.34 ± 12.04
Humanities	35.11 ± 12.31	Only Mother works	36.58 ± 11.96
Medical	36.52 ± 12.11	None of them work	36.03 ± 12.15
Scientific	36.10 ± 11.70	**Household Income Level**	**(6.9e-04[b]*)**
Class	(0.458[b])	Less than 200 JD	33.82 ± 12.64
Year 1	35.83 ± 12.02	200–400 JD	34.59 ± 12.56
Year 2	35.69 ± 12.18	400–600 JD	36.12 ± 12.04
Year 3	35.07 ± 12.34	600–800 JD	36.13 ± 11.85
Year 4	35.91 ± 11.53	800–1,000 JD	35.92 ± 11.92
> Year 4 (Year 5, Year 6, and more)	33.89 ± 12.40	1,000–1,200 JD	36.46 ± 11.15
GPA Level	(0.110 [b])	1,200–1,500 JD	36.13 ± 11.41
Excellent	35.74 ± 12.63	More than 1,500 JD	35.98 ± 12.33
Very Good	36.12 ± 11.95	**About to graduate**	(0.577 [a])
Good	35.20 ± 11.96	Yes	36.09 ± 11.56
Acceptable	35.62 ± 12.17	No	35.64 ± 12.10
Education Level (Father)	**(0.013 [b] *)**	**Cigarette Smoking**	(0.212 [a])
Post Graduates	35.27 ± 11.98	Yes	35.23 ± 12.08
Bachelor	35.71 ± 11.95	No	35.75 ± 12.08
Diploma	36.33 ± 11.59	**Education Level (Mother)**	**(0.030 [b] *)**
High School	35.90 ± 12.38	Post Graduates	36.08 ± 11.54
Others (did not reach high school)	34.43 ± 12.57	Bachelor	35.93 ± 12.06
Location of the house during the quarantine	**1.9e-06 [a] ***	Diploma	36.18 ± 11.92
Urban areas	35.96 ± 11.97	High School	35.25 ± 12.06
Rural areas	33.74 ± 12.59	others (did not reach high school)	34.66 ± 12.76
Home specification	**2.9e-10 [b] ***	**Household income during the quarantine**	0.184 [b]
Apartment with garden	35.92 ± 11.63	Increased	34.58 ± 12.57
Apartment without a garden	36.83 ± 11.63	Stay the same	35.54 ± 11.96
House with garden	34.96 ± 12.30	Decreased	36.00 ± 12.11
House without a garden	33.51 ± 13.25	Stopped completely	35.38 ± 12.20

*Total number of participants: 6,157 students; SAS-SV, Smartphone Addiction Scale Short-Version (25); SD, Standard Deviation; [a]P-value is obtained using t-test; [b]P-value is obtained using one-way-ANOVA. *Statistically significant p-value (≤ 0.05). Statistically significant values appear in Bold.*

addiction state. Quarantine in a house without a garden showed a significant negative association, indicating a SAS-SV score lower than other values, as listed in **Table 3**.

Around 85% (n = 5,234) of the students reported increased smartphone usage during quarantine, and only about 3% (n = 196) reduced their smartphone usage, which correlates well with the SAS-SV scores (**Table 6**). During this quarantine, around 42% (n = 2,575) of the students, despite their demographics, spent more than 6 h a day on their smartphones with very high SAS-SV scores (38.60 ± 11.18 for 6–8 h and 39.41 ± 13.23 for >8 h: **Table 6**). Only 3.6% (n = 223) of the students used their smartphones less than an hour per day, and they had relatively small SAS-SV scores (**Table 6**).

The top three applications widely used on smartphones before the quarantine were reported to be Facebook and its messenger, Instagram, then YouTube. These applications remained the top three applications used by the students during the quarantine (**Table 7**). However, the use of Facebook and Instagram was reduced by 5.4 and 9.6%, respectively, and the use of YouTube and Netflix increased by 6.8 and 9.9%, respectively (**Figure 2** and **Table 7**).

Finally, around three-quarters (n = 4,690) of the students self-reported that they wished to change their smartphone usage by reducing the number of hours they spent using them. Only 3.4% (n = 208) wished to increase their usage, and around 20% (1,259) reported that they were satisfied with their current smartphone usage.

DISCUSSION

The study was conducted on students at the University of Jordan, the largest public university in the capital, Amman (only 22.8% of

TABLE 4 | Smartphone addiction prevalence among the study participants based on SAS-SV scores.

Participant groups	Factor	Prevalence as *N* (N %)	SAS-SV score mean ± SD
Potential High-risk	Male	1,124 (63.5%)	42.33 ± 7.85
	Female	2,717 (61.9%)	43.53 ± 7.45
	Total	3,841 (62.4%)	43.18 ± 7.59
Potential low-risk	Male	645 (36.5%)	21.89 ± 6.18
	Female	1,671 (38.1%)	23.69 ± 6.63
	Total	2,316 (37.6)	23.19 ± 6.56

Total number of participants: 6,157 students: 1,769 males, and 4,388 females; SAS-SV, Smartphone Addiction Scale Short-Version (25); SD, Standard Deviation; Males cut-off is 31, and Females cut-off is 33, according to (25).

TABLE 5 | Association between addiction state and each of the identified significant factors, as assessed by logistic regression[+].

Coefficients	Estimate	*p*-value	Odd ratio	CI lower	CI upper
(Intercept)	0.092	0.549	1.096	−0.208	0.393
Sex (Male)	0.037	0.539	1.038	−0.082	0.157
House Location (Urban)	0.215	0.010 *	1.240	0.051	0.380
Specialization (Medical)	0.192	0.019 *	1.212	0.032	0.354
Specialization (Scientific)	0.161	0.007 *	1.175	0.045	0.278
Home specification (Apart. without a garden)	0.115	0.134	1.122	−0.036	0.264
Home specification (House with garden)	−0.122	0.119	0.885	−0.277	0.032
Home specification (House without a garden)	−0.303	0.004 *	0.738	−0.508	−0.098
Household income (1,000–1,200 JD)	0.242	0.098	1.274	−0.045	0.530
Household income (1,200–1,500 JD)	0.246	0.125	1.279	−0.068	0.562
Household income (200–400 JD)	−0.051	0.670	0.950	−0.289	0.185
Household income (400–600 JD)	0.119	0.327	1.127	−0.121	0.359
Household income (600–800 JD)	0.173	0.177	1.188	−0.079	0.422
Household income (800–1,000 JD)	0.121	0.349	1.128	−0.133	0.373
Household income (>1,500 JD)	0.176	0.218	1.193	−0.104	0.456
Father education level (Diploma)	0.187	0.018*	1.205	0.032	0.343
Father education level (High school)	0.124	0.097	1.132	−0.022	0.271
Father education level (Post graduates)	0.0005	0.995	1.001	−0.176	0.179
Father education level (Others)	−0.012	0.895	0.988	−0.195	0.171

CI: 95% Confidence Interval.

** Statistically significant p-value (≤ 0.05).*

[+]Dependent variable: addiction state; calculated based on the suggested SAS-SV scores threshold of ≥ 31 for males and ≥ 33 for females.

the study participants lived outside the capital). UJ hosts around 50,000 students studying undergraduate and postgraduate degrees in humanities, science, and health disciplines. Six thousand one hundred fifty-seven undergraduates voluntarily completed the online questionnaire, comprising around 12.3% of UJ students. This sample of participants is a good representative of the demographics of the university since 76% of the UJ students are female, 50.3% are studying humanities-related majors, 10.5% have excellent GPA, and 22.5% have acceptable GPA; the figures for the study participants are 71.3% females, 50.2% studying humanities, and 10.6 and 22.5% with excellent and acceptable GPAs, respectively. The questionnaire link was uploaded with several obligatory university requirements, usually taken by students in their first 2 years, thus explaining why around 77% of the participants were in years 1 and 2, with a mean age of 20 years; only 3.5% were in their final semester (**Table 1**).

This sample is also comparable with the Jordanian population, according to the National Council for Family Affairs (NCFA) national survey in 2017 (33). About 78% of the participating families had 3–7 members, consistent with our sample demographics (**Figure 1A**). Furthermore, 54.4 and 45.6% of the students lived in an apartment or individual house, respectively (**Table 1**), which is also similar to the corresponding NCFA survey results of 57 and 42%. The NCFA reported that 19% of female adults in Jordanian families work, a similar percentage to the 21.5% of students whose mothers worked. Non-communicable chronic diseases prevail in society as 14.5 and 7.2% suffer from diabetes and cardiovascular diseases, respectively. 23 and 8% of the students in this sample were quarantined with a family member suffering from diabetes or cardiovascular diseases, respectively (**Figure 1C**). Tobacco smoking in Jordan, as reported by WHO (34), is more prevalent

TABLE 6 | Smartphone usage during quarantine and their associations with smartphone addiction level (SAS-SV score).

Variable	*N* (N %)	SAS-SV score mean ± SD
Smartphone usage during the quarantine		
Largely decreased	63 (1%)	26.13 ± 12.67
Decreased	133 (2.2%)	29.62 ± 11.53
Stayed the same	737 (12.0%)	29.47 ± 10.63
Increased	1,699 (27.6%)	33.85 ± 9.84
Largely increased	3,525 (57.2%)	38.23 ± 12.56
Number of hours used on Smartphone during the quarantine		
0–0.5	95 (1.5%)	23.37 ± 12.06
0.5–1	128 (2.1%)	26.31 ± 9.45
1–2	328 (5.3%)	29.58 ± 10.88
2–3	617 (10.0%)	30.34 ± 10.39
3–4	1,008 (16.4%)	33.13 ± 10.60
4–6	1,406 (22.8%)	36.73 ± 11.00
6–8	1,178 (19.1%)	38.60 ± 11.18
Greater than 8	1,397 (22.8%)	39.41 ± 13.23

Total number of participants: 6,157 students.
SAS-SV, Smartphone Addiction Scale Short-Version (25); SD, Standard Deviation.

TABLE 7 | Top smartphone applications used by the students before and during the quarantine.

Smartphone applications	Usage before quarantine % (A)	Usage during quarantine % (B)	Difference between the usage before and during the quarantine (B–A)
Facebook	45.0%	39.6%	−5.4%
Instagram	31.4%	21.8%	−9.6%
YouTube	13.2%	20.0%	6.8%
Snapchat	6.2%	4.4%	−1.8%
Twitter	2.1%	2.2%	0.0%
Netflix	2.0%	11.9%	9.9%

Total number of participants: 6,157 students.

in males, with 70% of males aged more than 14 years being smokers (35); this explains the high proportion, nearly half, of the students quarantined with a smoker (**Figure 1C**). The preponderance of females in our sample might account for only 16.3% being smokers.

Regrettably, around 50% of parents in our sample had partially or entirely lost their jobs, reducing financial resources since the private sector was primarily affected by the countrywide closure (**Table 1**). Previous studies disagreed with the effect of household income on smartphone addiction (36, 37), while in this study, lower incomes were negatively associated with addiction scores (**Table 3**). Similarly, contradictory results were reported regarding parental education and phone usage (36, 38). Nevertheless, this study reported a significant association between parental education and smartphone addiction, precisely the difference between a diploma and below high school (**Table 3**).

Interestingly, the characteristics of a quarantine site had a significant effect on smartphone usage. Most of the Jordanian population lives in urban areas; hence, a small proportion of the participants were quarantined in rural areas (13.7%: **Table 1**). Quarantine in an apartment without a garden was significantly associated with addiction scores (**Table 3**). Additionally, a significant association between quarantine in urban areas and addiction scores is noted (**Tables 3, 5**). This can be explained by the tight surveillance and strict control the government imposed on the big cities compared to the rural areas, which provided fewer opportunities for practicing outdoor activities and encouraged spending more time on smartphones.

The COVID-19 pandemic home quarantine enforced a sudden and different lifestyle, an extended lockdown with strict rules for remaining indoors. About 70% of the students spent most of their time watching movies/series (**Figure 1D**). 85% reported an increase in smartphone usage, with about 42% spending more than 6 h a day on their smartphones. Additionally, with the limited available resources within families, many students relied on their mobile phones to attend the university's compulsory online teaching.

Several studies have assessed smartphone addiction among university students; however, none have evaluated its addiction

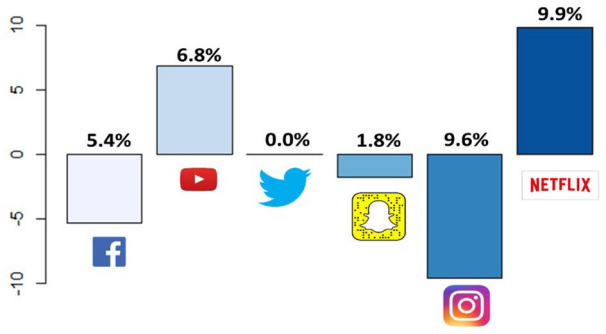

FIGURE 2 | Absolute difference of smartphone applications usage (in percentages) before and during the quarantine.

and prevalence during a quarantine. SAS-SV results indicated that smartphone addiction was prevalent in a total of 3,841 (62.4%) participants (63.5% in males and 61.9% in females). The mean SAS-SV score for the potential high-risk group was 43.18 ± 7.59 (42.33 ± 7.85 in males and 43.53 ± 7.45 in females). These alarming results warrant validation and intervention. In comparison, our results are different from those reported in China: 29.8% (17), South Korea: 24.8% (25), Spain: 12.8% (18), Belgium: 21.5% (18), Switzerland: 16.9% (21), but comparable to Lebanon: 44.6% (19), Morocco: 55.8% (30), and Saudi Arabia: 71.9% (20). All previously mentioned studies used the same assessment scale; SAS-SV. Interestingly, another study in Jordan conducted before the COVID-19 pandemic that used a different assessment scale and different cut-offs (39) reported addiction prevalence of 59.8%, compared to 27.2% in Saudi Arabia, 17.3% in Sudan, and 8.6 in Yemen, re-enforcing our findings of mobile phone overuse in Jordan.

The high prevalence of smartphone usage among the students is alarming and raises warning flags on the high risk of excessive use among Jordanians in general and during the quarantine in particular. Depression and anxiety are among the potential contributors to increased addiction to smartphones (40), factors which also increased under quarantine conditions (6, 41). A gender-based effect of mobile phone addiction was reported previously, with the prevalence of females showing more addictive symptoms and reporting more intensive use than males (39, 42–45), agreeing with our findings. Furthermore, a significant association between addiction levels and students' majors was observed in previous research; humanities, but not scientific and medical studies, were more commonly associated with smartphone addiction (39, 46–48). This contradicts our findings. Relying on smartphones for distance learning is more common in scientific/medical majors than humanities, which rely more on hard copy. Finally, although a few studies have demonstrated an association between academic performance and mobile addiction (49–51), no significance was reported in this study (p-value: 0.11).

Whether this can be classified as an addiction or overuse is still debatable (52). Panova et al. argue that the strict definition of addiction is not fulfilled in smartphone overuse. Smartphone soveruse is not associated with significant functional, financial or physical impairment. Besides, an increase in smartphone use is not equivalent to tolerance; nowadays, smartphone use is a normalized part of everyday life in many societies, even when engaged with very frequently (52). This is precisely what the students encountered during the quarantine. The dependence on distance learning, the substitution of hardcopy books and journal references with softcopies, affluence, and affordable free applications all helped direct the students toward smartphone overuse.

The study's limitations include the dependence on self-reporting of the use of smartphones, which might be associated with recall bias, thus under- or over-estimation. In addition, all students were from the same university, which might be associated with selection bias. However, the large number of participants (6,157), spread over various economic sectors, is an accurate reflection of Jordanian society, rendering the results generalizable. Another limitation is the potential selection bias resulted from having around 70% of female participants. More balanced selection criteria would be better to apply. However, this factor was controlled in the logistic regression model. Furthermore, increasing the reliance on remote learning during the imposed quarantine might be associated with the overuse of smartphones. The study should be repeated outside the quarantine period to give a better insight into the magnitude and the socio-cultural factors related to smartphone overuse.

CONCLUSIONS AND RECOMMENDATIONS

Quarantine is a stressful situation with several challenges, casting its shadow over routine life. No previous study has assessed the relationship between quarantine and smartphone addiction levels during the quarantine period. Female gender, urban areas, apartment quarantine, higher income, and scientific and medical majors had higher and significant overuse scores. The SAS-SV scores are higher than previously reported scores for other countries, although they are comparable to other countries in the region (39). Whether an addiction or overuse, the high scores and prevalence reported are alarming and indicate the severity of smartphone dependence among Jordanian university students during the quarantine. A repeat questionnaire on a comparable study population with follow-up interventions is warranted.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board and the Research Ethics Committee at the University of Jordan. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

HS conceived the idea, performed the analysis, and wrote the manuscript. RA performed the pre-processing and part of the statistical analysis and figures. HK performed part of the statistical analysis. AA, NS, and SA-S contributed to the literature search. MA-H co-wrote the manuscript and helped in designing the study. All authors contributed to the article and approved the submitted version.

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frontiers in Public Health

PERSPECTIVE
published: 22 September 2021
doi: 10.3389/fpubh.2021.653923

Is It Legitimate for Society to Intervene in the Way Citizens Live Their Lives When the Cost of Health Care Has to Be Borne by the General Public?—General Considerations and Special Implications During the Covid-19 Pandemic

Christoph Edlinger[1,2], *Dominic Klein*[3] *and Michael Lichtenauer*[4]*

[1] Department of Cardiology, Heart Center Brandenburg, Bernau/Berlin, Germany, [2] Brandenburg Medical School (MHB) "Theodor Fontane", Neuruppin, Germany, [3] Division of Cardiology, Department of Internal Medicine 5, Hospital Favoriten, Vienna, Austria, [4] Division of Cardiology, Department of Internal Medicine II, Paracelsus Medical University, Salzburg, Austria

OPEN ACCESS

Edited by:
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***Correspondence:**
Michael Lichtenauer
michael.lichtenauer@chello.at

Specialty section:
This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health

Received: 15 January 2021
Accepted: 18 August 2021
Published: 22 September 2021

Citation:
Edlinger C, Klein D and Lichtenauer M (2021) Is It Legitimate for Society to Intervene in the Way Citizens Live Their Lives When the Cost of Health Care Has to Be Borne by the General Public?—General Considerations and Special Implications During the Covid-19 Pandemic. Front. Public Health 9:653923. doi: 10.3389/fpubh.2021.653923

Over the last few decades, the perception of disease has changed significantly. In the concept of the sick person's role it should be the aim of every person to keep health at a good level for as long as possible. Several examples can be found where, however, a disease can be caused or worsened by a person. Examples include unhealthy diet, alcohol consumption leading to atherosclerosis and diabetes, or smoking, leading to lung cancer and COPD. There are also other appropriate examples where there is a potential for conflict between the autonomy of the individual and health. Improving public health should be the main objective of any health system. However, the more the impact is on personal freedom (and there is no extraneous danger), the more an attempt should be made to achieve this through the motivation of each individual to support the desire for a healthy lifestyle, rather than through legal prohibitions or penalties. The situation is even more complex in the case of the Covid-19 pandemic. In this context too, personal freedom is restricted in many areas and some people feel, for example, that compulsory masks or the prohibition of large crowds are serious encroachment on their autonomy. However, even in this case, the risk of possible external threats from the spread of the virus outweighs the right to personal choice and freedom. To sum up, it is necessary to balance the two principles - autonomy and interference in them in the interests of public health.

Keywords: autonomy, restrictions, COVID-19, sick person's role, public health

INTRODUCTION

The health system of several European countries is based on a social security system and is financed by compulsory insurance for all citizens. Such financing models can be found throughout Europe (e.g., very similar systems exist in Germany, France, Austria and the Benelux countries) and date back to the introduction of compulsory health insurance in 1883 by Otto von Bismarck (1). In

contrast, there are still models of a national health service financed by taxes, such as in Great Britain, Italy, Ireland, Denmark and Portugal, and predominantly privately financed models, such as in the USA. In an international comparison of these models, the Austrian health care system for example is regarded as rather expensive, but it is also among the best in terms of the quality of health care services. In this model of health financing, all citizens (or employers) pay a percentage of their income (or pension) into the health system or into the statutory health insurance funds in the form of contributions. In return, the costs of treating illnesses are covered by the system (2). There are also deductibles in some areas, such as the prescription fee for medication or dental treatment. The aim of this system is to create a social balance and to ensure that all sections of the population receive the same high quality health care. The aim of such a system is to compensate for social differences, for example in income, social environment, education and origin, all determinants of long-term health, and to be able to offer fair health care to the entire population. In addition, there is genetics, which means that the risk of a disease is unequally distributed in the population. Even though this system attempts to provide health care as broadly as possible for all strata of the population with low barriers, there are still potential conflict zones and moral hazards (3). The central theme of this essay is to present the conflict question "Since the costs of health care must be borne by the general public, is it legitimate for society to intervene in the lifestyle of the citizen?"

Over the last decades, the picture and the view of diseases have changed. Whereas in the past, for example in the Middle Ages, a disease was seen as God's punishment, the concept of disease changed in the following centuries and a disease was often seen later as a fateful process. The sick person was therefore not responsible for his/her condition in the eyes of society. The American sociologist Talcott Parsons explored this concept or viewpoint and described it in his treatise on the sick role (4). According to this concept, the sick role goes hand in hand with rights but also duties. These rights include the right to be removed from the normal social role (for example, the right to sick leave), the right to be accepted (in the sense of medical treatment), and the right not to be responsible or liable for his/her present condition. On the other hand, the sick person is also attributed duties, namely that the sick person should seek to recover and seek medical assistance. However, this model of the sick person's role is not ideally applicable in all areas and has led to criticism. This model is more tailored to acute illnesses and less appropriate in the setting of chronic illnesses or disabilities. Furthermore, the role of the sick person(s), which is seen as rather passive, and the view that the individual should not be responsible for the illness, also attracted criticism. Thus, several examples can be found in which an illness can very well be influenced or triggered by the individual. Examples include unhealthy diet and the occurrence of atherosclerosis or diabetes, smoking and most forms of lung cancer or COPD. Even as a counter-example, a study by Chalfont and Kurtz in 1971, which looked at alcohol addiction, showed that people with alcohol addiction are seen by society as responsible for their illness and stigmatized, or that alcohol addiction is sometimes not seen as a disease at all (5). Examples like these therefore do not fit into the model postulated by Parsons.

In modern society, the concept of illness has continued to change and the influence of the individual on health and illness is becoming increasingly important. Based on the results of medical research in recent decades, the connection between health and illness has been deciphered in detail in many areas. A suitable example of this would be atherosclerosis research, where studies have proven the various influencing factors such as nutrition, inflammation and family history (6). As mentioned above, one of the key driving factors is diet, as it has been shown that high blood lipid levels can lead to a rapid progression of the disease, which can significantly increase the risk of heart attack and stroke. Although decades of research and frequent media coverage of the most common risks, such as poor nutrition and lack of exercise, have led to the conclusion that every person should be aware of the lifestyle that leads to these diseases, a substantial part of the population refuses to accept these insights. This is partly due to traditional lifestyles and habits and certainly also to a certain amount of neglect of the risks of disease.

SMOKING AND LUNG DISEASE

Another appropriate example is smoking. Especially in Austrian politics, a general ban on smoking in restaurants and bars with its introduction and abolition has been a frequent topic of dispute in recent years. In the case of smoking, too, the health risks have long been known and a clear association with the occurrence of lung carcinomas and COPD, but also cardiovascular diseases, has been demonstrated. Despite this knowledge, many people are exposed to this risk every day through the consumption of cigarettes. Moreover, passive smoking can also affect uninvolved people.

At the same time, there is an inconsistent political line on the smoking ban in restaurants and bars within Europe.

For example, Berlin's gastronomic establishments are allowed to position themselves either as "smoking establishments" or as non-smoking establishments. The idea is that the customer decides for him/herself and his/her health which type of establishment he/she wants to visit.

Other countries such as Italy or Ireland, where smoking has been banned in public places for many years now, had a much stricter approach. Italy in particular, played a pioneering role in the inner-European comparison in terms of non-smoker protection. Examples include information campaigns, banning advertising for cigarettes or the placing of large-format warnings on tobacco products.

Nevertheless, public measures have been taken in many countries in recent years to reduce the risks of tobacco consumption.

ALCOHOL CONSUMPTION

Alcohol consumption offers a similar example. In this case too, it is known that high alcohol consumption can lead to addiction and mental and physical illness (for example, cirrhosis

of the liver or heart failure). In society, alcohol consumption has been a social convention for centuries and is an accepted consumer good in all walks of life. This ranges from excessive alcohol consumption by young people as a form of initiation rites (keyword binge drinking) to wine tastings at all ages and social settings. As already mentioned above, alcohol addiction continues to be a repressed and stigmatized disease, as described by Chalfont and Kurtz in the 1970s. This may be due to the fact that alcohol occupies a central place in Western society, even more so than smoking, and is ubiquitous as a consumer product in shops and restaurants.

In this context, there is a clear discrepancy within Europe. Central European countries such as Austria, Germany or the Czech Republic have always been at the forefront of per capita consumption, whereas consumption in southern European regions such as southern Italy or Spain is comparatively moderate.

In the Scandinavian countries and in Finland, there have been clear restrictions for many years, insofar as high-percentage alcoholic beverages are only sold in a few and are moreover taxed at a very high rate. On the one hand, this offers the advantage of government control, especially when it comes to the consumption behavior of minors. However, we know from times of prohibition in the USA that the danger of black market trade or even illegal own production might increase here, so that in many countries there is an increasing focus on targeted prevention.

Even though there have been repeated efforts in recent decades to launch educational campaigns to inform people about the dangers of alcohol, there have been few socio-political measures aimed at reducing alcohol consumption, with the exception of the blood alcohol limit in road traffic. In contrast to tobacco products, there are also hardly any restrictions on the sale or advertising of alcohol products, possibly because they occupy such a central social and economic place in many western countries.

SPECIAL IMPLICATIONS DURING THE COVID-19 PANDEMIC

The subject of this essay is whether society can intervene in the way people live their lives when it comes to the health of the general public, which, after all, has to bear the bulk of the costs due to compulsory insurance or government-funded healthcare. In this context, however, it is not only a question of the costs of illness, but also of whether, and if so to what extent, health policy makers should and can intervene in the lives of citizens when it comes to maintaining or improving public health. The Covid-19 pandemic is a very recent example in this context. No other health crisis in recent decades, or even centuries, has had such a profound impact on the daily life of the world's population. Governments all over the world tried to stop the spread of the virus and the associated risk of infecting large parts of the population by means of a lock-down of social life (closing of shops, cancellation of public events) and instructions on how to behave in public (social distancing and compulsory masks in shops and public transport). A year ago, it would hardly have been conceivable that our daily life could have changed so fundamentally and that such far-reaching measures on the part of the government would have been necessary to put into practice. Although the Covid 19 crisis is not yet over, it can be assumed that these farreaching measures, which also strongly affect the autonomy of the individual(s), could prevent a faster spread of the Sars CoV-2 virus and a resulting overloading of the health care system in the affected countries. In our opnion, the actions of those in power in this current pandemic crisis represent a particularly remarkable example of how far-reaching and stringent measures, which of course also have a negative impact on the autonomy of the individual, are being used to preserve the well-being and health of the general public. As is probably the case in most situations where such cuts in personal freedom occur, resistance to government measures (corona parties, demonstrations and conspiracy theories in social networks) has formed in some sections of the population. Such measures therefore always represent a tightrope walk between encroachments on personal freedom and desired positive effects on the health of the individual or individuals and the general public.

However, it is not only the COVID pandemic or the acute infection itself that raises a multitude of ethical questions. In many countries, opinions around COVID-19 vaccination are currently dividing societies. In particular, many nations are currently discussing compulsory COVID-19 vaccination. The challenging question here is - can the state impose compulsory vaccination on its citizens in order to achieve herd immunity? In this context, it must be considered that a vaccination of young adults or even children is also necessary, whose risk course for a severe course of the disease is considered to be comparatively low.

In this context, therefore, a balancing of interests takes place. There is a conflict between the "good of health (the general public)" and the "good of autonomy". In philosophy and ethics, a "good" represents a desired goal of human endeavor. The philosopher Plato described three different forms of goods, namely intrinsic goods in the sense of pleasure experiences, which are primarily striven for because of themselves and not because of their consequences, and extrinsic goods such as medical therapy, which are striven for because of their consequences and not for their own sake. In addition, there are goods that have both intrinsic and extrinsic values, such as health. Health is desired both for its own sake and for the sake of its consequences, as it provides momentary well-being and is the prerequisite for pursuing our goals in the future. Autonomy is also such an intrinsic and extrinsic good, since its presence is important both for our present well-being and for the realization of our future desires. It is precisely here that there is a particular potential for conflict in the context of general health vs. autonomy.

Nevertheless, the preservation of personal decision-making ability and autonomy is of great importance in medicine. If a patient is undergoing medical treatment due to a disease, the doctor treating him/her will prescribe a therapy or operation in order to achieve a cure or at least an improvement of the current condition. However, the decision whether the patient agrees to this recommendation is solely his/her responsibility. The doctor

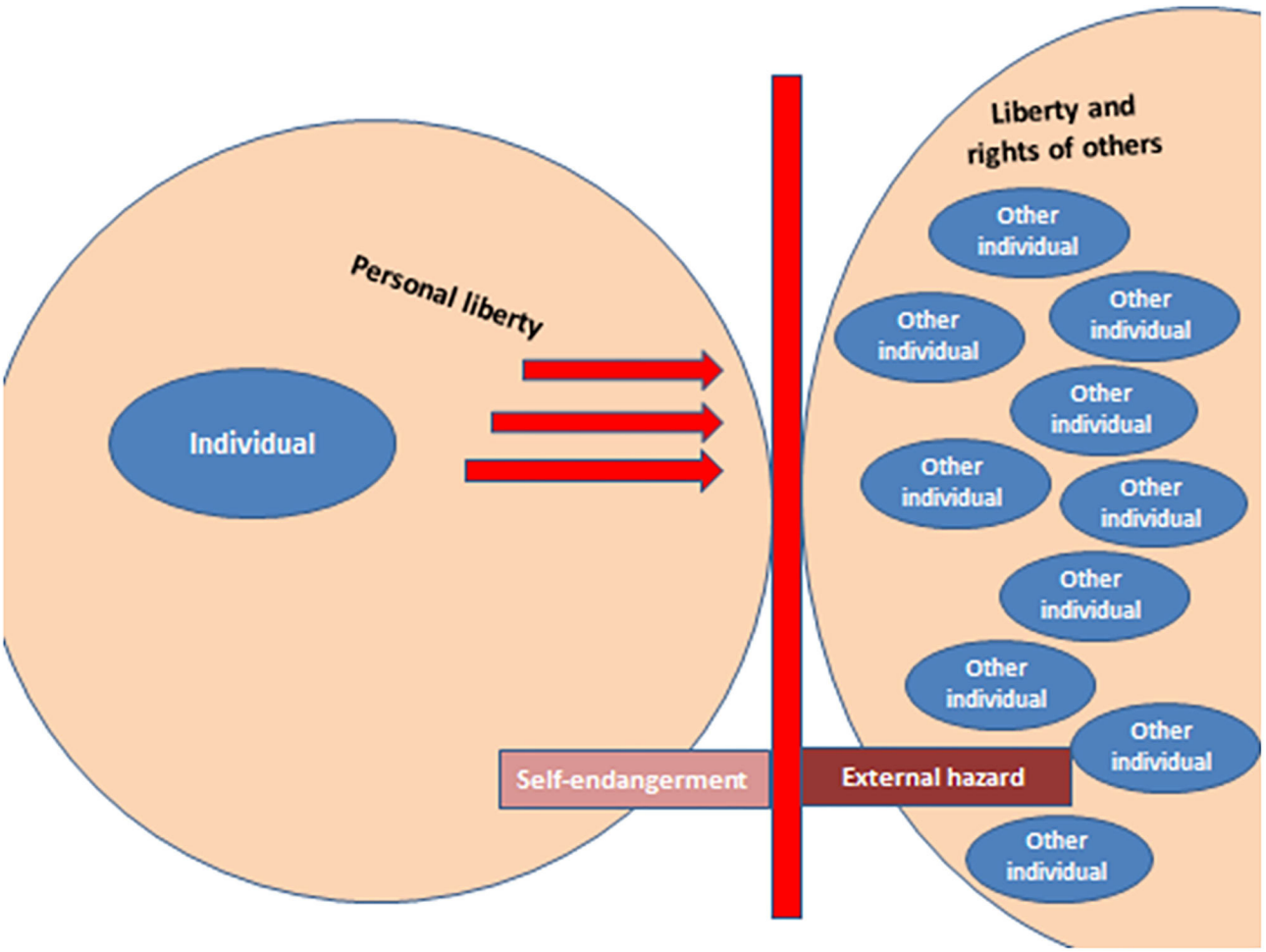

FIGURE 1 | The rights to autonomy and personal freedom generally go so far (including possible self-endangerment) as to reach the area of external danger to others [autonomy up to the external border of the other(s)].

can only inform the patient about the consequences of the illness, the course of the therapy and possible risks of action or inaction but cannot force the patient to undergo therapy or surgery. If the patient refuses treatment, he/she can also confirm this in writing by submitting a so-called reverse voucher. This means that the patient renounces treatment on his/her own responsibility and represents a personal decision that must be taken into account by the doctor. On the other hand, doctors cannot be forced to carry out a medical intervention if the patient wants or demands it, but there is no medical indication for it. One example would be plastic/aesthetic, non-reconstructive surgery. Another area of tension is abortion. Here too, the doctor is not obliged to carry out an abortion if it is against his/her ethical or religious understanding. There is, therefore, also a right of autonomy on the part of the doctors. These differences also represent the central issues in medical ethics. The medical ethicists Beauchamp and Childress established four basic principles of medical practice in their research at Georgetown University (7). These four principles of ethical action in medicine include the patient's right to self-determination (right to autonomy), the principle of avoiding harm, the well-being of patients and the goal of social justice.

In this context there are also regional differences which are based on different philosophical attitudes. While in the European countries the attitude of mind is based on Immanual Kant's philosophy and assumes autonomy equally distributed on both sides, in the USA the right of the patient to choose is more widespread. This difference probably developed not only because of other philosophical models but also because of other health care structures, as health in the USA is more a matter of personal choice due to the predominance of private insurance models than in Europe with compulsory health insurance. Therefore, in the USA, the good "health" is more determined by financial factors of the individual, while on the other hand, in some areas the sick person has more freedom of choice regarding medical therapy (right of choice), as long as he or she can afford it or is insured for it.

As mentioned above, the attitude of mind in medicine in Europe goes back more to the philosophical views of Kant. Kant derived the concept of human dignity primarily

from the autonomy of the human being. The individual has a choice, he/she can decide how he/she wants to act, and his/her decision depends on his/her moral and ethical values. Kant formulated the categorical imperative as the fundamental principle of ethical action. This is: "Act only according to that maxim whereby you can, at the same time, will that it should become a universal law" (8). According to Kant, personal freedom is of paramount importance, but only to the extent that it does not violate or restrict the freedom or rights of one or another. Consequently, the latter must have a social compatibility of his/her own actions. The principle of the golden rule, which is often confused with Kant's categorical imperative, goes back even further, but in linguistic usage it is expressed with the phrases "Treat others as you would like to be treated by them" or, conversely, "Do not do to others what you do not want them to do to you" is even more common.

DISCUSSION

When we look at the points of conflict between autonomy and public health, a red line can be drawn where the autonomy of the individual restricts the freedom or rights of others or the general population (see **Figure 1**). For example, although individuals are not forbidden to consume alcohol in large quantities that endanger their own health, the safety and physical integrity of other people may be endangered. In road traffic, for example, legal regulations are in place to prevent injuries as far as possible (e.g., blood alcohol limits, driving bans). The situation is similar with smoking. Although smokers are made aware of the risks of tobacco consumption through information on cigarette packets, smoking itself is not prohibited despite the known health risks, and doing or not doing so is the free, personal decision and autonomy of the individual. Here too, however, legal provisions only come into play as soon as a possible danger to others can arise, for example through passive smoking in restaurants. Passive smoking by children in the smoker's own four walls is certainly a gray area in this context, as although others/underage persons can also be endangered here, the right to personal freedom is more important in the private sphere than in public. In these two examples, legislation intervenes on behalf of the general public and its health in the rights to freedom of the individual(s) as soon as a mere self-endangerment can lead to a third-party risk. Another example is nutrition. Even though it is known that, as mentioned above, poor nutrition can lead to the development of diseases, in this case, however, it is primarily self-endangerment that exists. Excessive consumption of processed meat products or fast food in general, cannot cause a foreign hazard (apart from the ban on consumption of these in public transport, even if the foreign hazard in this case is of a more olfactory nature). It can therefore be assumed that in such cases there have not yet been any efforts to intervene in the diet of the population directly for the benefit of health through legal measures.

The situation is different in the case of the Covid-19 pandemic. Here, too, personal freedom is restricted in many areas and some people feel, for example, that compulsory masks or the prohibition of large crowds are a serious encroachment on their autonomy. However, even in this case, the risk of possible external threats from the spread of the virus outweighs the right to personal choice and freedom. To sum up, it is necessary to balance the two principles—autonomy and interference in them in the interests of public health. In a State of solidarity, it is up to each individual to decide how to manage his/her own health, as long as this does not create risks for others. Even if the costs of the health system are borne by the general public, this dilemma must seek to strike a balance between personal freedom or even possible behavior that is not beneficial to health and the best possible health of the population as a whole. The goal of improving public health should be one of the main objectives of any government. However, the more the impact is on personal freedom (and there is no extraneous threat), the more efforts should be made to achieve this through information campaigns aimed at the intrinsic motivation of the individual(s), thus supporting the desire for a healthy lifestyle, rather than through legal prohibitions or penalties.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

ML developed the concept and the first draft of the manuscript. CE and DK revised the manuscript. All authors contributed to the article and approved the submitted version.

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