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The global burden of COVID-19 on children's health

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The global burden of COVID-19 on children's health

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Editorial: Covid, Long Covid, Mental Health, Schools and Masks: how and why we failed child health communication during a pandemic

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Editorial on the Research Topic
The Global Burden of COVID-19 on Children's Health

As more than 2 years have passed since the beginning of the pandemic, the time has come for the consideration and analysis of the achievements and advances in the field of child health. Such considerations are needed to better understand the best ways of managing the next pandemic.

In terms of medical achievements, this pandemic will be remembered for the historically rapid development of trials, vaccines, and drugs that have saved millions of lives. However, results are more controversial in terms of public health responses, communication, public opinion, and, overall, in terms of balancing actions that take into account the wider concept of well-being not limited to the recovery from illness.

In this regard, children are in a unique position to allow us to analyze the impact of the pandemic from a child-centered perspective. This is possible because, on one hand, the burden of acute COVID-19 has been clearly less significant in children (1), but on the other hand, children are intrinsically more fragile and often overlooked politically.

These peculiarities have led to the birth of two opposing extremist positions that, in our opinion, have ultimately hampered the societal approach to defending children's needs during the pandemic.

Let us start from the beginning: SARS-CoV-2 infection. Since the first data emerged in China, COVID-19 has led to hundreds of hospitalizations and deaths in adults worldwide. This, along with rigorous early lockdowns, led to observations of very low numbers of pediatric cases during the first wave. However, pediatric deaths or intensive care unit hospitalizations were registered during the very first months of the pandemic and described in early publications from China, the US, and Europe (2). Nevertheless, polarized messages to the public led to the misconception that COVID-19 did not affect children. These incorrect messages affected and still affect the societal response to the pandemic, including influencing scientists and parents in the decision of whether or not to vaccinate children (3). These messages became even more extreme with the much misused or overused observation that most lethal cases occurred in children with comorbidities. To our knowledge, never in history has this concept been stressed so heavily before, creating a sort of stigmatization of children affected by pre-existing comorbidities. Moreover, children can develop Multisystem

Inflammatory Syndrome, which often requires intensive care unit admission and can even be fatal, a complication still poorly known to parents.

Such extreme opinions frequently led scientists to compare disease severities in unhelpful attempts to show which disease was more severe and therefore more important for pediatric health. In the media, this approach was not based on solid evidence but rather aimed at supporting a predefined position. A very common comparison was between respiratory syncytial virus (RSV), influenza, and COVID-19, highlighting the higher hospitalizations during RSV seasons or the more cardiovascular involvement of COVID-19. This approach is disrespectful toward all those families that have lost children to each of these conditions, or have disabled children from these viruses. A personalized risk approach is still far from routine practice and, unfortunately, every single pathogen has the potential to cause severe illness.

At the same time, although considered less at risk or "untouched" by the new virus, children had to pay the indirect price imposed by the new disease on the adult population, and possibly also by some wrong initial decisions. Risk of nosocomial transmission and public fear of in-hospital contagion led to delayed access to care, in many cases a reduction in elective surgeries (4), and restrictions for parent visits in hospitals, sometimes even in the PICU where the need for children (the patients) and their families to be together is at its highest (5). As with other decisions, the well-being of children was sacrificed for that of adults (**Figure 1**).

The extreme views regarding this discussion have had further negative consequences:

- Undermining the clinical burden of disease can create unrealistic expectations for families or diminish scientific interest and funds for the development of drugs or other necessary research/interventions focused on children.
- Exaggerating the clinical burden of COVID-19 in children creates unjustified fears which can lead to extreme, unnecessary actions that, in turn, can negatively affect the well-being of both children and families.

An example of a considered approach would be honest discussion around the real burden of children affected by Covid, regardless of them being either previously healthy or affected by other conditions. This leads to balanced decisions about which social measures to implement, balanced risk in schools, guidelines, and delays in care, and avoiding unnecessary closures and isolation of children, for example, in hospitals.

Long Covid entered later into the discussion. While it was quickly evident that a large subgroup of adults were not fully recovering after infection, this topic has been (and still is) much more debated in children. Observational studies of cohorts of children with COVID-19 without control groups, or studies including imperfect control groups (based on single negative PCR tests, or not fully sensitive serological studies), mostly based on phone calls or self-filled surveys, has led to heated debate (6). On one side is the incorrect argument that everything happening after COVID-19 is due to the infection itself; on the other, scientists have tried to undermine the problem by minimizing it as a psychologization of the condition, mainly due to the mental health impact of the restrictions rather than organic events. The debate is still raging, although scientific advances are starting to provide the rationale for the development of unexplained persisting symptoms in children. Observations of this problem throughout most of the world suggest that, at least for some families, pediatric Long Covid is a real problem.

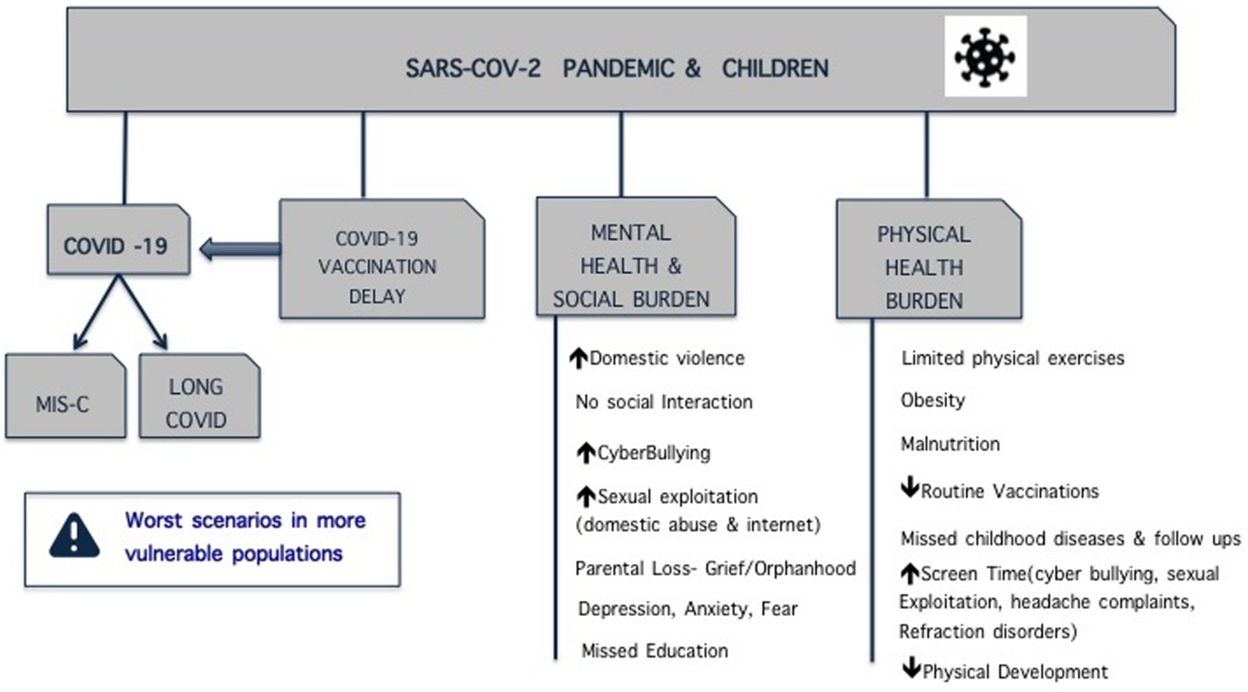

FIGURE 1.
Effects of COVID-19 on children's health.

Negative consequences from the extreme views in this discussion include:

- Reducing the problem to the idea that Long Covid is not a complication of the infection but a psychological problem. This leads to less research and funding in the field (slowing advances in terms of pathophysiology, diagnostics, and treatments), and inaccurate public risk perception of the overall burden of the SARS-CoV-2 infection in children. This can also make the families involved feel abandoned by healthcare systems.
- Conversely, exaggerating Long Covid creates inappropriate fear (which in turn can amplify the need for excessive restrictions), incorrect diagnoses, or late recognition of other treatable conditions. All of these can ultimately negatively affect children.

An example of a considered approach would be informing families about the benefit/risk ratio of vaccinations and other non-pharmacological interventions. It is important that families are made aware of all the possible complications of SARS-CoV-2 infection, from acute disease to post-covid complications, including MIS-C and Long Covid. Although the scientific community does not know yet the real incidence rate of Long Covid, there is agreement that at least a sub-group of children will develop it. Given the large number of undetected pediatric cases, it is possible that a low percentage of infected children will develop Long Covid, and luckily the pediatric disease seems less severe than the adult one. In any case, it is important that healthcare professionals take any child complaining of long-term clinical problems after Covid-19 seriously, rule out all possible alternative diagnoses with current available knowledge, and refer families to specialized centers. It is important for the family to receive care and that their children's conditions are not minimized.

One of the early responses to the sudden medical crisis was generalized lockdown, including school closures. This was initially justified by the massive number of sick adults filling hospitals, the still initially unknown impact of Covid-19 on children, and the possible role of children in viral transmission. However, while adult activities have been restored, in most of the world, school attendance was still being affected as of April 2022. Again, opposing arguments were raised. On one hand, the negative impact of school closures is evident: millions of children missed school, and most never came back, mainly in low- and middle-income countries (LMICs); children missed healthy school meals which, for struggling families, may represent an important source of nutrition; concerns regarding abuse or neglect of children living in difficult social environments were raised; there was an increase in mental health issues; and children with special needs were isolated at home for months if not years (7). On the other hand, certain groups actively argued there was a non-negligible risk for in-school transmission leading to acute Covid-19 or Long Covid (8). The distance between these positions led to indecision regarding difficult policies for in-school lessons that, in the best scenario, continued disrupting school attendance for months, or also led to unfeasible policies for LMICs. For two entire years, millions of children and adolescents have been considered cases, contacts, numbers, "positives or negatives", and lost their right to be what they are supposed to be, that is, learners, or simply, children.

Linked to this topic is the "mask debate". For some, while having a limited impact on covid transmissions, masks limit visual interaction and negatively affected neurocognitive development (9). For others, masks are a key solution and children of any age should be masked (8), even in the paradox that in many countries adults are not mandated to wear a mask yet 2-year-old children do.

Negative consequences from the extreme views in this discussion include:

- Schools being considered safe. That is, there is no need to improve current school statuses, therefore the chance to improve weak organizations or historical pre-covid problems is missed.
- Conversely, schools being seen as drivers of infection, leading to opinions asking for either a perfect solution or online learning, ultimately disrupting the whole school experience for years.

An example of a considered approach would be that schools represent a pivotal period in children's growth in terms of social, cultural, and physical relationships. The negative impact of indiscriminate school closures has become more evident than ever, while the key role of schools in significantly fueling the pandemic has never been proven. Therefore, school closures should only be considered in case of dramatic global or local scenarios, and in the context of generalized lockdowns, particularly during outbreaks that have a more significant impact on adults than on children. Importantly, school closures should only be employed for short periods and personalized programs for special needs children or those from very fragile social contexts should be implemented. At the same time, it is important to also recognize that several children living in a close environment may still be a risk scenario for transmission of airborne infections, and this pandemic should be taken as an opportunity to improve the prevention of airborne infections, as society has historically done with waterborne or foodborne infections. There is evidence that air cleaners may have a role in this regard and such a direction should be seriously considered (10). Additionally, there is no strong evidence either in favor of or against using masks, and therefore families should be informed of the risks and benefits and should be given the opportunity to choose whether to use them or not, according to their perception of the risk, community transmission, and child compliance.

Lastly, pediatric vaccinations have led to strong discussions mainly between, again, two different and distant factions: those in favor of or those against Covid-19 vaccinations. Those against vaccination highlight a non-irrelevant risk of myocarditis in young males and relatively fewer benefits in terms of prevention of complications as compared with adults, since the risk of severe disease in children is much lower. However, this approach does not take into account all the possible outcomes of infection, nor the possibility that families can translate doubts toward Covid-19 vaccinations to routine pediatric vaccinations (11). On the other side, the pro-vaccination group have undermined adverse events and exaggerated benefits, for example, in terms of the reduction of transmission which would have led also to better school attendance.

Negative consequences from the extreme views in this discussion include:

- Some countries only allowing vaccination in children aged 5–11 children at later phases of the pandemic without giving access to vaccines to families willing to be vaccinated. This generates distance between the public and national health systems. Highlighting only the negative effects of the vaccination and undermining all the short- and long-term outcomes of the infection does not give the public the opportunity to make an informed choice, and can reduce the overall favorable opinion of the general population towards all vaccinations.
- Exaggerating the benefits of vaccination increases the distances between the factions and impairs trust in science by those initially skeptical. Also, this can create false certainties and sense of security in vaccinated people.

An example of a considered approach would be to properly explain all the possible outcomes of SARS-CoV-2 infection in children, and highlight the risks of vaccination and what can be realistically expected from them. For example: setting targets for vaccinations, using realistic steps according to the main objectives of that particular period (e.g., deaths and hospitalizations in the early phases of a pandemic); and properly informing the public about the possible needs to adapt vaccine use as knowledge about new vaccines improve (in terms of safety, doses, goals, and technological implementation). This will allow families to make an informed choice with less risk of repercussion or criticism during rapidly changing scenarios.

We hope institutions, including scientific and societal ones, will develop a multilevel process for the critical analysis of the 2 years of the pandemic and develop appropriate plans for a balanced response to the next pandemic, taking into account the specific needs of children.

Author contributions

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

Conflict of interest

Author DB received funding from Pfizer and Roche to study long covid in children. The remaining 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.

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Caregivers' Attitudes Toward COVID-19 Vaccination in Children and Adolescents With a History of SARS-CoV-2 Infection

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Background: Limited data are available on the attitudes of caregivers toward COVID-19 vaccination in children and adolescents with a history of SARS-CoV-2 infection or Long Covid symptoms. The aim of this study was to investigate the vaccine hesitancy among caregivers of children and adolescents with a documented history of SARS-CoV-2 infection and to explore the possible associations between COVID-19 manifestations and the acceptance of the vaccine.

Methods: Caregivers of children or adolescents with a microbiologically confirmed diagnosis of SARS-CoV-2 infection evaluated in two University Hospitals were interviewed.

Results: We were able to contact 132 caregivers and 9 declined to participate. 68 caregivers (56%) were in favor of COVID-19 vaccination for their child. In the multiple logistic regression, child's age (OR 1.17, 95%CI 1.06–1.28) and hospitalization due to COVID-19 (OR 3.25, 95%CI 1.06–9.95) were positively associated with being in favor of COVID-19 vaccination. On the contrary, the occurrence of child's Long Covid was associated with a higher likelihood of being against the vaccination (OR 0.28, 95%CI 0.10–0.80).

Conclusions: This preliminary study shows that only about half of the interviewed parents of children and adolescents with a previous SARS-CoV-2 infection are willing to vaccinate them to prevent a repeated COVID-19 infection. These findings might help healthcare workers to provide tailored information to caregivers of children with a previous SARS-CoV-2 infection.

Keywords: hesitancy, pediatrics, parental, caregivers, vaccination, influenza, papillomavirus, long covid

INTRODUCTION

The immunization against Coronavirus Disease 2019 (COVID-19) is considered one of the key public measures to combat the pandemic and the most effective tool to prevent symptomatic or severe disease (1–3). Recent trials showed the efficacy and safety of BNT162b2 Covid-19 mRNA vaccine in children aged 5 years and older (4, 5).

Despite the increasing production and availability of the vaccine for children, several data point out that many caregivers are hesitant toward COVID-19 vaccination of their children (6–8). Previous studies have identified that many factors might underlie the refusal of pediatric COVID-19 vaccine including, among others, the perception of a low risk of SARS-CoV-2 infection and complications in children (9, 10). However, the spread of the virus in the worldwide population is leading to a growing number of children affected by SARS-CoV-2 and some of them require hospitalization or develop complications such as Long Covid (1, 11, 12). Moreover, a subgroup of children might develop rare but severe complications, such as the Multisystem Inflammatory Syndrome (MIS-C) which often requires intensive care admission (13). Importantly, two studies from France and United States provided preliminary evidence that COVID-19 vaccinations might also prevent the development of MIS-C (14, 15).

Since children, similarly to adults, might be re-infected by new variants of SARS-CoV-2 and the virus spread in the pediatric population is growing (16, 17), children eligible for vaccination and with a history of SARS-CoV-2 infection are likely to increase more and more over time. The Italian Society of Pediatrics currently suggests that children with previous infection should receive a regular vaccination schedule starting three to 6 months after the infection (18). Moreover, other social reasons may, at least theoretically, induce parents to vaccinate their children. For example, school closures have been implemented worldwide as a non-pharmaceutical approach to prevent the spread of the virus within the community, but detrimental consequences on children' physical and mental health have been observed (19–21). Therefore, high vaccinations rates in children and teachers might further support a return to a normal school attendance.

However, very limited data are available on the attitudes of caregivers toward COVID-19 vaccination in children with a history of SARS-CoV-2 infection or Long Covid. The aim of this study was to investigate the vaccine hesitancy among caregivers of children and adolescents with a documented history of SARS-CoV-2 infection and to explore the possible associations between COVID-19 manifestations and the acceptance of the vaccine.

METHODS

The study was conducted between November 01, 2021, and January 15, 2022. Eligible for the study were subjects admitted to the Pediatric emergency department (ED) of the Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan and the Fondazione Policlinico Universitario A. Gemelli, Rome, Italy between July 01, 2020, and June 31, 2021, with a diagnosis of SARS-CoV-2 infection, ascertained by a molecular test in the ED.

The caregivers were contacted by phone and were asked to answer a structured interview. The survey was composed by five sections and investigated the following items: 1) demographic data and educational level of the caregivers; 2) demographic data, the presence of chronic diseases, the manifestation of COVID-19 including the presence of symptoms, need for hospitalization or intensive care, and the development of Long COVID symptoms [defined as having persisting symptoms such as dyspnea, mental confusion, fatigue; chest pain, problems associated to speech, anxiety and altered mood, muscular pain, fever, loss of taste and smell - never reported before COVID-19—for at least 12 weeks (22)] of the child; 3) COVID-19 history in first-degree relatives including the need of hospitalization or intensive care, and the occurrence of death; 4) the caregiver attitudes toward COVID-19 vaccination, if they changed opinion about COVID-19 vaccination after the SARS-CoV-2 infection of their child and his/her opinion on other vaccinations (against Papillomavirus and *Streptococcus pneumoniae*). Finally, if the caregiver and/or the child received at least one dose of influenza vaccine in the previous 3 years was also investigated. The questionnaire is reported within the online **Supplementary Material**.

Before administration, the survey was pilot tested among 5 caregivers and 5 physicians.

Data Management and Statistical Analysis

All data were anonymously collected in a predefined, online database. Response rate was calculated as the number of subjects who accepted to participate divided by the number of subjects who participated plus those who declined. Continuous and categorical data are presented as median and interquartile range (IQR) or absolute frequency and percentage, respectively. Caregivers who were willing to vaccinate their children against COVID-19 or whose children had been already vaccinated were collapsed into the category "In favor of COVID-19 vaccination", whereas subjects in doubt or against the vaccination of their children against COVID-19 were collapsed into the category "Others". Wilcoxon rank sum test was used to compare continuous data of the above-mentioned two groups and the Fisher's exact test or Chi-squared test to compare categorical data, as appropriate. Furthermore, a logistic regression including being "In favor of COVID-19 vaccination" as dependent variable and the caregiver and child's sex, the educational level of the caregiver, the number of months since the child had the COVID-19, the presence of chronic diseases or Long Covid in the child, the need for child's admission for COVID-19, history of a first-degree relative who needed admission due to COVID-19, was performed. The Akaike information criterion was applied to select the best multiple model. Significance was assumed for a p-value <0.05. Analyses were performed using the open-source statistical software R, Vienna, version 3.5.3 (11 March 2019). The study was approved by the institutional ethics committee and consent was obtained before the interview from all participants.

TABLE 1 | Baseline characteristics of the caregivers and children.

N	121
Caregiver	
Age, years	42 [38–47]
Sex, female	97 (80)
Educational level	
Secondary school	19 (16)
High School	36 (30)
University	43 (35)
Post University	23 (19)
Influenza vaccination in the last 3 years, yes	35 (29)
Child	
Age, years	9.0 [2.0–12.0]
Sex, female	48 (40)
Underlying chronic disease, yes	18 (15)
Influenza vaccination in the last 3 years, yes	23 (19)
Months from COVID-19 infection	11 [6–13]
Symptomatic COVID-19, yes	89 (74)
Hospitalization due to COVID-19, yes	27 (22)
Need of intensive care due to COVID-19, yes	0 (0.0)
Long Covid symptoms, yes	45 (37)
COVID19 history in first-degree relatives	
History of COVID-19, yes	103 (85)
Hospitalization due to COVID-19, yes	17 (14)
Need of intensive care due to COVID-19, yes	8 (6.5)
Death due to COVID-19, yes	4 (3.3)
Long Covid symtoms, yes	46 (38)
Caregiver's opinion on other vaccinations	
Vaccination against papillomavirus	
I want my child to receive this vaccination/ My child has been already vaccinated	78 (64)
I know this infection, but I am unsure/I do not want my child to receive the vaccination	25 (21)
I do not know the disease	18 (15)
Vaccination against *Streptococcus pneumoniae*	
I want my child to receive this vaccination/ My child has been already vaccinated	89 (74)
I know this infection, but I am unsure/I do not want my child to receive the vaccination	15 (12)
I do not know the disease	17 (14)

Data are given as median and interquartile range or absolute frequency and percentage.

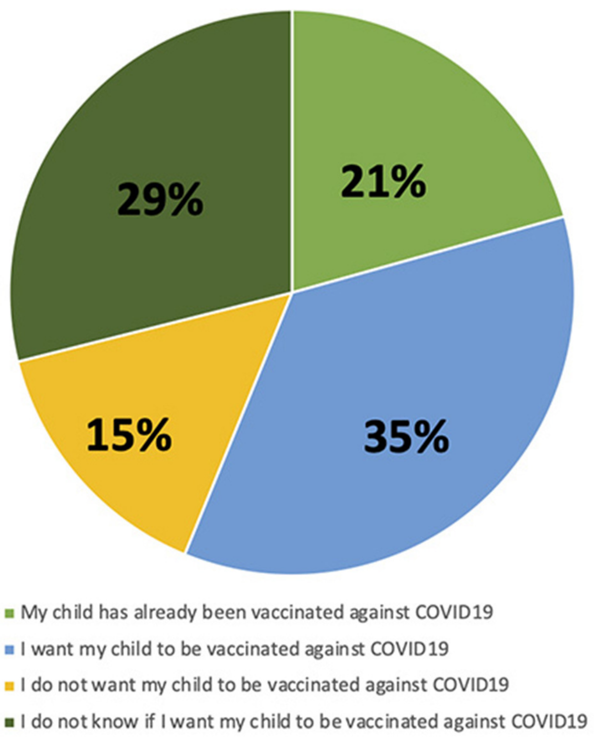

FIGURE 1 | Caregivers' attitudes toward COVID-19 vaccination of his/her child.

RESULTS

We were able to contact a total of 132 caregivers and 11 declined to participate. The median age of the caregivers who accepted to participate was 42 [IQR 38–47] years (males = 24, 20%), **Table 1**. The majority had a university or post university degree (N = 66, 54%). The median age of their child was 9.0 [2.0–12.0] years (males = 73, 60%). Most respondents (N = 103, 85%) had at least one relative with a history of COVID-19. The majority wanted to vaccinate or had already vaccinated their child against Papillomavirus (N=78, 64%) or *Streptococcus pneumoniae* (N = 89, 74%).

Most caregivers (N = 68, 56%) were in favor of COVID-19 vaccination for their child (**Figure 1**). A total of 81 (67%) caregivers stated that they have not changed their opinion about COVID-19 vaccination: 71 of them kept their willingness to vaccinate their child and 10 remain against to COVID-19 vaccination (**Figure 2**). On the contrary, 40 (33%) of the caregivers changed their opinion about COVID-19 vaccination after the SARS-CoV2- infection of their child: 29 became in favor and 11 against the vaccination.

Table 2 reports the characteristics of the caregivers in favor of COVID-19 vaccination as compared to the others (univariate analysis). The only differences between these two groups were the older age of caregivers (44 [40-49] vs. 40 [36-46] years, p = 0.008) and of the child (10.5 [4.0–14] vs. 6.0 [2.0–10] years, p = 0.001) in the group in favor of the vaccination as compared to the others. In the multiple logistic regression, child's age (OR 1.17, 95%CI 1.06–1.28) and hospitalization due to COVID-19 (OR 3.25, 95%CI 1.06–9.95) were positively associated with being in favor of COVID-19 vaccination. On the contrary, the occurrence of child's Long Covid symptoms was inversely associated (OR 0.28, 95%CI 0.10–0.80) with being in favor of COVID-19 vaccination (**Table 3**).

DISCUSSION

In this study, we have assessed parents' attitudes toward COVID-19 vaccination in children and adolescents with a previous SARS-CoV-2 infection. Overall, we found that $<$ 60% of the

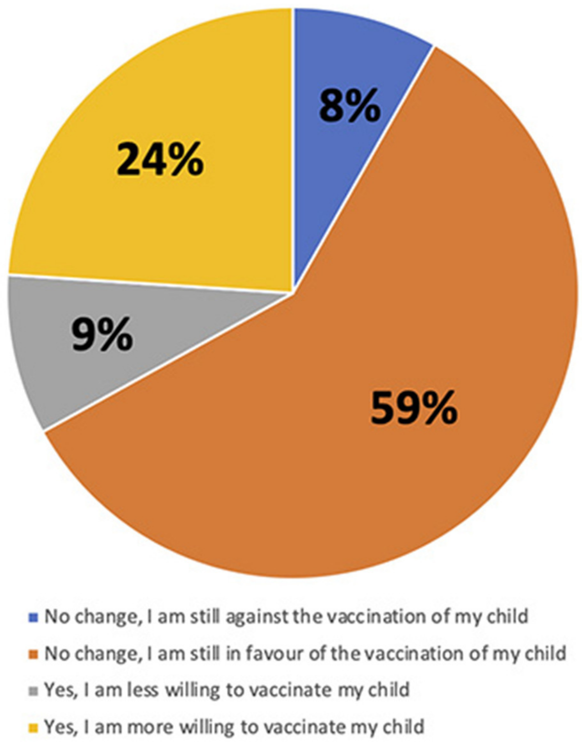

FIGURE 2 | Change of caregivers' attitudes toward COVID-19 vaccination of his/her child after the child's COVID-19 infection.

interviewed parents were willing to vaccinate their children. Interestingly, parents of children who experienced long Covid symtpoms, were more likely to be in favor of the vaccination, while those of children experience Long Covid were more frequently against the vaccination. To our knowledge, vaccine hesitancy among caregivers of children with a documented history of SARS-CoV-2 infection has never been explored so far, and our findings may support the development of personalized communication strategies, which will be crucial in the next months since a huge proportion of children with previous SARS-CoV-2 infection are now eligible for vaccination. This is a critical area for public health interventions since subjects infected during the first waves of the pandemic might not be protected against infection with new variants, including Omicron (23).

A significant association was found between being in favor of vaccination and having had a child previously hospitalized with COVID-19. These findings could be expected since parents that experienced the more severe spectrum of pediatric COVID-19 might be more worried of a new infection. During the first wave of the pandemic, early data from China (24), Italy (25, 26) and Europe (27) showed that children were mostly spared from COVID-19 and only a minority developed a complicated disease. These findings, along with the severe clinical picture and high mortality rates in adults, translated to the public misconception that COVID-19 was not a serious danger for children and that known short term complications, including myocarditis, and unknown long-term effects, could not justify the benefit of preventing COVID-19 by a vaccination (28). However, during the following waves of the pandemic, increasing evidence showed that not only COVID-19 can be severe in childhood, but children can also develop the MIS-C (29). Since COVID-19 vaccination might also prevent MIS-C (14), it is expected that parents of children who experienced severe COVID-19 might prefer to avoid a new infection and its possible acute complications. Accordingly, our data suggest that better communication strategies should be developed to successfully inform the public opinion that children can have severe complications from SARS-CoV-2 infections, leading to a higher adherence to the vaccination campaign for previously infected children. In this regard, the role of family pediatricians (or general practitioners) in appropriately informing parents is pivotal since they usually have a close and long-lasting relationship with the family.

Conversely, the finding that parents of children and adolescents with Long Covid symptoms are more likely against vaccination is unexpected and might rely on a complex scenario. So far, the real burden of pediatric Long Covid is still unclear (22), however there is recognition from independent studies that a subset of children may experience it (30, 31). Although it is still unclear if COVID-19 vaccination can prevent Long Covid (32), it is possible to speculate that preventing the infection might also prevent its consequences. A recent study from Israel found that vaccinated adults were at lower risk of developing Long Covid, even after a breakthrough infection (33). Therefore, since parents of children with history of Long Covid are aware of the impact that long-lasting symptoms may have on a child's routine, we would have expected a more propension toward the vaccination to prevent a new infection and a Long Covid relapse. On the other hand, it is possible that these parents can be worried that an immune stimulation can relapse the symptoms and make their child's routine worse. However, preliminary data showed that a group of Long Covid patients had their symptoms improved after vaccination (34), leading to the hypothesis that vaccination itself might become a part of Long Covid management. The rationale behind this is that vaccines might re-equilibrate immune responses or help the organism in viral clearance or divert autoimmune lymphocytes through innate cytokines (35). Overall, uncertainties on the pathogenesis of Long Covid, along with the possible effects of vaccination on improvement or worsening of symptoms, may justify parents' fears for vaccination of their children with Long Covid. Since this is a delicate point of public health interventions, our findings can be used to develop appropriate public health strategies including the development of new studies on the relationship between vaccination and Long Covid in children.

In Italy, similarly to the other European countries, a priority for vaccination was given to subjects at higher risk of worse outcomes (e.g., elderly) and those more at risk of infection (e.g., healthcare workers) (36). In December 2021, after the approval of COVID-19 vaccination in children and adolescents,

TABLE 2 | Comparison of the characteristics of caregivers in favor of COVID19 vaccination for their children and the other caregivers.

	In favor	Others	*P*
N	68	53	
Caregiver			
Age, years	44 [40–49]	40 [36–46]	**0.008**
Sex, female	51 (75)	46 (87)	0.12
Educational level			
Secondary school	8 (12)	11 (20)	0.35
High School	23 (34)	13 (25)	
University	26 (38)	17 (32)	
Post University	11 (16)	12 (23)	
Influenza vaccination in the last 3 years, yes	19 (28)	16 (30)	0.84
Child			
Age, years	10.5 [4.0–14]	6.0 [2.0–10]	**0.001**
Sex, female	24 (35)	24 (45)	0.35
Underlying chronic disease, yes	9 (13.2)	9 (17)	0.61
Influenza vaccination in the last 3 years, yes	11 (16)	12 (23)	0.48
Months from COVID19 infection	12 [7–13]	8 [5–12]	0.15
Long Covid, yes	23 (34)	22 (42)	0.26
Symptomatic Covid, yes	48 (71)	41 (77)	0.53
Hospitalization due COVID19, yes	18 (26)	9 (17)	0.27
COVID19 history in first-degree relatives			
History of COVID19, yes	55 (81)	48 (91)	0.19
Hospitalization due to COVID19, yes	10 (16)	7 (14)	0.79
Need of intensive care due to COVID19, yes	4 (8.9)	4 (9.5)	1.00
Death due to COVID19, yes	1 (2.4)	3 (7.5)	0.36
Long Covid symptoms, yes	23 (41)	23 (52)	0.31
Caregiver's opinion on other vaccinations			
Vaccination against papillomavirus			
I want my child to receive this vaccination/ My child has been already vaccinated	49 (72)	29 (55)	0.06
I know this infection, but I am unsure/I do not want my child to receive the vaccination	9 (13)	16 (30)	
I do not know the disease	10 (15)	8 (15)	
Vaccination against Streptococcus pneumoniae			
I want my child to receive this vaccination/ My child has been already vaccinated	49 (71)	40 (75)	0.96
I know this infection, but I am unsure/I do not want my child to receive the vaccination	9 (13)	6 (11)	
I do not know the disease	10 (15)	7 (13)	

Data are given as median and interquartile range or absolute frequency and percentage. Significant p-values (i.e. p-values < 0.05) are in bold.

TABLE 3 | Results of the logistic regression.

	OR	Lower 95%CI	Upper 95%CI	P
Child's age	1.17	1.06	1.28	**0.001**
Child's sex	2.48	0.98	6.26	0.06
Presence of child's chronic disease	0.34	0.09	1.26	0.11
Child's Long Covid symptoms	0.28	0.10	0.80	**0.017**
Child's hospitalization due to COVID-19	3.25	1.06	9.95	**0.039**

The favor towards COVID-19 vaccination of the child was considered as dependent variable. The following independent variables were included: the caregiver and child's sex, the educational level of the caregiver, the child's age, the months since the child had the COVID-19, the presence of chronic diseases or Long Covid symptoms in the child, the hospitalization of the child for COVID-19, history of a parent who needed admission due to COVID-19. The Akaike information criteria was applied to select the best model. Significant p-values (i.e. p-values < 0.05) are in bold.

the vaccine has been offered to these subjects in dedicated healthcare structures. Although Italian family doctors have not been involved in children vaccination so far, they might play a key-function in the parental counseling. Their role, which was not investigated in the current survey, deserves consideration in future studies.

The results of our study should be also analyzed in view of the rapidly changing pandemic scenario. Very recent data showed that hybrid immunity is stronger than natural immunity (37). Therefore, it is possible that many participants of this study believed that natural immunity sufficed to prevent a new infection. Similarly, the caregivers' perception of the severity of Omicron infection might have modified during the study period. When this variant appeared media from around the world reported that an increasing number of infected children had been hospitalizing (38) and it was mainly due to a higher severity of disease (39). Later, a few studies have argued against such hypotheses (40, 41). These changing scenarios may have affected parents' responses, but our sample was not large enough to address this potential variability.

Our study has limitations. First, our preliminary study involved a relatively low number of participants and it could not be planned to analyze the possible role of MIS-C development on the vaccine acceptance. Second, data were collected from two main centers in Center and North Italy, while no centers from Southern Italy have been included. Given cultural differences along the country, our data might not be extrapolated to different areas. Third, we have not analyzed in depth the reasons behind a specific family position, nor we have investigated the children' perspective. Mostly, our study does not provide a response to the question "why parents want, or do not, their children to be vaccinated against COVID-19?" Future multicenter studies addressing this question are necessary to support transnational efforts to increase vaccine confidence (42). Fourth, most collected information was based on parents' reporting on not ascertained on medical records. Finally, we did not investigate if the caregivers were infected by COVID-19 and the possible manifestations of such infection. The evaluation of the possible role of previous COVID-19 experience in both children and relatives with and without Long Covid, represents a strength of our study.

In conclusion, our study shows that only about half of the interviewed parents of children and adolescents with a previous SARS-CoV-2 infection are willing to vaccinate them against COVID-19. Parents were more in favor of vaccination if their children were hospitalized for COVID-19, but less if children had experienced Long Covid symptoms. These findings might help healthcare workers to provide tailored information to caregivers of children and adolescents with a previous SARS-CoV-2 infection. Finally, this study and the evolving scenario of this pandemic point out that new international studies addressing the reasons behind parents' attitudes toward COVID-19 vaccine are necessary.

DATA AVAILABILITY STATEMENT

The raw data are available upon resonable request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico | Policlinico Agostino Gemelli Roma. The patients/participants provided their informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DB, MFP, CA, SC, ML, MLG, PM, and GM conceptualized and designed the study. PV, MM, FF, and CP collected the data. GM performed the statistical analyses. DB and GM draft the first version of the manuscript. All authors gave a significant contribution to data interpretation in their field of expertise. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.867968/full#supplementary-material

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REVIEW
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Post COVID-19 Condition in Children and Adolescents: An Emerging Problem

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection became a pandemic in 2020 and by March 2022 had caused more than 479 million infections and 6 million deaths worldwide. Several acute and long-term symptoms have been reported in infected adults, but it remains unclear whether children/adolescents also experience persistent sequelae. Hence, we conducted a review of symptoms and pathophysiology associated with post-coronavirus disease 2019 (post-COVID-19) condition in children and adolescents. We reviewed the scientific literature for reports on persistent COVID-19 symptoms after SARS-CoV-2 infection in both children/adolescents and adults from 1 January 2020 to 31 March 2022 (based on their originality and relevance to the broad scope of this review, 26 reports were included, 8 focused on adults and 18 on children/adolescents). Persistent sequelae of COVID-19 are less common in children/adolescents than in adults, possibly owing to a lower frequency of SARS-CoV-2 infection and to the lower impact of the infection itself in this age group. However, cumulative evidence has shown prolonged COVID-19 to be a clinical entity, with few pathophysiological associations at present. The most common post-COVID-19 symptoms in children/adolescents are fatigue, lack of concentration, and muscle pain. In addition, we found evidence of pathophysiology associated with fatigue and/or headache, persistent loss of smell and cough, and neurological and/or cardiovascular symptoms. This review highlights the importance of unraveling why SARS-CoV-2 infection may cause post-COVID-19 condition and how persistent symptoms might affect the physical, social, and psychological well-being of young people in the future.

Keywords: COVID-19, post COVID-19 condition, long-COVID-19, long-haul COVID, post-acute COVID-19 syndrome, children, adolescents

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen responsible for coronavirus disease 2019 (COVID-19). Infection by this virus was declared a pandemic by the World Health Organization (WHO) in March 2020 (1). During the SARS-CoV-2 pandemic, the significant efforts made to define the main factors leading to serious illness seemed to focus on the presence of comorbidities, especially advanced age (2). Data provided by the Centers for Disease Control and Prevention (CDC) (March 2022) revealed a total of more than 970,000 deaths, with a COVID-19 mortality rate of 1.2% in the United States of America. Mortality in children is lower than in adults, and it has been widely reported that the disease is less severe in this population (3–5) of children, with mostly mild and asymptomatic cases. Although the vast majority of children and adults with COVID-19 do not experience any change and live normally after the acute infection, it has recently been reported that some people (both adults and children) cannot recover their previous health after being infected by SARS-CoV-2, as they have long-term symptoms, such as persistent cough, fatigue, altered taste and/or smell, and memory loss. The scientific community refers to this group of persistent symptoms as "long-COVID-19," "post-acute COVID-19 syndrome" (PACS), or "post-COVID-19 condition," which is the preferred term of the WHO (6). While some researchers are trying to unravel the mechanisms causing persistent symptoms in adults, few studies focus on children with post-COVID-19 condition. In this study, we aimed to review and summarize current knowledge on post-COVID-19 condition in children, with emphasis on clinical symptoms and potential pathophysiologic mechanisms, and to share our experience in the Pediatric Persistent COVID Unit of the Germans Trias Hospital (Badalona, Spain).

FROM ACUTE DISEASE TO POST-COVID-19 CONDITION

The clinical features and symptoms of acute COVID-19 have been widely described and reviewed (7–11). The most common symptoms in adults include fever, fatigue, and dry cough. Although infected children experience similar symptoms, the severity of acute infection in this group is lower than in adults. Several reports (3–5) show that 5.9% of children are asymptomatic (compared with 1% of adults) and that the infection is mild in 99.3% of cases in children (compared with 81% in adults) (**Figure 1**). A study performed in China with 341 children aged 4–14 years (median, 7 years) found that the most common symptoms were fever (77.9%), cough (32.4%), and diarrhea (4.4%) (3). Of note, multisystem inflammatory syndrome (MIS), in which various body parts can become inflamed (heart, lungs, kidneys, brain, skin, eyes, and gastrointestinal organs), has been associated with COVID-19. Despite data showing that acute infection is not as severe in children as in adults, a recent study suggested that MIS in children (MIS-C) is more common than previously thought (12). The authors analyzed the symptoms of 1,200 hospitalized children with a median age of 4.7 years and observed that 10.6% had MIS-C during the infection (127/1,200). In this same study, 3 patients with MIS-C eventually died, although they had serious comorbidities, such as acute leukemia and bone marrow transplant, overweight, and malignant neoplasm. MIS-C due to COVID-19 has been analyzed elsewhere (13). MIS affecting adults is less common, although it has been demonstrated and described in patients with severe COVID-19 (14–16).

Vertical transmission of SARS-CoV-2 has been reported in pregnant women (17, 18), and while it seems to be rare (3.2% in a review of 38 studies (18)), a recently published article (19) demonstrated that SARS-CoV-2 can infect trophoblasts in the placenta and provoke fetal demise in 2.5% of cases (5 out of 198 placental tissue samples).

One interesting trait during the pandemic was that some children developed chilblains (more common than in adults). In an earlier investigation (20), it was concluded that chilblains were not associated with COVID-19, as none of the patients were positive for SARS-CoV-2 antigens, nucleic acids, or SARS-CoV-2 antibodies. However, this was later contradicted in a recently published review (21), where the authors found an association between the spike protein and chilblains and reported that type 1 interferon (IFN) production was important for the development of chilblains, even if patients remained asymptomatic or had negative antibody titers.

Although symptoms resolve satisfactorily in most acutely infected adults, a significant percentage of patients with COVID-19 experience long-lasting symptoms weeks or months after infection. Long-term symptoms after severe viral infection are not novel, as post-viral syndrome and sequalae after viral infections have previously been described (22–27). Moreover, similar symptoms, such as fatigue or persistent shortness of breath, were previously described by survivors of SARS and Middle East respiratory syndrome (MERS) (28–30). The novelty of post-COVID-19 condition is that it is independently associated with the severity of the acute illness, according to a prospective cohort study of 312 adult patients (247 self-isolating patients and 65 hospitalized) (31). In this study, 61% of patients had persistent symptoms 6 months after the acute phase of the infection, regardless of symptoms and disease severity. The most common symptoms in self-isolating patients with COVID-19 after 6 months included fatigue (30%), absence of or disturbed taste or smell (27%), concentration problems (19%), memory problems (18%), and dyspnea (15%). Similar symptoms were found in another study based on an online survey of 3,762 participants (32), with fatigue being the dominant symptom 6 months after infection. Interestingly, 45.2% of those surveyed required shorter work hours than before their illness, likely owing to the long-lasting effect of their COVID-19 symptoms. A recent report (33) also highlighted fatigue, dyspnea, cough, headache, loss of taste and/or smell, and cognitive or mental health impairment as the most common symptoms in people with post-acute sequelae of SARS-CoV-2 infection. Moreover, age $>$ 40 years, female sex, reverse transcription PCR (RT-PCR) low cycle threshold (Ct) values, and ageusia have been reported to be associated with persistent symptoms after COVID-19 in adults (34).

Recent studies have shown that children also experience post COVID-19 condition. In a preliminary report of 5 cases (35), all children reported fatigue and dyspnea 2 months after acute infection. However, no specific PCR-based diagnosis of SARS-CoV-2 was available, and 4 did not develop specific antibodies. A second study conducted in Italy with 129 children diagnosed with SARS-CoV-2 infection also showed evidence of post-COVID-19 condition (36). The most persistent symptoms

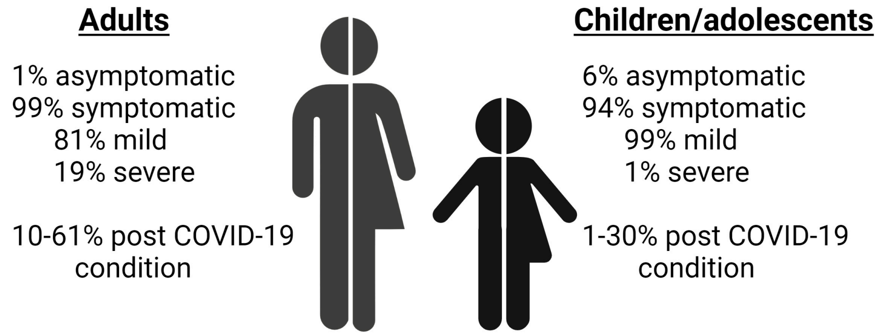

FIGURE 1 | Diagram comparing the frequencies of acute and post-COVID-19 condition between adults and children/adolescents (3–5, 31, 32, 35–38, 42–44).

were insomnia (18.6%), respiratory symptoms (such as pain and chest tightness) (14.7%), nasal congestion (12.4%), fatigue (10.8%), concentration difficulties (10.1%), and muscle pain (10.1%). The study also showed that 42.6% of patients presented at least 1 symptom 60 days after acute infection. Similar findings were reported in a study of 58 children and adolescents (37), where 44.8% reported symptoms of post-COVID-19 condition, the most common being fatigue (21%), shortness of breath (12%), exercise intolerance (12%), weakness (10%), and walking intolerance (9%). Another report (38) (the CLoCk study) found the most common persistent symptoms in children and adolescents who tested positive for SARS-CoV-2 to be sore throat, headache, tiredness, and loss of smell. Similar results were reported in a Dutch study (39), where the most common complaints were fatigue, dyspnea, and concentration difficulties in 89 children suspected of having post-COVID-19 condition. A recently published pre-print meta-analysis, reviewing 68 articles focused on post-COVID-19 condition in children and adolescents, showed that the most prevalent clinical manifestations were mood symptoms (16.5%), fatigue (9.7%), and sleep disorders (8.4%); and more interestingly that, when compared with controls, children infected by SARS-CoV-2 had a higher risk of persistent dyspnea (odds ratio [*OR*] 2.69 95% *CI* 2.30–3.14), anosmia/ageusia (*OR* 10.68, 95% *CI* 2.48, 46.03), and/or fever (*OR* 2.23, 95% CI 1.22–4.07) (40).

In children, an interesting comparison was recently reported between persistent symptoms after COVID-19 and those related to non–SARS-CoV-2 infection (41). Persistent symptoms of 236 pediatric patients with COVID-19 were compared with those of 142 children with non–SARS-CoV-2 viruses. It was concluded that persistent symptoms were more apparent in COVID-19 than in any other SARS-CoV-2 infection, thus highlighting the importance of post-COVID-19 condition in children.

FREQUENCY OF POST-COVID-19 CONDITION IN CHILDREN AND ADOLESCENTS

As observed in the study by Buonsenso et al. conducted in Italy (36), a high percentage of children had at least 1 symptom 60 days after acute infection, suggesting that post-COVID-19 condition in children is a major problem that may have been underestimated. More recent data and reports from the United Kingdom's Office for National Statistics (ONS) (42) showed varying results on the prevalence of post-COVID-19 condition in adults and children with confirmed SARS-CoV-2 infection. Data reported up to 1 April 2021 showed that 9.8% of infected children aged 2–12 years and 13% of those aged 12–16 years reported long-lasting symptoms at least 5 weeks after infection. These rates increased with age, peaking in the 35–49-year age group, where 25.6% of infected people reported long-lasting symptoms at least 5 weeks after infection. After 12 weeks of acute infection, the frequency of persistent symptoms decreased to 7.4% in children aged 2–12 years and to 8.2% in adolescents aged 12–16 years. A recently published study, which analyzed 1,734 children in the United Kingdom who tested positive for SARS-CoV-2 (43), revealed lower rates than previously seen in the ONS data, where 4.4% of children had long-lasting symptoms at least 28 days after acute infection, i.e., a lower frequency than in the previous study. Similar findings were reported in a study that analyzed data from 4,678 children in England and Wales (44), where only 174 had a history of SARS-CoV-2 infection (4.6% with persistent symptoms). In contrast, a recently published pre-print meta-analysis showed a prevalence of 25.2% (40). Despite the variability in persistence between studies, post-COVID-19 condition is clearly a more important health condition than initially thought.

ACUTE VS. POST-COVID-19 CONDITION SYMPTOMS IN CHILDREN AND ADOLESCENTS

It is very important to identify the differential symptoms of post-COVID-19 condition in children and adolescents to facilitate diagnosis. However, although some symptoms are exclusively related to post-COVID-19 condition, the most common symptoms are shared with acute infection. Fatigue is the most frequent symptom of post-COVID-19 condition in children and adolescents, with percentages varying between 10.8 and 20.1% depending on the study. Fatigue is also one of the

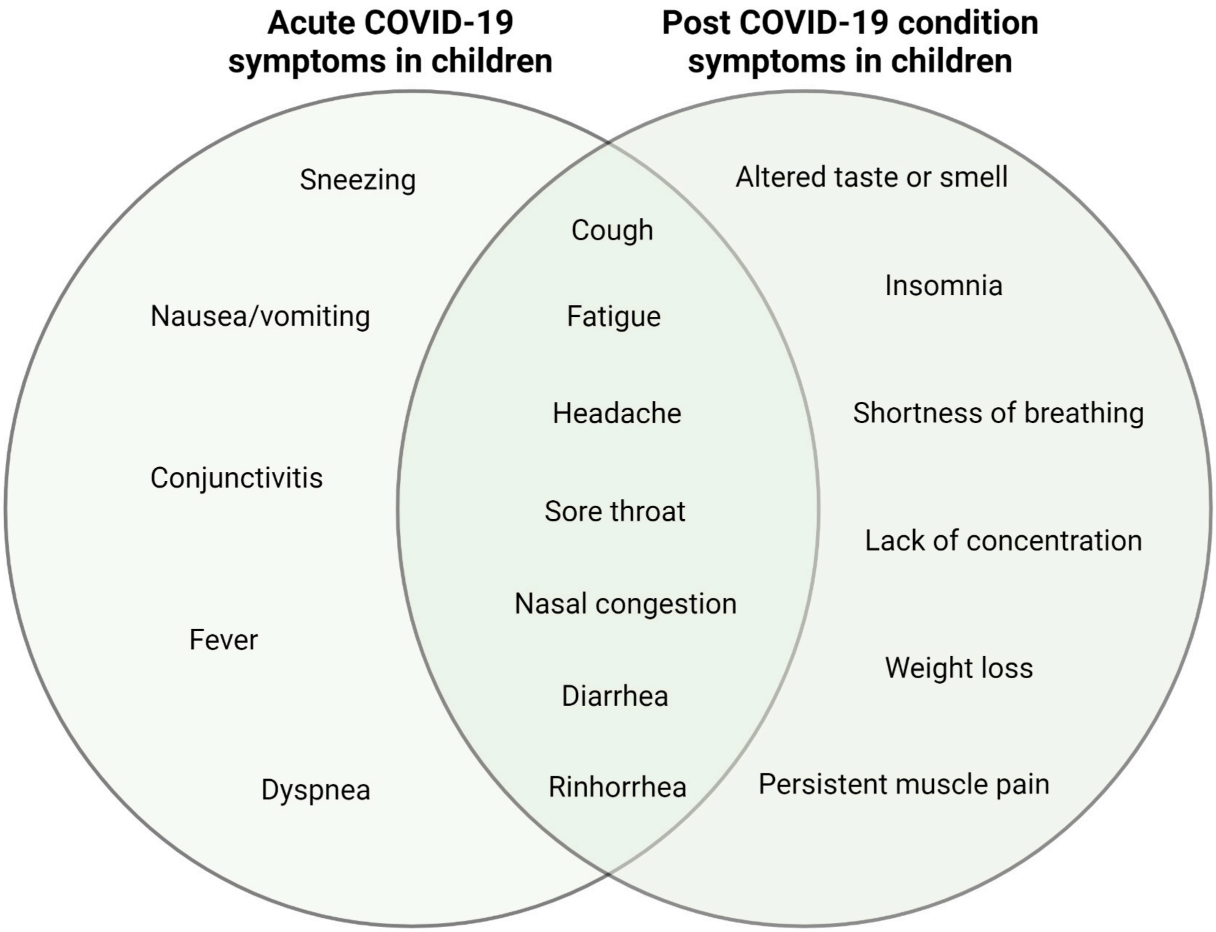

FIGURE 2 | Diagram representing specific and shared symptoms of acute and post-COVID-19 condition in children and adolescents.

symptoms most frequently associated with the acute phase of the disease, and percentages vary from 2.2 to 9% depending on the study. Headache, which is present in acute COVID-19, is also a highly prevalent symptom during post-COVID-19 condition. Other common symptoms during post-COVID-19 condition include cough and diarrhea (more prevalent during acute illness), sore throat, nasal congestion, and rhinorrhea. Symptoms exclusively associated with the post-COVID-19 condition in children differ between studies but include taste and/or smell disturbances, insomnia, shortness of breath, poor concentration, weight loss, and persistent muscle pain. On the other hand, the main symptoms associated exclusively with acute disease are fever, sneezing, nausea/vomiting, conjunctivitis, and dyspnea (**Figure 2**).

PATHOPHYSIOLOGY OF POST-COVID-19 CONDITION: AN AREA THAT HAS YET TO BE UNRAVELED

Although there is clear evidence that post-COVID-19 condition is pathological in both children and adults, the pathophysiology of this disease remains unknown. However, several hypotheses have been put forward (**Figure 3**). The predictors of post-COVID-19 condition in children and adolescents include older age, muscle pain at hospital admission, and admission to the intensive care unit (ICU) during acute infection (37). As occurs in adults, the risk associated with initially severe COVID-19 has been associated with the exacerbated immune response that can lead to organ damage, as well as the medical and therapeutic interventions required, which may cause lasting sequelae. Moreover, the virus has been shown to persist in intestinal biopsies at 4 months after the onset of COVID-19 (45), suggesting that viral persistence might/could be associated with post-COVID-19 condition.

A recent study comparing the immune profiles of children who recovered fully from COVID-19 and those with long-term symptoms (46) revealed persistently high levels of interleukin (IL)-6 and IL-1β, thus attributing a relevant role to the innate immune response during the post-COVID-19 condition. Since IL-6 and IL-1β act as mediators in the inflammatory response, persisting levels of these cytokines could explain persistent symptoms, such as fatigue or headache after acute illness.

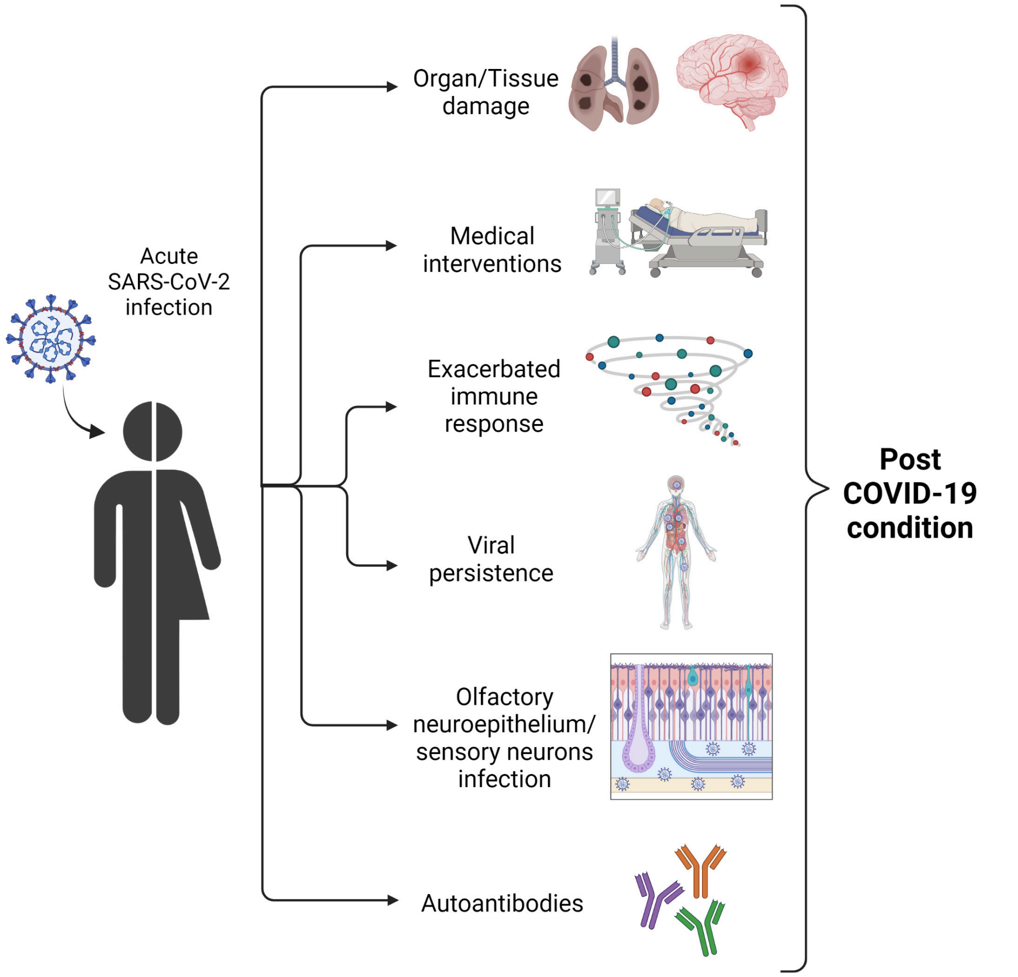

FIGURE 3 | Diagram showing potential pathophysiological mechanisms of post-COVID-19 condition symptoms.

As mentioned above, loss of taste and/or smell is a common symptom during persistent COVID-19. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the entry receptor to infect cells. ACE2 is expressed in cells of the human respiratory system (47, 48). Although SARS-CoV-2 predominantly affects the respiratory tract, studies in human brain organoids have shown that SARS-CoV-2 can also infect neurons (49, 50). Moreover, a recent report (51) found evidence that the olfactory neurepithelium (olfactory sensory neurons, support cells, and immune cells) can be infected by SARS-CoV-2. The study was carried out with samples from seven patients with COVID-19 who presented with acute loss of smell. The authors showed the presence of viral transcripts and SARS-CoV-2–infected cells in olfactory mucosa samples from patients with long-term persistent anosmia due to COVID-19, suggesting that the loss of smell in patients with symptoms persisting after several months of infection could be due to persistence of SARS-CoV-2 and inflammation of the olfactory neurepithelium.

Persistent cough is one of the most common symptoms of the post-COVID-19 condition. The potential underlying mechanism was discussed in a recent personal view published in April 2021 (52). The authors suggested that persistent cough might be associated with neuroinflammatory and neuroimmune mechanisms related to vagal sensory nerves. These mechanisms resemble those that infect the olfactory neurepithelium, highlighting that some symptoms reported in post-COVID-19 condition could be related to the potential neurotropism of SARS-CoV-2.

Autoimmune diseases triggered by infection are well documented and include rheumatic fever and Guillain-Barré syndrome (53, 54). Several reports have already demonstrated that autoantibodies are generated during COVID-19 according to the severity of the disease (55–57). Moreover, a recent study revealed the presence of autoantibodies against G-protein coupled receptors (GPCRs) in patients with post-COVID-19 condition (58). Given that GPCRs can disrupt the balance of neuronal and vascular processes, their presence could explain some of the neurological and/or cardiovascular symptoms observed in post-COVID-19 condition.

CAN GENETICS PREDISPOSE TO POST-COVID-19 CONDITION?

As of March 2022, the role of genetics in post-COVID-19 condition remains unclear. Most studies investigate genetic factors that might explain differences in the course of acute SARS-CoV-2 infection, including those related to innate errors of immunity (59). Moreover, several studies had reported several genetic factors associated with severe COVID-19 (60–63), such as epigenomic markers (61), blood group (60), and traits associated with protection against severe disease (63).

A search of clinicaltrials.gov based on the terms "host" & "genetics" & "COVID" revealed 40 studies attempting to unravel the link between the genotype and susceptibility to infection. However, when using the terms "host" & "genetics" & "long-COVID" or "post COVID-19 condition" or "post-acute COVID syndrome," we found no studies exploring the potential contribution of genetic factors to post-COVID-19 condition. Therefore, it could be interesting to design studies aimed at identifying potential genotypic markers of predisposition to post-COVID-19 condition in both adults and children.

SOCIOPSYCHOLOGICAL CAUSES OF POST-COVID-19 CONDITION: SARS-CoV-2 INFECTION OR LOCKDOWN?

In addition to the pathological effects previously described in pediatric post-COVID-19 condition, other sociopsychological conditions related to lockdown may have contributed to the symptoms of post-COVID-19 condition. A study conducted in 1,560 students in the United Kingdom (median age, 15 years, interquartile [IQR] [14–17]) (64) tried to determine whether there were differences in symptoms between seropositive children and seronegative children. The study found no significant differences between the symptoms of the 1,356 SARS-CoV-2–seronegative children and the 188 seropositive children, suggesting that most of the symptoms could be due to lockdown syndrome rather than viral infection. However, this study is limited to a very specific age range, suggesting that there is a need for alternative studies covering several pediatric age ranges.

A more recent report (38) showed that having 3 or more persistent symptoms at 3 months after testing was more common in PCR-positive children (30.3%) than in PCR-negative children (16.2%). The conclusions of the report are similar to those of a recent systematic review of 23 studies on persistent COVID-19 symptoms in children (65). Both highlight the importance of having a SARS-CoV-2–negative control group to assess the real differences between persistent symptoms.

In addition, a report by P. Zimmermann and colleagues noted the challenges of studying post-COVID-19 condition (66). After the examination of 27 studies, they found a large variation in results, highlighting how difficult it is to study post-COVID-19 condition. Therefore, better guidelines, characterization of exclusive post-COVID-19 condition symptoms and studies with an uninfected control group must be drawn up to distinguish between long-term symptoms caused by SARS-CoV-2 infection and pandemic-related symptoms (67).

OUR EXPERIENCE IN THE PEDIATRIC PERSISTENT COVID UNIT OF THE GERMANS TRIAS HOSPITAL

In December 2020, Germans Trias i Pujol University Hospital (Barcelona, Spain) created one of the first Pediatric Persistent COVID Units in Spain and is currently following a cohort of 120 children/adolescents with post-COVID-19 condition from the metropolitan area of Barcelona. The unit consists of a multidisciplinary team, such as pediatricians and other medical specialists (infectious disease specialists, pulmonologists, neurologists, cardiologists, and nutritionists), and experts in rehabilitation and physical therapy, psychiatry, psychology, radiology, and neuropsychology who participate in the clinical study and treatment of post-COVID-19 condition in children and adolescents. The unit has also partnered with research groups specialized in virology, immunology, and genetics to perform an in-depth analysis of the causes of and the mechanisms underlying this phenotype.

The cohort includes pediatric patients younger than 18 years old, diagnosed with SARS-CoV-2 infection and with at least 12 weeks of persistent COVID-19 symptoms after COVID-19 disease. The median age of the cohort is 14 years (IQR, 12.2–15.8; 66% female), and patients have at least 3 symptoms associated with post-COVID-19 condition (**Table 1**). The most common symptoms are asthenia/fatigue (98%), headache (75%), muscle weakness (74%), dyspnea (68%), myalgia/arthralgia/paresthesia (64%), and cognitive neurological disorders (decreased attention) (44%). These had been present for more than 6 months in 36% of patients.

Fatigue was evaluated using the Pediatric Functional Assessment of Chronic Illness Therapy-Fatigue (pedsFACIT-F) Scale. Most patients (68%) had moderate to very high grades.

TABLE 1 | Demographic and clinical characteristics of the pediatric post–coronavirus disease 2019 (COVID-19) condition study cohort (pediaCOVID, *n* = 50) at the Germans Trias i Pujol Hospital.

Characteristics	Value
Age, median (IQR)	14.1 (12.2–15.8)
Female sex, n (%)	33 (66)
Number of acute symptoms, median (IQR)	6 (4–8)
Days of duration of acute symptoms, median (IQR)	10 (4.8–20.3)
Number of post COVID-19 condition symptoms, median (IQR)*	10 (7–16)

**List of considered post-COVID-19 condition symptoms: asthenia/fatigue, muscular weakness, neurocognitive neuro disorders, headaches, dyspnea, myalgia/arthralgias, insomnia, chest oppression/pains, orthostatic hypotension, hyporexia/anorexia, deafness/tinnitus/sonophobia, anosmia, ageusia/dysgeusia, abdominal pains, palpitations/tachycardia, paresthesia, photophobia, dizziness/vertigo, cough, skin signs, diarrhea, weight loss, epigastric pains/dyspepsia/food impaction, odynophagia/dysphagia, vomiting/nausea, dysphonia, and fever/chills, rhinorrhea.*

Health status was evaluated using the Pediatric Quality of Life instrument (PedsQL), which revealed that quality of life was affected in 37.5% of children and adolescents assessed, and psychosocial health in 60%; in particular, 23% had emotional and behavioral problems. Furthermore, because of post-COVID-19 condition, most pediatric patients were unable to attend school full-time (54%) or engage in extracurricular activities (>70%).

These findings further highlight the urgent need for studies to unravel the underlying causes of post-COVID-19 condition and to develop a treatment that will enable patients to return to their pre-COVID-19 health status.

CONCLUSION

A recently published viewpoint (68) highlighted the potential legacy of post-COVID-19 condition. There has been significant resistance to recognizing post-COVID-19 condition as a clinical entity in adults and even more so in children. Although clinical guidelines are being developed to facilitate the diagnosis and treatment of post-COVID-19 condition in adults, as well as to study its pathophysiology and sociopsychological causes and consequences, progress in pediatric disease is slower (35–37). To ensure the health of future generations, post-COVID-19 condition should be addressed decisively and effectively, especially in children and adolescents.

SEARCH STRATEGY AND SELECTION CRITERIA

References for this Review were identified through searches of PubMed and Google scholar with the search terms "long-COVID," "post-acute COVID-19 syndrome," and "post COVID-19 condition" from January 2020 until March 2022. Articles were also identified through searches of the authors' own files. Only articles published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

AUTHOR CONTRIBUTIONS

JI-P, SM-L, and JM-P performed the search strategy and selection criteria and wrote and reviewed the manuscript. JD wrote and reviewed the manuscript. AG-A, CC-A, MM, and CR provided the clinical data and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Pediatric Surgical Care During the COVID-19 Lockdown: What Has Changed and Future Perspectives for Restarting in Italy. The Point of View of the Italian Society of Pediatric Surgery

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Background: The coronavirus disease 2019 (COVID-19) time exacerbated some of the conditions already considered critical in pediatric health assistance before the pandemic. A new form of pediatric social abandonment has arisen leading to diagnostic delays in surgical disorders and a lack of support for the chronic ones. Health services were interrupted and ministerial appointments for pediatric surgical healthcare reprogramming were postponed. As a result, any determination to regulate the term "pediatric" specificity was lost. The aim is, while facing the critical issues exacerbated by the COVID-19 pandemic, to rebuild future perspectives of pediatric surgical care in Italy.

Methods: Each Pediatric Society, including the Italian Society of Pediatric Surgery (SICP), was asked by the Italian Federation of Pediatric Associations and Scientific Societies to fill a questionnaire, including the following the main issues: evaluation of pre-pandemic criticalities, pediatric care during the pandemic and recovery, and current criticalities. The future care model of our specialty was analyzed in the second part of the questionnaire.

Results: Children are seriously penalized both for surgical treatment as well as for the diagnostic component. In most centers, the pediatric surgical teams have been

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integrated with the adult ones and the specificity of training the pediatric operating nursing is in danger of survival. “Emotional” management of the child is not considered by the general management and the child has become again an adults patient of reduced size.

Conclusion: A new functional pediatric surgical model needs to be established in general hospitals, including activities for day surgery and outpatient surgery. To support the care of the fragile child, a national health plan for the pediatric surgery is required.

Keywords: child, COVID-19, criticalities, pediatric surgery, neonate

INTRODUCTION

The Italian Society of Pediatric Surgery (SICP) is one of the oldest in Europe, having been founded in Livorno on the 24 February 1963. It aims to promote the progress of surgical art and science in the pediatric field, to promote and maintain the highest standard in the quality of surgical treatment provided to children in Italy, to protect the prestige and interests of pediatric surgery and its practitioners, and to facilitate the relationships of association and the exchange of ideas between pediatric surgeons. Since those early days, pediatric surgery has enormously evolved and is today one of the most vigorously growing fields in surgery. Pediatric surgery is unique in many instances. It is one of the last true general surgeries. The pediatric surgeon deals with a completely distinctive set of disorders, namely, congenital malformations that are largely unknown to the general adult surgeon. Finally, the pediatric surgeon operates on a future, as most of patients have a long life expectancy in front of them. This brings with it the greatest responsibility for the caring surgeon. Despite, or maybe due to these peculiarities, pediatric surgery has long faced several critical issues. Diagnosis Related Groups (DRG) dedicated to the child are largely lacking, leading to the application of DRG created based on adult surgery necessities that do not take into account the peculiar aspects of the pediatric patient. Additionally, a clear definition of the pediatric patient is missing, which may change from region to region. As a consequence, pediatric patients may be treated in pediatric or general surgical units, depending on the region where they are located. This leads to treatment disparities due to the lack of specific pediatric expertise for patients admitted to general surgical units. In addition to the confusion on the definition of the pediatric patient, there are no projects involving the whole of Italy on the number of centers necessary to cover the needs of the population. The regions work without general coordination, which should give behavioral guidelines to the identification and authorization to open centers that should respond to clear and precise criteria. Finally, there is a shortage of pediatric surgeons in part due to mistakes made in the past regarding the forecast of future needs and in part to the fact that trainees in pediatric surgery have strict limitations on their clinical and surgical activity.

These critical issues were further exacerbated during the COVID-19 pandemic. Management of patients with COVID-19 became a priority. For all other patients, the pandemic modified and slowed down hospital admittance and disarrayed the daily routine programs of diagnosis and treatment. From a healthcare point of view, there was no determination to regulate the term “pediatric” specificity. Pediatricians and pediatric surgeons were moved to adult medicine, either directly to adult patients with COVID-19 or to “free” adult colleagues to be employed in COVID-19 units or hospitals (1, 2). The “stay at home” orders during the COVID-19 period have led to a complete change in the daily social activities of children. A new form of pediatric social abandonment has arisen with an increase in domestic accidents (3–5), obesity, and psychiatric disorders. There was above all a diagnostic delay in surgical disorders and a lack of support for the chronic ones (6–8).

As result, the COVID-19 time exacerbated some of the conditions already considered critical in pediatric health assistance before the pandemic. All elective health services were interrupted and ministerial appointments for pediatric healthcare reprogramming were postponed with the consequence that restrictions placed pediatric needs in the last position on the social ladder.

The aim of this report is, while facing the critical issues exacerbated by the COVID-19 pandemic, to rebuild future perspectives of pediatric surgical care in Italy. To propose a perspective of the surgical children’s care, a collection of data from before and during the pandemic period, as well as the current situation, was considered.

METHODS

The Italian Society of Pediatric Surgery is institutionally included in the Italian Federation of Pediatric Associations and Scientific Societies (FIARPED). Each pediatric society was asked by the FIARPED to describe how their field was impacted by the COVID-19 pandemic following predefined questions (as shown in **Appendix**) as a canvas. The main issues of the questionnaire were: the evaluation of pre-pandemic criticalities, pediatric care during the pandemic and recovery, and current criticalities.

The future care model of our specialty was analyzed in the second part of the questionnaire.

RESULTS

Italy, with over 60 million inhabitants, has 66 pediatric surgery units. Among these, 22 units (33%) operate in exclusively pediatric hospitals, whereas, 21 units (31%) operate in institutions offering both adult and pediatric surgery services and belong to university centers.

Pre-pandemic Criticalities

The type of pediatric care is completely different from that of adults with completely peculiar implications related to age, fragility, and complexity. Specific and updated DRGs are missing. The current ones are obsolete and most of the time derive from those of adults very far from the needs and complexity of pediatric ones. Although about 10 years ago, a special ministerial commission, including pediatricians and pediatric surgeons, studied and drafted a hypothesis, this hypothesis has never been supported as a project, nor applied to clinical practice.

The age of admittance in pediatric wards ranges between 0–14 and 0–18 years and they are strictly related to decisions established by local authorities or regions in almost all cases. As a consequence, the lack of shared indications creates confusion that finds its maximum expression in adolescent patients who are treated in both pediatric and adult centers, causing inequality in treatment and a lack of acquisition of correct expertise.

Moreover, there is a great deal of confusion between day surgery and outpatient surgery activities imposed by the regions, probably because they have been imported *sic and simpliciter* from adulthood without taking into account the objective limitations related to age and particular to the *fragile* pediatric patients. Not without greater importance, it should be emphasized that the uncontrolled proliferation of pediatric surgery units on the territory of the country due to a lack of national planning for the distribution. Currently, there are 56 pediatric surgery units in Italy and with about one million inhabitants per unit as a reference. The lack of a project involving the whole of Italy on the number of centers necessary to cover the needs of the population penalizes not only the existing ones but also the local new acquisitions. There is a formal and substantial disorder because the regions work without general coordination that should give behavioral guidelines to the identification and authorization to open new centers that should respond to clear and precise criteria. An adequate national plan with precise indications would facilitate the identification of existing references and real territorial needs.

It is not always when children are hospitalized that they end up in the pediatric wards. In Italy, about 25% of children do not receive care in child-friendly pediatric wards. The little ones are frequently and willingly enticed together with the older patients, potentially causing psychological discomforts for the child, who would need a more protective environment. According to the National Agency for Regional Health Services, Agenas, in 2019 over 175,000 hospitalizations of patients between 0 and 17 years, accounting for over 25% out of 695,215 admissions, were carried out in adult departments, in particular when surgery was required. The most frequent admissions in adult surgical units are for orthopedics, ENT, testis disorders, and appendicitis.

Last but not least, the problem of surgeons in training who, due to a reduction in number in the pediatric surgery area, do not help the necessary generational turnover. This point fits perfectly with the previous one. National central planning is needed to define the number of pediatric surgery units in the country.

Pediatric Care During the Pandemic and Recovery

SICP at the Beginning of the Pandemic

To deal with the COVID-19 pandemic, SICP has identified the following recommendations to avoid and contain the infection, guaranteeing the protection of children, surgeons, anesthetists, nursing staff, and personnel belonging to the "surgical team," providing timely surgical treatments to children with pathologies of surgical interest, and optimize the resources needed for child care. SICP identified a list of surgical emergencies (**Tables 1**, **2**) for which a delay in treatment could represent a significant short-term threat to patient's life, therefore requiring immediate treatment.

What Happened Compared to What We Had Assumed

The programming of the elective interventions has been taken, with everything that follows: instrumental examinations, anesthesiologic examinations, and expected date of intervention.

The pediatric surgery units in non-pediatric hub hospitals resulted in being seriously penalized concerning the scheduled activities that were expunged due to the wide use of the operating rooms as intensive care rooms for COVID-19 admittance. Every center suffered from a dramatic reduction of ward spaces because some rooms were dedicated to surgical patients with COVID-19, operating rooms in general hospitals were used for adults and children, and some pediatric hospitals were converted to intensive care units (ICUs). Some pediatric hospitals accepted

TABLE 1 | Surgical emergencies.

Acute intestinal occlusions
Volvulus
Incarcerated inguinal hernia
Hypertrophic pyloric stenosis
Acute intestinal intussusception (after contrast enema failure)
Need for extracorporeal life support (ECMO)
Intestinal perforation
Worsening necrotizing enterocolitis
Thoraco-abdominal trauma (closed, open and hemorrhagic)
Ischemia: testicular torsion, ovarian torsion, limb ischemia (iatrogenic or traumatic)
Congenital disorders:
- Esophageal atresia with T-E fistula
- Congenital and symptomatic diaphragmatic hernia
- Intestinal atresia
- Congenital intestinal occlusion (anorectal malformations; Hirschsprung's disease not responding to nursing)
Acute appendicitis with suspected peritonitis
Foreign body in the esophagus or trachea*
Burns requiring immediate treatment under sedation or general anesthesia

There is an increased risk for transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in endoscopic procedures. Non-deferrable surgery. Additionally, a list of disorders that may be treated with some delay of few days to few weeks was highlighted by the Italian Society of Pediatric Surgery (SICP) (Table 2**).*

TABLE 2 | Disorders treatable with deferred surgery.

Surgical oncology
Biliary atresia
Abscess incision and drainage
Inflammatory bowel disease not responsive to medical treatment
Central venous line insertion
Symptomatic inguinal hernia
Gallbladder surgery for symptomatic gallstones
Feeding gastrostomy (if needed for discharge)
Hydronephrosis with renal function impairment or with high risk for pyelonephritis
Surgery for urethral valves
Urethral stenosis

TABLE 3 | Current criticalities in pediatric surgery units.

In general hospitals the surgical child has not priority in emergencies compared to other adult specialties, both for the surgical and diagnostic step
In the operating rooms, the need to place side by side nurses and scrub nurses of various specialties, to optimize the operating slots, led to loss of skills for the staff already trained for the pediatric patient
With the "excuse" of covid time the "emotional" containment of the child takes a back seat and the pediatric patient has become like an adult of "reduced size"
No paths designed to contain stress (single parent during hospital stay, disappearance of the recovery rooms)

adult patients with positive COVID-19 for a period in intensive care (9).

Pediatric surgeons needed to manage some patients with abdominal conditions that were different from those they were used to. Many pediatric centers were seriously affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related multisystem inflammatory syndrome in children (MIS-C), a new nosological entity that has mainly affected small children and adolescents with serious consequences (10, 11). In these patients, surgeons had to question whether or not a surgical approach was indicated, often *a posteriori*, when, entering an abdomen in the suspicion of acute appendicitis or peritonitis from complicated acute appendicitis, complex peritonitis in the absence of macroscopic appendiceal disease, or bowel ischemia without a macroscopically obvious explanation were found. The highest degree of abdominal involvement associated with lower age, even less than 5 years of age with a high risk of morbidity and mortality. The seriousness of this new disease has not been adequately taken into consideration by the national healthcare.

How Did We Reorganize Ourselves?

The centers have slowly and gradually rescheduled their activities, reclassifying the disorders according to recommendations given by the SICP. Reclassification of patients on the waiting list by severity classes was made, trying to highlight that even "routine" disorders (e.g., undescended testes) must be operated on at certain times (12).

Current Criticalities (Table 3): What Are the Criticalities That Our Specialty Is Experiencing in This Moment of Change?

Due to the COVID-19 pandemic, the "emotional" aspects of the admitted child have lost their central position in patients' management. A single-parent admittance is allowed during the whole hospital stay, surveillance in the recovery room has completely disappeared, and the reception paths dedicated to fragile and chronic children have been suppressed. In addition, in non-pediatric hub centers (general hospitals), the child is heavily penalized and is not prioritized in emergencies compared with other adult surgical specialties. Children are seriously penalized both for surgical treatment as well as for the diagnostic component. In the operating theaters, the COVID-19 time brought together nurses and scrub nurses of various surgical specialties. The result is that surgical teams have been integrated with the adult ones and pediatric nurses and scrub nurses have been shifted to adult operating theaters. In this way, the specificity of training the pediatric nursing staff to manage the premature and critically low weight children is affected.

The child has become again as an adult patient of smaller size.

DISCUSSION

The COVID-19 pandemic affected every phase of emergent and scheduled activity in pediatric surgery. Interactions with the territory, already critical in a pre-COVID-19 pandemic, indicated a lack of organization of the pediatric hub-spoke network.

The goal of pediatric surgeons is to ensure specific care dedicated to the pediatric patient, in a devoted environment, and with dedicated methods. The pediatric surgery unit must be the "container" of specialists in the subject and related specialties and must offer expertise in the care of the child. Infections of COVID-19 are reported to be milder in children than in the adult population. However, COVID-19 infection in children may cause concerns both for the risk of contributing to the spread of the infection and for the appearance of the MIS-C, which is considered a serious complication (13). To deal with the risk of spreading, several institutions have reorganized their pediatric departments to provide a separate flow for high-risk and low-risk patients with COVID-19 and increase the number of beds in dedicated negative pressure areas (14). This was also implemented in pediatric surgical departments. The categories at highest risk of MIS-C are children affected by disabilities, tumors, malformations associated with related syndromes, and patients with immunological deficiency. Based on lessons learned during the Covid-19 pandemic, the admission of these patients needs dedicated pediatric treatment paths. A better prognosis would be provided by a possible model of pediatric surgery reorganization capable of guaranteeing the respect of pediatric surgical patient flows during a pandemic event. The pediatric ICU of COVID-19 hospital should provide a temporary arrangement of the number of beds to obtain the recruitment of frailly sick children from the network between territorial pediatrics and hospitals.

A "functional pediatric surgical model" for the pediatric area can also be established within a general hospital (**Table 4**).

TABLE 4 | Pediatric surgery future care model in general hospitals.

Give the child the whole dignity of a "pediatric care"
The child must be operated by the pediatric surgeon
The dedicated and skilled surgical nursing team: to be recovered
The "functional pediatric surgical model": establish in General Hospitals
Spoke centers: surgery ensured by a pediatric team

To achieve this fundamental objective, it is necessary to resort to some urgent measures. First, it is a formalization of the concept that pediatric patients should be operated on by pediatric surgeons. Second, the development of a collaborative relationship with other satellite pediatric surgical specialties (ENT, maxillofacial, orthopedics, neurosurgery, etc.) is urgently required to identify pediatric paths dedicated to children to give back the child the dignity of care that the COVID-19 has subtracted. The COVID-19 pandemic has increased the already high number of children admitted to adult wards while children should be admitted only in a dedicated pediatric environment. Considering the high number of pediatric patients hospitalized in adult wards, the time has come to reiterate the concept of pediatric age limits valid for all Italian hospitals. It must be recalled that the first article of the "Convention on the Rights of the child" defines a child as "every human being below the age of 18 years".[1] Furthermore, the obligation to treat children only in the pediatric environment is proposed by force, as also confirmed by the charter of the rights of the child. The implementation of pediatric surgery in spoke centers can promote the hub-spoke network and help limit the hospitalization of children in adult wards. This project must be supported by a pediatric anesthesiology team that recruits children over the age of 5 years in spoke centers. Accordingly, an anesthesiologist at spoke centers needs dedicated training as required by the regulation on hospital care standards.

On the other hand, there is a complete lack of a project involving the whole of Italy on the number of centers necessary to cover the needs of the population. There is formal and substantial disarray because the regions work without general coordination that should give behavioral guidelines to the identification and authorization to open centers that should respond to clear and precise criteria. Pediatric surgery centers must be identified based on the needs of the population and the territory and divided into treatment areas (who is authorized to do what). Having, for example, 150 cases of kidney tumors operated in 56 different centers in Italy does not allow to develop and maintain the needed skills neither for surgeons nor for the whole structures.

Table 5 summarizes the administrative proposals to limit pediatric surgical patients treated in general hospitals.

Needs are changing rapidly. Day surgery function is increasing in all units, which constitutes a very important percentage of pediatric surgical activity. Alongside this, outpatient surgery, which has helped to reduce hospitalization, especially in chronic

[1]https://www.ohchr.org/en/professionalinterest/pages/crc.aspx (accessed November 25, 2021).

TABLE 5 | Criticalities and proposals to limit admissions of children in adult wards.

Criticalities	Intervention
N of Pediatric Surgery Centers in Italy	National vision and coordination needed
Pediatric age limits in the wards	A national uniformity is needed
Hospitalization of children in adult wards	A national provision should limit and put an end
DRG not appropriate in pediatric age	Updated DRGs according to the "complexity" of pediatric surgery management

TABLE 6 | Training of new pediatric surgery specialists.

Organization of post-graduate training schools: commonality of programs among all schools
Rigorous accreditation criteria, commonality of programs, interchangeability to acquire knowledge and skills also from comparison with other Centers
Give an operational role—now very forced by legislation—to doctors in training

patients, requires space and time and dedicated staff, as well as a reorganization of nursing activities. Day surgery, outpatient surgery, and day hospital, all require investment and adaptation as they offer a quick service to the territory by reducing hospitalization, related costs, and inconveniences for the family. Such important projects of quality childcare and cost reduction are not supported by national health projects for the requalification of personnel, spaces, and related regulations.

Surgical technology is advancing rapidly. In recent years, we have witnessed technological innovations in pediatric surgery with the integration of minimally invasive, robotic, and virtual reality surgery even in young patients. The response that pediatric surgery has given to the reorganization required by the pandemic has reinforced the need to implement telemedicine in clinical practice, especially aimed at chronic and frail patients. According to data reported by the activity of social and health professionals, the use of telemedicine increased significantly during the COVID-19 pandemic, also in some pediatric surgery settings (15). Pediatric surgery centers could be placed to expand and regulate innovations, such as images, in real-time. The role of the pediatric nursing staff nurses dedicate to such technologies need to be included in a national health project that protects the figure of the pediatric nurse with the same rights as the professional nurse.

Finally, there is a lack of specialists due to past mistakes and this creates enormous discomfort. In the current attributions to post-graduate training schools (therefore with a 5-year vision), old evaluations have been used that do not meet the criteria of receptive as well as didactic capacity. Regarding surgeons in training, the legislation is very restrictive in Italy. Absurdly, a recent graduate could, in theory, be hired in cardiac surgery and operate as the first heart operator, but a surgical trainee, for example, in pediatric surgery cannot do tutoring on call.

Table 6 shows proposals to improve training in pediatric surgery in Italy. It is necessary to give an operational role to post-graduate training schools in terms of rigorous accreditation criteria, commonality of programs, interchangeability to acquire knowledge and skills also from comparison with other centers.

The legislation is also lacking from the point of view of the responsibility of health professionals operating in the national pediatric field. Italian legislation is not the same as that enjoyed by other professionals (magistrates, notaries, lawyers, etc.), and in most cases, pediatric expertise is supported by adult professionals who have no experience in pediatric surgical pathology.

New protocols of pediatric care could be taken into consideration as possible scenarios for each hospital. Surgical teams are asked to adhere to national and regional guidelines, to evidence their expertise, and the availability of resources dedicated to children.

CONCLUSION

The COVID-19 pandemic has upset the assistance in the pediatric area. As a consequence, the pediatric surgical organization in general hospitals and pediatric hospitals has been completely subverted. The COVID-19 infection is still spreading and children are seriously penalized both for surgical treatment as well as for the diagnostic component. In most centers, the pediatric surgical teams are the adult ones and the specificity of training the pediatric operating nursing is in danger of survival. Moreover, the pandemic has removed the "emotional" aspects of the admitted child has lost its central position in patients' management and the risk is real that in general hospitals the child will once again be considered a small adult. Given all these criticalities, all efforts should be done to define guidelines on the management of surgical children, both in pandemic times and in normal ones to ensure the specificity of treatment and give back the child the dignity of care that the COVID-19 has subtracted.

AUTHOR CONTRIBUTIONS

FM and GP contributed to the conception and design of the study and wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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APPENDIX

Predefined questions to be used as a canvas:

1. Pre-pandemic criticalities: starting with the criticalities that each pediatric society had expressed in the FIARPED white paper.
2. Pediatric care during the pandemic and recovery describing:
   - What happened compared to what we had assumed?
   - How we reorganized?
   - What if the reorganization has remained in our daily business now that we are emerging from the pandemic?
3. Current criticalities: What are the criticalities that your specialty is experiencing in this moment of change?
4. The future care model of our specialty.

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BRIEF RESEARCH REPORT
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Very High Negative Concordance Rate of RT-PCR for SARS-CoV-2 in Nasopharyngeal Swab and Tracheo-Bronchial Aspirate in Children

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Reliable testing methods for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children are essential to allow normal activities. Diagnosis of SARS-CoV-2 infection is currently based on real-time reverse transcriptase-polymerase chain reaction (RT-PCR) performed on nasopharyngeal (NP) swabs; concerns have been raised regarding NP swab accuracy in children to detect the virus because of potential lack of cooperation of the patients or due to general uncertainties about concordance between high and low respiratory tract specimens in children. The aim of the study (IRB approval: ST/2020/405) is to prospectively compare RT-PCR results on NP and tracheo-bronchial aspirate (TA) in children admitted to the hospital for surgery or admitted to the Pediatric Intensive Care Unit (PICU) of a tertiary children hospital in Milano, Italy, during a peak of COVID-19 infections in the city. A total of 385 patients were enrolled in the study: 364 from surgical theater and 21 from PICU. Two patients (0.5%) tested positive on TA and were negative on NP; both cases occurred in November 2020, during a peak of infection in the city. Specificity of NP swab was.995 (95% CI: 0.980–0.999). Two patients with positive NP swabs tested negative on TA.

Conclusion: Our study shows that the specificity of SARS-CoV-2 RT-PCR on TA swab, compared to results of SARS-CoV-2 RT-PCR on NP, was very high for negative cases in our pediatric cohort during a period of high epidemiological pressure.

Keywords: SARS-CoV-2, naso-pharyngeal swab, tracheo-bronchial aspirate, children, RT-PCR-Real-Time PCR

INTRODUCTION

While children have shown lower incidence and severity of COVID-19, they have often had restrictions placed on their activities because they are considered a potential reservoir for the disease and source of infection for the adult population (1).

Diagnosis of SARS-CoV-2 infection is currently based on RT-PCR performed on nasopharyngeal (NP) swabs (2). The same diagnostic method can also be applied to other specimens (sputum, tracheal aspirate, bronchoalveolar lavage, urines, feces, etc.) (3). However, concerns have been raised regarding NP swab accuracy in children to detect the virus because of the potential lack of cooperation of the patients (4) or due to general uncertainties about concordance between high and low respiratory tract specimens in children with viral and bacterial respiratory infections in previous studies (5). While alternative methods to collect suitable material for SARS-CoV-2 research in upper respiratory tract specimens, such as nasal and nasopharyngeal fluid (6), have been described, the current standard diagnostic method in the pediatric population remains NP swab.

This prospective study aims to compare RT-PCR results on NP and tracheo-bronchial aspirate (TA) in children.

METHODS

This is a prospective observational study conducted at a tertiary pediatric hospital in Milano, Italy (IRB approval: ST/2020/405) between 2 November 2020 and 2 June 2021 on children admitted to the hospital for surgery or admitted to the Pediatric Intensive Care Unit (PICU). The chosen period coincided with the peak of COVID-19 infections in the city (7). All consecutive patients meeting the inclusion criteria underwent NP and TA RT-PCR for SARS-CoV-2.

Usual Testing Pathway for Patients Admitted to Hospital

All patients admitted to our hospital undergo an NP swab, together with the caregiver who will stay in the hospital with them; in the case of planned surgery, this is obtained 48 h before surgery, and if it gives a positive result for any of the two (patient and caregiver), surgery is postponed. In the time frame between NP swab and surgery, both patient and caregiver are officially quarantined. The maximal interval between evaluation with swab and surgery is 72 h; after this time, if surgery is for any reason delayed, the swab is to be repeated.

In case of urgent/emergent surgery, patients receive NP swabs upon hospital admission and are treated as suspected cases in both ward and Operatory Room (OR) until the result of the swab is available for both patient and caregiver. If one of the two is positive, the case is treated as positive throughout the hospital stay.

Patients admitted to the PICU are tested with an NP swab together with the caregiver; until the result of the swab, patients are treated as positive cases even if admitted for non-respiratory reasons. If they are intubated, a sample of TA is collected for SARS-CoV-2 RT-PCR too.

For both surgical and patients in PICU, if in case the TA was positive, then the patient was treated as positive, and NP was repeated according to local protocols[1].

RT-PCR

On available samples, molecular analyses are performed to detect SARS-CoV-2 RNA, using the automated Real-Time PCR ELITe InGenius® system and the GeneFinder™ COVID-19 Plus RealAmp Kit assay (ELITechGroup, France). The reaction mix is manually prepared, according to the instructions of the manufacturer and loaded into the system with other reagents, while RNA is extracted from 200 μl of sample and eluted in 100 μl; the final reaction volume consists of 5 μl of RNA plus 15 μl of reagents mix. The RT-PCR profile is set up as follows, according to the instructions of the manufacturer: 50°C for 20 min, 95°C for 5 min plus 45 cycles at 95°C for 15 s, and 58°C for 60s. Three targeted regions in the RNA-dependent RNA polymerase (RdRP), Nucleocapsid (N), and Envelope (E) genes were simultaneously amplified and tested. A cycle threshold value (Ct-value) fewer than 40 is defined as a positive test result according to the instructions of the manufacturer.

Patient Population

Inclusion criteria are defined as follows:

- Age 0–18 years.
- Tracheal intubation due to surgery requiring general anesthesia or tracheal intubation as part of life support in PICU.
- Written consent of caregiver.

During the enrolment period, samples of TA were collected from the anesthesiologist/intensivist in charge of the case. In the surgical patients, TA was collected after induction of anesthesia and intubation; in the patients in PICU, it was collected right after intubation if this occurred in the PICU, or upon admission, if the patient was transferred already intubated from another hospital.

When dealing with sample collection, the highest level of personal protective equipment was mandatory for the person involved (sheltering facepiece (FFP) 3 mask or equivalent; visor; long-sleeved gown; and gloves). After collection, the samples were immediately sent to the laboratory for analysis.

Statistical Analysis

Categorical data are expressed as count and percentage; specificity is reported along with binomial exact 95% confidence interval. Quantitative data are expressed as mean and standard deviation or median and interquartile range (25-75th centile). Data were analyzed with Stata v17.0 (StataCorp USA).

RESULTS

A total of 385 patients have been enrolled in the study: 364 from surgical theater and 21 from PICU. Among the surgical patients' group, 213 (58.45%) were scheduled for elective procedures and

[1]http://www.salute.gwww.salute.gov.it

TABLE 1 | Results of NP and TA samples in the studied cohort.

	TA +, N	TA -, N	Total, N
NP+, N	0	2	2
NP-, N	2	359	361
Total, N	2	361	363

NP, naso-pharyngeal swab; TA, tracheo-bronchial aspirate; N, number.

151 (41.55%) for urgent surgery. The mean age was 7.30 ± 4.89 years. No patient showed COVID-19-related symptoms.

Among PICU patients, 14 were intubated due to respiratory failure, 5 due to neurologic events, and 2 due to trauma/burns. The mean age was 5.85 ± 4.88 years.

Of the surgical group, 22 samples were insufficient for testing, leaving 342 adequate samples for study.

The total number of adequate samples for testing was therefore 363:342 from surgical theater and 21 from PICU.

In total, four patients tested positive for SARS-CoV-2 during the study (**Table 1**).

Two patients (0.5%), one in the surgical elective patients and one in the PICU group, tested positive on TA while being negative on NP; both cases occurred in November 2020.

Two urgent surgical patients, whose preoperative NP swab was positive, tested negative at TA.

Specificity of TA was 0.995 (95% CI: 0.980–0.999).

DISCUSSION

The NP swab is currently considered the "Gold Standard" for SARS-CoV-2 detection (8, 9). NP swab can however give false negative results, sometimes also related to suboptimal sample collection, especially in children (10). We decided to analyze and compare the results of both NP swab and TA in children who required intubation for surgical procedures or life support. Our cohort consisted mostly of healthy children, who do have a normal community life, who do not show COVID symptoms, and who had proven negative on the pre-operatory swab (and whose caregiver had tested negative too), but in a geographical and chronological setting characterized by high levels of virus circulation.

This is, to our knowledge, the first study analyzing concordance of results of SARS-CoV-2 RT-PCR in NP swabs and TA in children. Our results show that the specificity of TA was high in our cohort for the negative patients.

We cannot draw the same conclusion for the positive patients, where half of the cases were detected by NP and half cases by TA. It can be postulated that these results depend on a sample size problem, that is, the very low rate of positive patients that were enrolled in our cohort.

Overall, four patients in our study had discordant results. The negativity of RT-PCR on TA in the two patients whose NP swab was positive can be explained by a longer persistence of the virus in the upper respiratory tract compared to the lower respiratory tract. RT-PCR positivity could be due to persistent infection as well as the presence of non-transmissible virus fragments (11). We, unfortunately, do not have the relative viral cultures to check this possibility; it was not part of our protocol and the data collection was implemented during a period of high COVID-2019 circulation with relative resource limitation in all hospitals.

Another explanation can be that children usually mount a robust innate immune response within the upper airways that can limit the spread of the virus to the lower respiratory tract, as recently demonstrated in a study involving adult and pediatric patients (12).

Conversely, two patients had negative NP and positive TA tests. The discordance of upper and lower respiratory samples has been previously documented. Specifically, a recent study evaluated differences between swab results in the trachea and in the nasopharynx in 25 totally laryngectomized subjects, showing that results were overall divergent and no statistically significant correlations emerged between results of the tests performed in the two sites, suggesting that both tracheal and nasopharyngeal swabs are recommended in these kinds of patients, to obtain a reliable test and to avoid false negatives (13).

Our study has some limitations to address. First, the low number of positive samples did not allow us to calculate the sensitivity of the tests. Second, we did include only a small number of children with acute lower respiratory tract infections, therefore, our findings cannot be translated to these type of patients. Third, we neither have the viral load of the discordant samples or their ability to grow in culture nor the Cycle-Thresholds Values of RT-PCR which limits our ability to speculate if positive NP swabs with negative TA represent viral traces due to older infection.

In conclusion, our study showed that the specificity of SARS-CoV-2 RT-PCR on TA, compared to results of SARS-CoV-2 RT-PCR on NP, which is actually considered the gold standard, was very high for negative patients in our pediatric cohort, even during a period of high epidemiological pressure.

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 Comitato Etico Milano Area 1. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AC designed the study and wrote the first draft of the manuscript. Material preparation, data collection and analysis were performed by AC, VD, SF, ADS, GP, DB, FM, ADF, LE, and DM. All authors commented on previous versions of the manuscript, read, and approved the final manuscript.

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BRIEF RESEARCH REPORT
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Clinical Characteristics of Children With SARS-CoV-2 Infection in a Hospital in Latin America

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Objective: COVID-19 infections have shown a different behavior in children than in adults. The objective of this study was to describe the clinical characteristics and severity of SARS-CoV-2 infection in pediatric patients seen at a reference hospital in Colombia.

Method: A descriptive, observational study in patients under the age of 18 years with a positive test for SARS-CoV-2 infection (RT-PCR or antigen) between April 2020 and March 2021. Multiple variables were studied, including demographic data, clinical characteristics, lab measurements, treatments administered, intensive care unit admission, and mortality.

Results: A total of 361 patients were included of whom 196 (54%) were males. The median age was 3 years. Of all the patients, 65 (18%) were asymptomatic. The majority of patients had no comorbidities ($n = 225$, 76%). In those who were symptomatic ($n = 296$, 82%), the most frequent complaints were fever ($n = 178$, 60%), nasal congestion ($n = 164$, 55%) and cough ($n = 149$, 50%). Chest x-rays were normal in 73 patients (50%). When abnormalities were found, interstitial (29%) and alveolar (12%) patterns were the most prevalent. One hundred and fifty-seven children (53%) required general ward hospitalization, and 24 patients (8%) required pediatric intensive care admission. The global mortality was 0.8% (3 patients).

Conclusions: The majority of cases were asymptomatic or mild. However, a significant percentage of patients required general ward admission, and some even required intensive care. The main symptom of COVID-19 infections in newborns was apnea. A second COVID-19 RT-PCR may be necessary to detect infections in critically ill patients with a high clinical suspicion of the disease if an initial test was negative.

Keywords: pediatrics, comorbidity, inpatients, pediatric intensive care unit, Latin America, COVID-19

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INTRODUCTION

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus infection was described in Wuhan, China. As of March 2020, a global pandemic had been declared. A wide array of disease manifestations has been observed, ranging from no symptoms at all to serious respiratory distress and even death. Adults, especially the elderly, have suffered the greatest impact of this disease (1). At the time of writing, the World Health Organization (WHO) had confirmed over 500 million cases worldwide, with almost 6 million deaths attributed directly to COVID-19 infection (2). In Latin America, around 56 million cases and more than 1.2 million deaths have been reported (3). In Colombia, an upper-middle-income country, around 6 million cases and more than 100,000 deaths had been reported as of February 2022 (4). Of all the positive cases in Colombia up to February 2022, 11% were reported in people under the age of 19 (5).

The reported pediatric COVID-19-related deaths have been higher in low and middle-income countries (91.5%) compared to high-income countries (8.5%), with an excess of deaths in Latin America (6). In South America, there are economic, social, and health disparities. Previous studies have shown that certain traits of poor countries have a direct impact on COVID-19 outcomes. This includes low socioeconomic status, overcrowding, higher use of public transportation, absence of potable water, and informal work (7). As a result of the worst scenarios experimented on by infected adults, healthcare services, including pediatric ones, were rearranged to meet the increasing requirements of that age group (8). This came to destabilize vulnerable health systems in which lack of government support, excessive centralization, inequities, and inadequate access were already historical. As a consequence, the pandemic became a major challenge (9).

As the pandemic has progressed, several papers have provided a better understanding of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This includes a glimpse into its pathophysiology, immune response, treatments, as well as the spectrum of manifestations in the pediatric population, in whom the disease has been less severe. Previous studies carried out in countries with limited resources are mainly focused on the characteristics of the multisystem inflammatory syndrome in children (MIS-C) due to its particular specificity for this age group (10–13). Therefore, case series not related to MIS-C are lacking.

The objective of this study was to describe the clinical and imaging characteristics of the infection, the use of specific diagnostic tests and the severity of the SARS-CoV-2 infection in patients admitted to a reference pediatric hospital in Colombia, an upper-middle-income country in Latin America.

METHODS

A descriptive, observational study was carried out at a tertiary care hospital in Medellín, Colombia. The Hospital is a high complexity reference center, with 78 pediatric hospital beds and 27 pediatric and neonatal intensive care beds. Around 928 patients per month (11,139 during the study period) were seen in the emergency department and 2,928 were admitted during the study period.

Population

Children under 18 years of age who had a positive test for SARS-CoV-2 [real-time reverse transcription-polymerase chain reaction (RT-PCR) or COVID-19 antigen] and were treated in one of our hospital services: ambulatory care, pediatric emergency room (ER), hospitalization ward, or pediatric intensive care unit (PICU) between April 2020 and March 2021 were included.

COVID-Protocol Attention in the Institution

The institutional protocol for diagnosing SARS-CoV-2 infection was based on RT-PCR. Indications for testing included at least one of the following: respiratory distress, odynophagia, asthenia, anosmia, hypogeusia, runny nose, or fever. If a positive result was available, then no further workup was carried out. In hospitalized patients, if the initial test was negative, then a second RT-PCR test 48–72 h was done. Patients transferred from other institutions were also tested if a previous test was negative; no mattered if was either antigen or RT-PCR. Also, RT-PCR was customary in patients who had surgery or as part of a stem cell transplantation protocol.

Data Collection

The medical charts were reviewed and the data was registered on an Excel form previously designed for this purpose with the following variables: age, sex; clinical variables such as the onset of symptoms, presenting symptoms of the disease, epidemiological contact, comorbidities, area of care (hospital ward, ER, PICU, ambulatory care); complications like multisystem inflammatory syndrome in children (MIS-C), PICU admission, and respiratory failure; lab and diagnostic test results; treatment received during hospitalization (pharmacological treatment, mechanical ventilation, vasopressor support, dialysis); length of hospital and PICU stay; and outcome at discharge: death or recovery.

Statistical Analysis

A descriptive analysis was performed. Qualitative variables are presented as frequencies and proportions. For quantitative variables, normality was assessed using the Shapiro-Wilk test and they are reported as median or mean with interquartile range (IQR) or standard deviation (SD). The data were processed on SPSS version 20 (SPSS Inc. Chicago, IL, USA). The study was approved by the institution's ethics committee and did not require informed consent because of the national statements.

RESULTS

Demographic and Epidemiological Characteristics

A total of 361 patients were included. The median age was 3 years (IQR 1–10 years). Seven patients were newborns (2%). The demographic characteristics of all the patients are reported in **Table 1**. In **Figure 1** we present a flowchart of the included patients.

Clinical Characteristics

Out of all the patients, 65 (18%) were asymptomatic. The vast majority were tested because of positive close contact, 51(79%) were outpatients and eight (12%) received attention in the ER. Also, six patients (9%) underwent testing as a part of the stem cell transplantation protocol.

The bulk of the sample, 269 (82%), was composed of symptomatic patients, and all received pediatric medical care. Of these, 157 (53%) patients were hospitalized. Most of the children admitted to ER were 2 years old or younger ($n = 159$, 52%); the youngest was 7 days old and the oldest was 17 years old.

The longest time that elapsed between the onset of symptoms and consultation was 20 days, in one patient. **Table 2** shows the characteristics of the symptomatic patients.

The main diagnosis on admission was directly related to SARS-CoV-2 infection in 213 patients (72%) and included: upper-respiratory infection (common cold, pharyngitis, sinusitis, or laryngitis), lower-respiratory infection (bronchiolitis and pneumonia) and MIS-C. In 83 patients (28%) the reason for admission was another non-COVID-related diagnosis and a test was performed as a part of the institutional protocol. The most frequent symptoms were fever in 60%, rhinorrhea in 55%, and cough in 50% of the cases (**Table 2**). Of all the patients treated, 9 (3%) had MIS-C and were treated with immunoglobulin infusions and high-dose steroids. Another form of presentation was apnea, characteristic of newborns ($n = 4/5$, 80%). None of these patients had other viruses detected, like respiratory syncytial virus (RSV) or influenza. If asymptomatic cases and those with mild respiratory infections are grouped, they add up to 204 (57%).

SARS-CoV-2 infection was diagnosed with an initial positive test in 271 cases (92%); the remaining 25 patients (8%) required a second RT-PCR test to confirm the diagnosis. Of those initially negative, 23 were RT-PCR and 2 were antigen tests.

Coinfections were detected in 42 patients (14%); 20 children (48%) had an associated viral infection, 9 (45%) due to RSV, 5 (25%) due to influenza; 4 (20%) due to both, RSV and influenza. One patient had cytomegalovirus infection, and another had Epstein-Barr virus. Twenty-two patients (52%) had bacterial coinfections. The isolated microorganisms were *E. coli, E. cloacae*, *P. mirabilis*, *Staphylococcus aureus*, *S. epidermidis*, *Salmonella*, *S. agalactiae, E. faecalis*, *Pseudomonas aeruginosa*, *Clostridium difficile* and *Candida parapsilosis*. *Mycoplasma pneumoniae* was found in 5 of 28 (18%) patients.

Table 3 describes the results of laboratory tests. A C-reactive protein (CRP) >10 mg/dl was found in 28/169 patients (16%), neutropenia was reported in 30/180 patients (16%) and moderate thrombocytopenia (<100,000) was found in 12 patients (7%).

Two patients (0.5%) were suspected of having healthcare-associated COVID-19 infection after 14 days of hospitalization for a different cause, one for aplastic anemia and another undergoing bone marrow transplantation due to leukemia.

The global mortality for the entire cohort was 0.8% (3 patients). Two patients died of septic shock and multiple organ dysfunction: a healthy 4-year-old with *Staphylococcus aureus* infection and a newborn with suspected immunodeficiency with

TABLE 1 | Demographic characteristics of all the patients.

Variable	*n* (%)
Age	
<1 year	82 (23)
1–5 years	135 (37)
6–11 years	71 (20)
12–17 years	73 (20)
Female sex	165 (46)
Place of origin	
Antioquia	347 (96)
Major cities	315 (91)
Peripheral towns	32 (9)
Chocó	4 (1)
Colombian Caribbean region	4 (1)
Others	6 (2)

Peripheral town: is a town that does not have a health infrastructure for pediatric care.

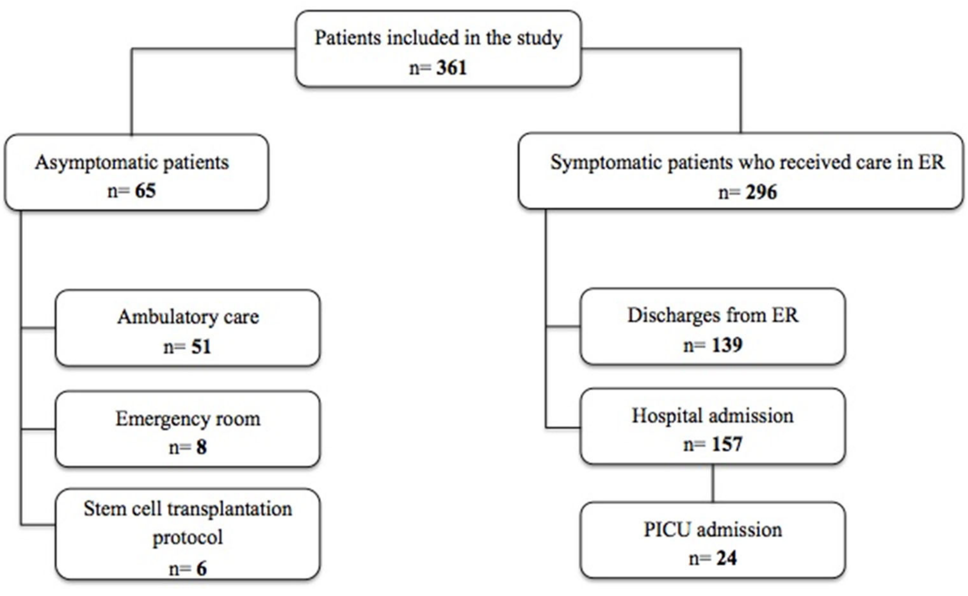

FIGURE 1 | Flowchart of the included patients.

TABLE 2 | Characteristics of patients with COVID-19 symptoms.

Variable	$N = 296$
Time elapsed from the onset of symptoms to consultation, median (IQR)	3 days (1–4)
Principal diagnosis on admission, *n* (%)	
Upper-respiratory infection due to COVID-19	176 (60)
Lower-respiratory infection due to COVID-19	33 (11)
Bronchiolitis	16 (48)
Pneumonia	17 (52)
Acute gastroenteritis	18 (6)
Asthma	15 (5)
Neurological (epilepsy, seizures, hydrocephaly)	10 (4)
Sepsis	9 (3)
Urinary tract infection	7 (2)
MIS-C	4 (1)
Others[a]	24 (8)
Symptoms or signs present on admissions, *n* (%)	
Fever	178 (60)
Rhinorrhea/nasal congestion	164 (55)
Cough	149 (50)
General malaise	75 (25)
Gastrointestinal symptoms	74 (25)
Respiratory distress syndrome	42 (14)
Odynophagia	32 (11)
Headache	24 (8)
Stridor	11 (4)
Rash	9 (3)
Hypoxemia	8 (3)
Seizure	6 (2)
Apnea	5 (2)
Ageusia	5 (2)
Anosmia	4 (1)
Comorbidities, *n* (%)	
None	225 (76)
Asthma	25 (8)
Chronic lung disease	15 (5)
Immunosuppression / immunodeficiency	14 (5)
Hemato-oncological disease	9 (3)
Others[b]	8 (3)
Chest x-ray, *n* (%)	$N = 145$
Normal	73 (50)
Interstitial pattern	42 (29)
Alveolar opacity	17 (12)
Atelectasis	8 (6)
Others[c]	5 (3)
Positive first test, *n* (%)	271 (91)
PCR	267 (99)
Antigen	4 (1)
Positive second test (RT-PCR), *n* (%)	27 (9)
Positive IgM serology, *n* (%)	1 (0.3)
Complications, *n* (%)	17 (6)
Coinfection, *n* (%)	44 (15)
Viral	20 (48)
Bacterial	22 (52)
Hospitalization, *n* (%)	157 (53)
Admission to intensive care, *n* (%)	24 (8)
Hospital stay, median (IQR)	2 days (1–3)

IgM, immunoglobulin M; MIS-C, Multi-system inflammatory syndrome in children. [a] Others: BRUE, trauma, arterial hypertension, appendicitis, bone marrow aplasia, acute myeloid leukemia, bacteremia, tachycardia, malnutrition, cystic fibrosis, mononucleosis, syncope, sickle cell anemia, sexual abuse, osteomyelitis. [b] Others: pulmonary hypertension 3 patients, arterial hypertension 2 patients, obesity 2 patients, biological therapy 1 patient. [c] Others: hyperinflation 3 patients, pleural effusion 1 patient, ground glass 1 patient.

TABLE 3 | Laboratory tests performed on patients with COVID-19 infection.

Variable	*n*	
PCR (mg/dL)[a]	169	1 (0.2–4.2)
ESR (mm/hour)[a]	24	37.5 (18.2–63.7)
Leukocyte count (mm^3)[a]	180	9,200 (6,400–12,500)
Absolute neutrophils (mm^3)[a]	180	5,038 (2,400–8,046)
Hemoglobin (g/dL)[a]	181	12.6 (11.8–13.5)
Platelets (mm^3)[a]	180	302,000 (238,250–371,500)
D-dimer (ng/mL)[a]	13	2,633 (1,284–11,732)
LDH (U/l)[a]	17	299 (226–398)
Ferritin (ng/mL)[a]	14	527 (169–1,091)
Fibrinogen (mg/dL)[b]	14	617 (±263)

[a]median and interquartile range; [b]mean and standard deviation.

Candida parapsilosis infection. The third child, a 5-year-old with cerebral palsy and epileptic encephalopathy, was receiving palliative care and died of respiratory failure. In this case, no other etiological agent other than SARS-CoV-2 was identified.

Intensive Care

Of the 296 symptomatic patients, 24 (8%) were admitted to the PICU or the neonatal care unit with a positive test for COVID-19. Only in six patients (25%), the cause of admission was related to COVID-19. The median length of stay in intensive care was 4 days (IQR 3–6 days). Of the patients that were admitted to the PICU, seven (29%) had a false negative initial test, five RT-PCR tests, and two antigen tests. **Table 4** describes the characteristics of the patients admitted to the PICU.

The treatment received in the intensive care unit was as follows: invasive or non-invasive mechanical ventilation in 9 patients (38%), including two patients who required prone positioning, with a median duration of 3 days (IQR 1.5–16 days). Three patients required a high flow cannula. Seven (78%) patients who required mechanical ventilation had bacterial coinfection. Four patients (15%) received vasopressor support, and three patients (11%) received renal replacement therapy. Chest x-rays

TABLE 4 | Characteristics of patients admitted to the pediatric intensive care unit.

Variable	No (%)
Age, *n* (%)	
<1 year	10 (42)
1–5 years	4 (16)
6–11 years	5 (21)
12–17 years	5 (21)
Female sex, *n* (%)	12 (50)
Time elapsed between the onset of symptoms and consultation, median (IQR)	3 days (1.2–5)
Coinfection, *n* (%)	10 (42)
Principal diagnosis on admission, *n* (%)	
Sepsis	8 (35)
Acute COVID-19 respiratory infection	5 (22)
BRUE	4 (17)
Hypertensive urgency/emergency	2 (9)
Asthma	1 (4)
Status epilepticus and respiratory failure	1 (4)
Urinary tract infection	1 (4)
MIS-C	1 (4)
Comorbidities, *n* (%)	
None	13 (54)
Chronic neuropathy	6 (25)
Immunodeficiency	2 (8)
Asthma	1 (4)
Hemato-oncological disease	1 (4)
Arterial hypertension	1 (4)
Chest x-ray, *n* (%)	*N* = 22
Normal	3 (14)
Interstitial pattern	11 (50)
Alveolar opacity	4 (18)
Atelectasis	4 (18)

IQR, interquartile range; BRUE, Brief resolved unexplained events; MIS-C, Multi-system inflammatory syndrome in children.

characteristics of those admitted to the intensive care unit are reported in **Table 4**.

DISCUSSION

This study describes the demographic, diagnostic, clinical, and imaging characteristics of 361 patients under the age of 18 years diagnosed with SARS-CoV-2 infection at a tertiary care hospital in an upper-middle-income Latin American country. The majority of cases were either symptomatic or mild. We found a highly variable clinical and radiological presentation, perhaps a reflection of the diverse geographical and economical background of the population studied. Additionally, the diagnostic protocol carried out in our institution was successful in detecting false-negative cases, thus possibly preventing in-hospital infections.

The burden placed on health services during the COVID-19 pandemic substantially affected the care of pediatric patients. Given the fact of higher complications and mortality rates, infrastructure and human resources were redirected towards adults' attention. Evidence suggests that children suffered a drop in quality and delays in healthcare access (14). Moreover, as described by Kitano et al. (6) these differences may have been accentuated in low and middle-income countries, which further deepened the gap between nations concerning diagnosis, progression, and follow-up. This disparity is exemplified in mortality rates 35 times higher than those seen in high-income countries (0.43 vs. 0.012). Furthermore, there is an inverse relationship between PICU admissions and income so that access to these units is truncated in countries with limited resources (6).

Latin America is an example of the negative effects that lack of resources and a faulty healthcare structure had on the outcomes of this global emergency. Before the pandemic, most Latin American countries did not have the bare minimum recommended facilities to take care of patients as recommended by the WHO: at least 2.9 hospital beds per 1,000 inhabitants. For instance, Colombia and Peru had 1.6 and Ecuador 1.5. Similarly, only Argentina and Brazil met the essential critical care bed requirement of 6 per 100,000 inhabitants. Moreover, qualified human resources for critically ill patients in Latin America are scarce (9). Therefore, when available means were heavily shifted towards adult care, the already deficient pediatric infrastructure suffered a shortage of hospital and PICU beds. Our institution, aware of the situation caused by the pandemic, had to reduce pediatric critical care beds by 26% and general hospital beds by 22%. In 2020, there was a considerable reduction in pediatric admissions to hospitalization wards and pediatric intensive care units. A phenomenon registered throughout Latin America, mainly evidenced by lower admissions due to lower respiratory tract infections (15).

No less important were the effects of the pandemic on the global health of children and the socioeconomic factors that influence them. In the years 2020-2021 in Colombia, there was a notable decrease in morbidity and mortality due to respiratory diseases. On the other hand, child malnutrition increased significantly after lockdowns were lifted, evidencing low employment rates and high rates of informal work in the region and the country (9, 16). In this series, only 4% of patients lived in peripheral rural areas even if infection rates were similar to those of cities. This is a reflection of the limited access those populations have to the country's health system.

A notable difference from other studies was the prevalence between age groups. While in other studies, the infection was more prevalent in children over 6 years old, in this series we observed more cases in infants under 2 years old (52%). This age distribution could be explained by a selection bias in which parents of younger children seek medical attention in the ER worried about potentially worst outcomes and because the access to ambulatory care is difficult.

Although this study was carried out in a tertiary care center, the occurrence of comorbidities was low and 76% of patients did not have any comorbidity. Data from other studies are inconsistent in this regard. Li et al. (17) results are aligned with our findings whereas others report a greater proportion of comorbidities, for instance, studies from Peru (42%), Argentina (53.9%), and Brazil (38.9%) (18–20).

Every study reviewed, and ours, show that COVID-19 symptoms are similar to and indistinguishable from those of other common viral diseases affecting preschoolers and school-age children and comprise: fever, respiratory and gastrointestinal complaints (18, 19, 21–23). In this series, most patients suffered from acute upper respiratory infection, with a few cases of pneumonia and hypoxemia. Also, of all the patients admitted to the PICU, only 25% had a diagnosis directly related to COVID-19, unlike the clinical presentation in adults (24, 25).

In these series, the majority of patients had mild symptoms or were asymptomatic; just 6% had pneumonia and 5% had bronchiolitis, which explains the lower frequency of hypoxemia at the moment of ER admission. A similar trend was found by Rodriguéz-Portilla et al. (18). For many reasons and hypotheses, the severe COVID-19-pneumonia experienced by adults is very rare in children (26).

The largest Colombian study was carried out by Bolaños-Almeida (27). The records of around fifty thousand patients under 18 years with COVID-19 were reviewed. Hospital admissions only represented around 2.8% of cases, whereas PICU admissions were even lower, with <1% requiring intensive care, similar to another population-based study in Chile, where hospitalization in patients with COVID-19 was 2% (28). These data are not comparable to our results given the type of studies, but they give us a broader picture of the behavior of the disease in the pediatric population. Half of our patients required admission. This high figure could be explained by the nature of our institution and the complexity of our patients, as well as our center's protocols for care and follow-up. Ferraro et al. (19) in a single-center study in Argentina, found even higher admissions rates with a tally of 74.8%.

The performance of the diagnostic tests for COVID-19 infection, either antigen or RT-PCR, seems to be variable. Specifically, sensitivity is greatly influenced by the time elapsed since the onset of symptoms and the nasal swabbing (29). Moreover, significant false-negative rates and discordance between different RT-PCR have been described, although not in children (30, 31). In our case, 8% of tests were initially negative and this was even higher in PICU patients (29%). We believe that this is not negligible because COVID-19 infections are significantly contagious and entail confinements in affected patients. Thus, we hypothesize that a second test may be necessary to rule out or confirm the infection in critically ill patients with high clinical suspicion of COVID-19.

Hospital-acquired COVID-19 infections were rare (0.5%) and at a rate lower than previously estimated. For instance, Hendler et al. (20) found a frequency of 7.9% of nosocomial infections. We strongly believe that our diagnostic strategy contributed to these numbers. Since symptomatic patients were required to have two negative RT-PCRs for COVID-19, 48–72 h apart, for isolation measures to be lifted, the probability of hospital contagions was significantly lowered.

We found that 3% of patients suffered from MIS-C. Similar results have been reported in the series from Australia (1.3%) and Argentina (4.6%). On the other hand, a Peruvian study found higher rates of severe disease with 16.8% affected with MIS-C (18, 19, 32). Compared with other studies, our PICU admission rate (8%) was similar to that described by Ferraro et al. (18–20, 32, 33) (6.8%) and is rather average. PICU admissions figures range from 0.5 up to 28%.

A striking finding was that previously healthy patients were the ones mainly admitted to the PICU, although this has also been described in previous studies (10, 18). Besides, SARS-CoV-2 severe respiratory disease is rare in children when compared to adults and in our cohort was present in only 9 patients, 77% of whom had previous ailments.

A common complaint in neonates was apnea (80%), which prompted admission to the neonatal intensive care unit. These patients did not have a viral co-infection that frequently causes this symptom. This granted a greater risk in this population whit confirmed COVID-19 infection, a finding not described in other series (34). Regarding respiratory coinfection, the study by Wu et al. (35) reported similar germs but in different proportions; Mycoplasma infection being the most frequent in that series and RSV in ours.

Deaths were rare with an estimate of 0.8% and resembled those of most studies (19, 27, 36, 37). Patients with chronic illnesses such as pulmonary disease, immunodeficiencies, congenital heart disease, or neurological disease are more susceptible to death (22, 23, 38). Higher mortality rates have been reported and probably are explained by healthcare access constraints in the studied populations (18, 20).

Positive imaging findings were scarce in our series and general x-rays did not disclose abnormalities, except for patients in the PICU where pathological findings were the norm. Studies that have evaluated radiological variables differ somehow. Investigations carried out in Latin America and Spain found that peribronchial thickening, ground-glass opacities, consolidation, and vascular thickening were frequent (39, 40).

Patients were treated with immunomodulators, steroids and immunoglobulin, when severe infection or MIS-C ensued. In those cases with a diagnosis of asthma exacerbation, steroids were used. There are no other approved treatments for SARS-CoV-2 in Colombia.

An important limitation of this study is that being retrospective, we were sometimes unable to retrieve information for some variables. In addition, the study was conducted at a local and national reference center, which allows for selection bias, especially for critically ill patients.

In summary, this study provides insights into COVID-19 infection in children cared for at a high complexity hospital. By and large, the disease is mostly mild. However, a substantial number of patients required hospital or PICU admission. Therefore, specific arrangements should be implemented in these settings to confront the pandemic.

Finally, we found that, after an initially negative result, a second COVID-19 RT-PCR may be necessary to detect the infection in critically ill patients with a high clinical suspicion of the disease. This strategy may lower the rate of nosocomial infections.

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 Comité de Investigaciones y ética en Investigaciones del Hospital Pablo Tobón Uribe (Research and Research Ethics Committee of Pablo Tobón Uribe Hospital). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LN-S conceptualized and designed the study, performed the data collection, the statistical analyses, drafted the initial manuscript, and reviewed the final manuscript. CT-M conceptualized and designed the study, performed the data collection, drafted the initial manuscript, and reviewed the final manuscript. IM and EL-B performed the data collection, drafted the initial manuscript, and reviewed the final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SARS-CoV-2 B.1.1.529 (Omicron) Variant Causes an Unprecedented Surge in Children Hospitalizations and Distinct Clinical Presentation Compared to the SARS-CoV-2 B.1.617.2 (Delta) Variant

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Background: In the midst of successive waves of SARS-CoV-2 variants, the B.1.1.529 (omicron) variant has recently caused a surge in pediatric infections and hospitalizations. This study aimed to describe and compare the symptoms, explorations, treatment and evolution of COVID-19 in hospitalized children during the successive B.1.617.2 (delta) and B.1.1.529 (omicron) waves.

Methods: This observational study was performed in the Pediatric Pulmonology Department of a University Hospital in Paris, France. All hospitalized children aged between 0 and 18 years who tested positive for SARS-CoV-2 using reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swabs from July 15th to December 15th 2021 (delta wave), and from December 15th 2021 to February 28th 2022 (omicron wave) were included.

Results: In total, 53 children were included, 14 (26.4%) during the delta wave and 39 (73.6%) during the omicron wave (almost three times as many hospitalizations in half the time during the latter wave). During the omicron wave, hospitalized patients were mostly aged $<$ 5 years (90 vs. 71% of all the children during omicron and delta waves, respectively), and tended to have fewer underlying conditions (56 vs. 79% during omicron and delta waves, respectively, $p = 0.20$). The omicron variant was also responsible for a different clinical presentation when compared to the delta variant, with significantly higher and often poorly tolerated temperatures ($p = 0.03$) and increased digestive symptoms ($p = 0.01$). None of the three patients who were older than 12 years were fully vaccinated.

Conclusion: The dramatic increase in the hospitalization of children with COVID-19 and the modification of the clinical presentation between the latest delta and omicron waves require pediatricians to remain vigilant. It should also encourage caregivers to ensure vaccination in children older than 5 years, for whom the BNT162b2 COVID-19 vaccine has been deemed safe, immunogenic, and effective.

Keywords: COVID-19, children, SARS-CoV-2, delta variant, omicron variant, hospitalization

INTRODUCTION

In France and throughout the world, the surge in coronavirus diseases (COVID-19) caused by the variant of concern B.1.1.529 (omicron), reached a peak that was five to six times higher than that caused by any of the previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants (1–3). After an important decrease in the SARS-CoV-2 circulation in June 2021, the French public health agency observed a progression in infections due to the B.1.617.2 (delta) variant that began in mid-July (4). The later switch between the delta and omicron variants began in mid-December 2021 (5). Whereas the incidence of COVID-19 had been far lower in children than in adults, it multiplied in children more than eight times during the period of this change in the SARS-CoV-2 virus variant. Specifically, the incidence of COVID-19 increased from 634/100,000 in the age groups 0–9 and 10–19 years at the delta-wave peak (week 49, 2021) to 4,877 and 6,828/100,000, respectively, in the same age groups at the omicron-wave peak (week 3, 2022) (4).

However, concerns about the high infectivity of the omicron variant have been balanced by its apparent lower severity in adults, with less severe symptoms and decreased hospitalization rates (2, 6, 7). This reduction in disease severity has partly been attributed to the widespread use of COVID-19 vaccines in adults (8, 9).

In contrast, pediatricians observed a surge in pediatric hospitalizations due to COVID-19 during the omicron wave (5, 10, 11). In the United States and South Africa, the peak of child hospitalizations resulted in a patient load that was four times higher than during the delta wave, with the largest increase occurring in children under 4 years of age (12, 13). Further, more children needed hospitalization in the intensive care unit (ICU) and/or invasive ventilation (12, 13). Interestingly, the monthly hospitalization rate in children aged 12–17 years was six times higher in non-vaccinated patients than in fully vaccinated patients (13). Compared to the delta variant, the omicron virus appears to have a predilection for the upper respiratory airways and digestive tract (5, 12). Reports have also described atypical cases of convulsions and cerebral venous thrombosis in children, making this a variant of concern, especially for pediatricians (14, 15).

To date, few studies have compared children with SARS-CoV-2 infection during the delta and omicron waves. Moreover, for the development of vaccines for children, it is important to precisely describe how children are affected by successive waves (16). Therefore, this study aimed to describe and compare the symptoms, explorations, treatment, and evolution of COVID-19 in children during the delta and omicron waves.

PATIENTS AND METHODS

This observational study was performed in the Pediatric Pulmonology Department of the University Hospital Trousseau, Assistance Publique Hôpitaux de Paris (APHP) Paris, France. According to the information on SARS-CoV-2 circulation in France, the arrival of the B.1.617.2 (delta) variant began in mid-July 2021 and that of the B.1.1.529 (omicron) variant began in mid-December 2021 (5). As such, patients between 0 and 18 years of age hospitalized in this department for COVID-19 between July 15th 2021 (arrival of the delta wave) and February 28th 2022 (end of the omicron wave) were identified using the hospital's *"Programme de Médicalisation des Systèmes d'Information"* (PMSI) database. This allowed for an exhaustive search of all children testing positive for SARS-CoV-2 by real-time reverse transcription polymerase chain reaction (RT-PCR) using nasopharyngeal swabs, who were admitted to this hospital. The study was approved by the local ethics committee of our institution, which waived the need for patients' consent (Study PED_COVID N°20200717191204).

Patient information was retrieved from medical records, including COVID-19 transmission history, clinical, biological (blood tests and viral RT-PCR findings) and radiological information, and the medical evolution. Considering the SARS-CoV-2 variant circulation in France, children hospitalized between July 15th 2021 and December 15th 2021 were included in the "delta-group," and children hospitalized between December 16th 2021 and February 28th 2022 were in the "omicron-group."

Continuous data were expressed as median [interquartile range (IQR)], while categorical data were expressed as numbers and proportions (%). Descriptive statistics are presented for all study variables. We used Fisher's exact test or Pearson's chi-squared test (with Yates' continuity correction when necessary) to compare categorical and qualitative data and implemented the Wilcoxon rank sum test to evaluate continuous variables. A p-value of <5% was interpreted as evidence of a statistically significant difference. The analyses were performed using SAS software (version 9.4; Cary, NC, USA).

RESULTS

Distribution of the Hospitalizations According to SARS-CoV-2 Waves and to Age

The total number of children hospitalized monthly for COVID-19 between 1 January 2021 and 28 February 2022 is presented in **Figure 1**. During the study period (July 15th 2021 to February 28th 2022), 53 children aged 0–18 years were hospitalized for

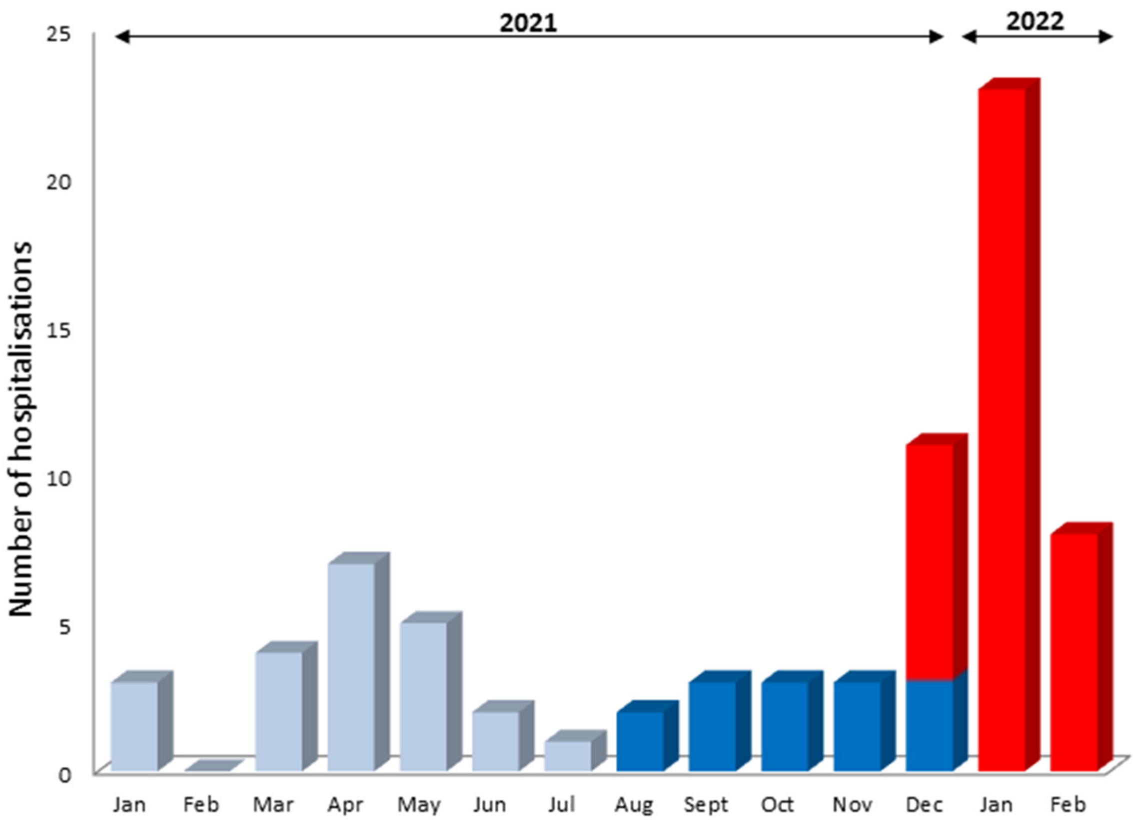

FIGURE 1 | COVID-19 associated hospitalizations in children (January 2021–February 2022). Light blue (January 1st–August 31st 2021): alpha, beta, and gamma waves; deep blue (August 1st–December 15th 2021): delta wave; red (December 15th 2021–February 28th 2022): omicron wave.

COVID-19 in our Pediatric Pulmonology Department. Among them, 14 (26.4%) were included in the delta group and 39 (73.6%) in the omicron group, while the duration of the study period was double that of the omicron wave. Indeed, the first group extended over 5 months (i.e., from July 15th to December 15th, 2021), whereas the second only over 2.5 months (i.e., from December 15th 2021 to February 28th 2022). While all of the 53 included children had positive PCR for SARS-CoV-2 in nasopharyngeal swab, only part of the SARS-CoV-2 variants were identified by Novaplex[TM] SARS-CoV-2 Variants I and IV Assays (Seegene, South Korea). Among the 14 children of the delta group, 7 (50%) were confirmed SARS-CoV-2 delta variant; and among the 39 children of the omicron group, 22 (56%) were confirmed SARS-CoV-2 omicron variant.

The distribution of hospitalizations according to age group (<5, 5–11, and >11 years) is reported in **Figure 2**. Of the three patients in the omicron group who were older than 12 years, none were fully vaccinated. Two of them had not been vaccinated, and one had received an incomplete vaccination with only one injection 2 weeks prior to the onset of symptoms.

Baseline Clinical Characteristics

The patients' baseline clinical characteristics according to the wave group are detailed in **Table 1**. During the omicron wave, hospitalized patients were mostly aged < 5 years (90 vs. 71% during the omicron and delta waves, respectively), and tended to have fewer pre-existing conditions (56 vs. 79% during the same period, respectively, $p = 0.20$). During the delta wave, 5/14 infants (36%) aged <3 months were hospitalized, compared to 8/39 (20%) during the omicron wave.

TABLE 1 | General characteristics of the children hospitalized for COVID-19 during the delta and omicron waves.

	Delta wave[a]	Omicron wave[b]	*p*-value
Patients (*n*)	14	39	
Age (years): median [IQR]	0.6 [0.1; 6.5]	0.6 [0.3; 1.6]	0.97
Age class (*n*, %)			0.18
<5 yrs	10 (71%)	35 (90%)	
> 5 yrs	4 (29%)	4 (10%)	
Male (*n*, %)	10 (71%)	26 (67%)	>0.99
Pre-existing condition, i.e. underlying comorbidity or age < 3 months (*n*, %)	11 (79%)	22 (56%)	0.14

[a] *Delta wave: from July 15th to December 15th, 2021.*
[b] *Omicron wave: from December 15th 2021 to February 28th 2022.*

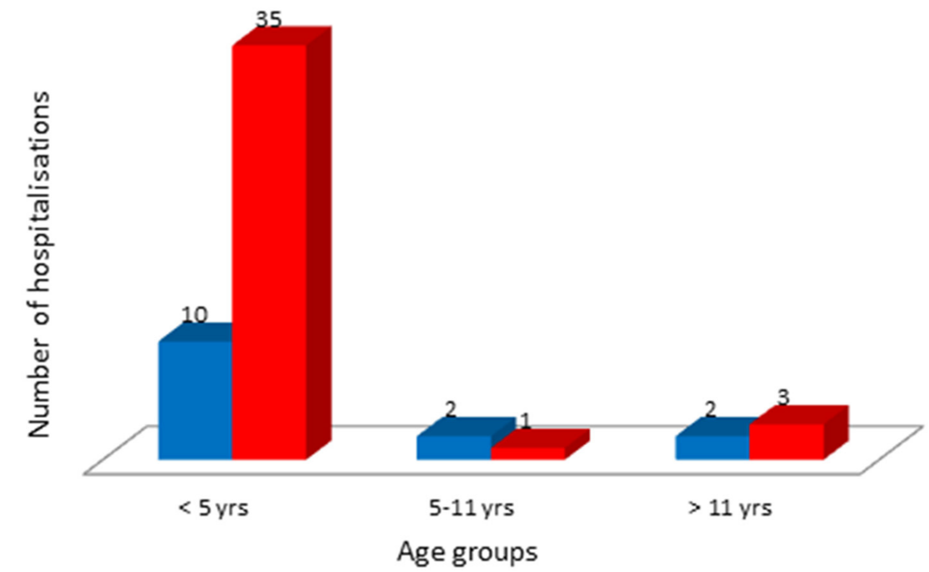

FIGURE 2 | Distribution of children hospitalized for COVID-19 per age class. Deep blue (August 1st–December 15th 2021): delta wave; red (December 15th 2021–February 28th 2022): omicron wave.

In the delta group, the large majority of patients (11/14, 79%) had a pre-existing condition such as asthma, interstitial lung disease, congenital myopathy, obesity, Crohn's disease, and sickle cell disease; and 5 were infants under 3 months of age. In the omicron group, 22/39 (56%) children had an underlying condition: 7 had a respiratory disease (asthma, tuberculosis, cystic fibrosis, bronchodysplasia, interstitial lung disease, Langerhans histiocytosis, and Schwachman-Diamond syndrome), 2 a hematologic disease (sickle cell disease, Hodgkin's lymphoma), 2 a genetic disorder (Prader-Willi, CHARGE syndrome), one a cardiologic defect (pulmonary valvular stenosis), and 8 were infants under 3 months of age.

Clinical Presentation and Explorations at COVID-19 Onset

The clinical presentation at COVID-19 onset is described in **Table 2**. The omicron variant caused significantly more digestive symptoms, such as diarrhea (33% vs. 0) during the omicron and delta waves respectively ($p = 0.01$), and refusal to eat (46 vs. 7%) during the omicron and delta waves respectively ($p = 0.01$). No patient in the omicron group presented with hemoptysis, compared to three patients (21%) in the delta group ($p = 0.01$). Body temperature was significantly higher during infections with the omicron variant than in those with the delta variant [39.2°C (38.9; 39.4) vs. 38.5°C (38.5; 38.7), respectively; $p = 0.02$]. Although not statistically significant, the proportion of children with poor symptom tolerance and deterioration of general health status was higher in the omicron group (59 vs. 36%) during the omicron and delta waves respectively, $p = 0.21$.

Detailed information on the main explorations performed at admission is provided in **Table 3**. Six children (50%) were co-infected with other respiratory viruses during the delta wave and 22 (63%) during the omicron wave (details on the different viruses are provided in **Table 3**). Chest X-ray and thoracic CT-scan, when abnormal, were similar in both groups, with features of lung consolidation without specific localization. One patient in the delta group presented with pleural effusion and one in the omicron group with bilateral pneumothorax. No pulmonary embolisms were observed during these waves in our department.

Management and Evolution

The management and clinical evolution are detailed in **Table 4**. Two patients (14%) required nutritional support during the delta wave and 11 (28%) during the omicron wave. During the latter period, the median [IQR] duration of nutritional support was 2 [1.25; 3] days. There were no differences in patient management or disease evolution between the two groups. Two patients (one during the delta wave and one during the omicron wave) were already on home oxygen therapy and non-invasive ventilation due to chronic respiratory insufficiency prior to hospitalization for COVID-19. For both, oxygen or ventilation needs increased respectively during 2 and 11 days before returning to previous support levels.

DISCUSSION

This study compared the incidence and clinical symptoms of children hospitalized for COVID-19 during the delta and omicron waves. During the omicron wave, there was a major increase in the number of hospitalizations, with almost three times as many hospitalizations in half the time when compared to the delta variant, with the vast majority of children younger than 5 years. There were also distinct clinical characteristics, with higher temperature and poorly tolerated fever and a predilection for upper respiratory airways and digestive symptoms during the omicron wave.

TABLE 2 | Clinical presentation of the children hospitalized during the delta and omicron waves at COVID onset.

	Delta wave[a]	Omicron wave[b]	*p*-value
General symptoms			
Fever (*n*, %)	11 (79%)	29 (74%)	>0.99
Poor fever tolerance (*n*, %)	2 (18%)	8 (28%)	>0.99
Fever duration [days, median (range)]	1 (1; 15)	2 (1; 9)	>0.99
Fatigue/deterioration of general status (n, %)	5 (36%)	23 (59%)	0.21
Respiratory symptoms			
Cough (*n*, %)	9 (64%)	26 (67%)	>0.99
Dyspnea (*n*, %)	9 (64%)	20 (51%)	0.53
Hemoptysis (*n*, %)	3 (21%)	0	0.02
Upper respiratory airway			
Acute rhinitis (*n*, %)	6 (43%)	23 (59%)	0.36
Pharyngitis (*n*, %)	1 (7%)	7 (18%)	0.67
Laryngitis (*n*, %)	0	3 (8%)	0.56
Digestive symptoms			
Vomiting (*n*, %)	1 (7%)	9 (23%)	0.26
Diarrhea (*n*, %)	0	13 (33%)	0.01
Refusal to eat (*n*, %)	1 (7%)	18 (46%)	0.01
Initial vital signs			
Highest temperature (°C) [median (IQR)]	38.5 [38.5; 38.7]	39.2 [38.9; 39.4]	0.03
Respiratory rate (/min) [median (IQR)]	42 [24; 54]	46 [35; 50]	0.53
Oxygen saturation (%)[median (IQR)]	98 [94; 99]	98 [95; 99]	0.93
Cardiac rate (/min) [median (IQR)]	135 [123; 151]	143 [133; 157]	0.31

[a]*Delta wave: from July 15th to December 15th, 2021.*
[b]*Omicron wave: from December 15th 2021 to February 28th 2022.*

TABLE 3 | Results of the main explorations performed at admission of the children hospitalized for COVID-19 during the delta and omicron waves.

	Delta wave[a]	Omicron wave[b]	*p*-value
Nasopharyngeal result on PCR assay			
Positive for SARS-CoV-2 (*n*, %)	14 (100%)	39 (100%)	
Positive for ≥1 other respiratory viruses (%)*	6/12 (50%)	22/35 (63%)	0.75
Respiratory Syncytial virus (*n*)	3	2	
Rhinovirus (*n*)	0	10	
Influenza virus (*n*)	0	3	
Parainfluenza (*n*)	2	2	
Coronavirus (*n*)	1	3	
Bocavirus (*n*)	0	6	
Adenovirus (*n*)	0	1	
Metapneumovirus (*n*)	0	1	
Thoracic imaging			
Chest radiography			
Number of patients, % of abnormal results	5 (60%)	26 (38%)	0.63
Computed tomography			
Number of patients, % of abnormal results	6 (100%)	3 (33%)	0.08
Blood tests [median (IQR)]			
WBC (x10^9/L)	7.5 [4.5; 9.4]	10.5 [7.1; 14.3]	0.26
Lymphocytes (x10^9/L)	2.4 [1.9; 2.6]	3.2 (1.4; 5.4]	0.32
Neutrophils (x10^9/L)	1.5 [0.7; 5.4]	3.1 [1.8; 8.0]	0.26
Hemoglobin (g/dL)	11.5 [10.7; 12.5]	11.1 [10.0; 11.8]	0.29
Platelets (x10^9/L)	318 [241; 387]	312 [256; 388]	0.73
CRP (mg/L)	8 [5; 20]	7 [0; 42]	0.72

**These analyses were performed by means of Allplex Respiratory Panel Assays (Seegene).*
[a]*Delta wave: from July 15th to December 15th, 2021.*
[b]*Omicron wave: from December 15th 2021 to February 28th 2022.*

According to the World Health Organization (WHO) data, the omicron variant has been responsible for five to six times more confirmed SARS-CoV-2 infections in Europe and America (1). Although it has been suggested that the omicron variant is associated with lower hospitalization rates due to a suspected reduction in disease severity, this wave has caused an important increase in the number of hospitalizations in children (1, 7, 11–13). This is in line with the surge in the number of hospitalizations for COVID-19 observed in our pediatric pulmonology department, which almost tripled between the two waves in half of the time. The higher infectivity of the omicron variant has been attributed to an exceptional number of mutations in the spike glycoprotein-binding human ACE2, resulting in increased infectivity of nasal epithelial cells and ACE2-positive cells (3, 17). These alterations in virus conformation influence antibody neutralization and facilitate viral immune escape, making it a variant of concern (3, 18).

In the light of these findings, questions have arisen regarding the vaccine efficacy. Although studies have suggested a decrease in vaccine-induced immunity after the second dose, others have shown that boosters can restore neutralizing immunity (19–21). Lauring et al. showed in adults that three doses of mRNA vaccine were necessary to obtain the same protection for the omicron variant as that provided for other variants after two doses (22). Similar results were observed in immunocompetent adolescents (12–17 years old), where vaccine efficacy toward the omicron variant was restored after three doses (23). In our study, none of the three patients older than 12 years hospitalized during the omicron wave were fully vaccinated. This result, along with the observation by others that children were more susceptible to infections/reinfections during the omicron wave despite vaccination or previous infection, requires that children be vaccinated when possible, and this includes the need for the booster dose (13, 24). This is supported by the 6-fold increase in the monthly hospitalization rate in non-vaccinated adolescents compared to that in vaccinated children during the omicron wave (13).

Along with the increased number of child hospitalizations, the symptoms observed at COVID-19 onset were somewhat different when subsequently infected by the omicron variant or by the delta and previous variants (12, 25–28). In Italian children, an analysis of online search trends suggested increased upper respiratory airway symptoms and possibly poorly tolerated fever, whereas dyspnea and anosmia/ageusia seemed less frequent (25). The latter finding could also be an indicator of the younger age of infected children and their inability to report such

TABLE 4 | Management and evolution of the children hospitalized for COVID during the delta and omicron waves.

	Delta wave[a]	Omicron wave[b]	*p*-value
Symptoms prior to hospitalization			
Duration (days): median (IQR)	3 (2; 3.8)	3 (2, 4)	0.63
Hospitalization duration (days): median (IQR)	2.5 (2.0; 3.8)	3.0 (2.0; 4.8)	0.29
Intensive Care Unit (*n*, %)	0	4 (10%)	0.56
Oxygen therapy (*n*, %)	5 (36%)	12 (31%)	0.75
Oxygen therapy duration [days, median (IQR)]	2.0 (1.0; 2.0)	3 (1.5; 9.0)	0.18
Non-invasive ventilation (*n*, %)	0	3 (8%)	>0.99
Invasive ventilation (*n*, %)	0	2 (5%)	>0.99
Nutritional support (*n*, %)	2 (14%)	12 (31%)	0.31

[a]*Delta wave: from July 15th to December 15th, 2021.*
[b]*Omicron wave: from December 15th 2021 to February 28th 2022.*

symptoms. Indeed, we found that hospitalized children were mostly aged under 5 years (90% during the omicron wave and 71% during the delta wave). We observed similar symptoms at the onset of infection to those reported by Cloete et al. in South African children (12). As such, we found that omicron caused significantly higher temperatures, diarrhea, and refusal to eat. The rate of underlying conditions was also in agreement with that reported by Cloete et al., with only 56% of the children hospitalized during the omicron wave vs. 79% during the delta wave. Similar to other studies, this study observed slightly more frequent upper respiratory airway symptoms during omicron waves (29, 30). The higher susceptibility to target upper airways could be a real concern in young children, a population prone to severe upper airway infections due to a smaller respiratory tract (29). A recent retrospective cohort study showed results similar to ours, with adults infected by the omicron variant being younger, with less frequent comorbidities and dyspnea, and more frequent upper respiratory airway symptoms (31). Finally, although these symptoms were not observed in this study, others have highlighted the risk of convulsions and venous cerebral thrombosis in children infected with the omicron variant (12, 15). Nevertheless, neurological signs have already been described in previous waves and should remain a cause of concern in children (27, 28).

The main limitation of this study is its retrospective and monocentric nature, which led to small number of inclusions. However, the scarce literature on the infections caused by the omicron variant in children makes it important to report the clinical features in the pediatric population and the specificities compared to previously described waves.

In conclusion, during the omicron wave, there was a major increase in the number of hospitalizations of children for COVID-19. These children were mostly under 5 years of age, younger than during previous waves (27). Unfortunately, children under 5 years of age cannot benefit from the vaccination as available SARS-CoV-2 vaccines are recommended for older children. Although the BNT162b2 COVID-19 vaccine has been deemed safe, immunogenic, and effective in preventing COVID-19 infection (16), concerns have arisen regarding the risk of myocarditis, especially in adolescents (32–35). This could explain why vaccination rates remain low in children aged 5–11 years old (36). For example in France, although the BNT162b2 COVID-19 vaccine is available for the children aged 5–11 years old since December 22, 2021, only 5% received at least one dose of as of April 29, 2022. Thus, describing the continuous evolution of COVID-19 symptoms and severity in children is essential for improving vaccination adherence.

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 Local Ethics Committee of our institution, which waived the need for patients' consent (Study PED_COVID N°20200717191204). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JT, BP, and HC were involved in the methodology, formal analysis, investigation, data curation, writing the original draft, reviewing and editing the manuscript, designing of tables and graphs, and verified the underlying data. AS, GA, LBe, LBi, AD-A, GT, and NN data were involved in data provision and reviewing and editing the manuscript. All authors had full access to all data in the study and accept responsibility for the decision to submit for publication.

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Disruptions to routine childhood vaccinations in low- and middle-income countries during the COVID-19 pandemic: A systematic review

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Background: The COVID-19 pandemic has disrupted routine childhood vaccinations worldwide with low- and middle-income countries (LMICs) most affected. This study aims to quantify levels of disruption to routine vaccinations in LMICs.

Methods: A systematic review (PROSPERO CRD42021286386) was conducted of MEDLINE, Embase, Global Health, CINAHL, Scopus and MedRxiv, on the 11th of February 2022. Primary research studies published from January 2020 onwards were included if they reported levels of routine pediatrics vaccinations before and after March 2020. Study appraisal was performed using NHLBI tool for cross-sectional studies. Levels of disruption were summarized using medians and interquartile ranges.

Results: A total of 39 cross-sectional studies were identified. These showed an overall relative median decline of −10.8% [interquartile range (IQR) −27.6%, −1.4%] across all vaccines. Upper-middle-income countries (upper-MICs) (−14.3%; IQR −24.3%, −2.4%) and lower-MICs (−18.0%; IQR −48.6%, −4.1%) showed greater declines than low-income countries (−3.1%; IQR −12.8%, 2.9%), as did vaccines administered at birth (−11.8%; IQR −27.7%, −3.5%) compared to those given after birth (−8.0%; IQR −28.6%, −0.4%). Declines during the first 3 months of the pandemic (−8.1%; IQR −35.1%, −1.4%) were greater than during the remainder of 2020 (−3.9%; IQR −13.0%, 11.4%) compared to baseline.

Conclusion: There has been a decline in routine pediatric vaccination, greatest in MICs and for vaccines administered at birth. Nations must prioritize catch-up programs alongside public health messaging to encourage vaccine uptake.

Systematic review registration: Identifier: CRD42021286386.

KEYWORDS

immunization, routine vaccines, LMICs, child health, vaccine-preventable diseases, vaccination hesitancy

Background

The Coronavirus Disease 2019 (COVID-19) pandemic (hereafter, "the pandemic") and its control measures have disrupted access to healthcare globally. A systematic review performed during the first months of the pandemic found an overall 37% reduction in health service utilization, including hospital admissions, diagnostic and treatment services, highest during March and April 2020 (1). In May 2020, the World Health Organization (WHO) released the first Pulse Survey amongst Ministry of Health officials globally; nearly 90% reported disruptions to essential health services (2). Disruptions were greater in low-income countries (LICs) than high-income countries (HICs) (2). Immunization services were amongst those most frequently reported to be affected (2), with UNICEF estimating that 23 million children did not receive routine vaccinations during 2020; 3.7 million more than in 2019 (3).

Two further Pulse Surveys were published in May 2021 (4) and February 2022 (5). These showed that over 90% of countries reported continued healthcare disruptions. Of particular importance is the increased disruption to immunization services; whilst in May 2021 over one third of nations reported disruptions to immunization services (4), this rose to nearly half of nations in the subsequent survey (5). These findings raise concern regarding vaccine-preventable childhood morbidity and mortality. A modeling study by researchers at Johns Hopkins School of Public Health estimated a possible 9.8–44.7% increase in monthly deaths in children under-5 years caused by pandemic-related disruptions to healthcare, including vaccinations (6).

Routine vaccinations are fundamental for the health of children. A modeling study, investigating 10 pediatric vaccines, predicted that between 2000 and 2019, ~37 million deaths were prevented in low- and middle-income countries (LMICs) through vaccination (7). This represents a 45% decrease in mortality compared to a no-vaccine scenario, with most of the avoided deaths in children under 5 years (7). Most vaccines in this study are part of the WHO list of universally recommended immunizations, which include: Bacille Calmette-Guérin (BCG), Hepatitis B, Polio, diphtheria-tetanus-pertussis-containing (DTP) including Pentavalent, *Haemophilus influenzae* type b, Pneumococcal (conjugate), Rotavirus, Measles-containing (MCV), Rubella and Human Papillomavirus (HPV) vaccinations (8). Widespread access to these vaccines is essential to achieve universal health and wellbeing—part of Sustainable Development Goal (SDG) 3—in addition to other SDGs indirectly, including the reduction of poverty, malnutrition and achieving economic prosperity (9, 10). However, prior to the pandemic, the WHO had already highlighted large disparities in vaccine coverage worldwide. For example, in 2019, coverage of the third dose of DTP vaccine was only 73% in Africa, compared to 95% in Europe (11); inequalities which may widen with pandemic-related disruptions (9, 10, 12, 13).

Given a lower initial coverage of routine vaccinations, greater disruptions to healthcare during the pandemic, higher burden of vaccine-preventable diseases and lower available financial and infrastructural resources, LMICs are likely to encounter further challenges in the recovery of missed vaccinations (2, 4, 5, 11, 12). Gaining insight into the extent of pandemic-related disruptions to vaccination services is essential to plan effective catch-up vaccination programs, avoid vaccine-preventable disease epidemics and establish guidance to prevent disruptions in future global health emergencies. Therefore, the aim of this study is to measure the impact of the COVID-19 pandemic on routine childhood vaccination in LMICs.

Methods

A systematic review of published and pre-print literature were performed.

Search strategy

Six databases were searched: Medline, EMBASE and Global Health *via* Ovid, CINAHL, and Scopus. No field limits were applied. MedRxiv titles and abstracts were also searched, using the "medrxivr" package on R (14, 15). All searches were performed on the 11th of February 2022 and limited to publications from January 2020 onwards. The search strategy contained three concepts: COVID-19, immunization and specific vaccines or vaccine-preventable diseases (Supplementary Table S1). Additionally, a concept on general terms for routine vaccines was included, using proximity Boolean terms. This limited the number of irrelevant results, namely those related to COVID-19 vaccines. The search contained relevant keywords, including variations, and subject headings (Supplementary materials 2–7 contain full search strategies).

References of all relevant reviews, meeting and conference summaries, and all included studies, were screened for inclusion. Full-text versions of relevant abstracts were searched for in the previously mentioned databases and relevant journals. If unavailable, abstract authors were contacted to request access to full-texts.

Inclusion and exclusion criteria

Primary research studies reporting the levels, or changes in levels, of vaccine coverage or administration before (any time between January 2015 to March 2020) and during the pandemic (March 2020 onwards) in LMICs were included. Studies had to include data for LMICs regarding any vaccine universally recommended by the WHO, published from 2020 onwards. Non-primary research and modeling studies, such as those predicting the impact of the pandemic on future vaccination levels without accompanying observed measurements, were excluded. Language restrictions were only applied at full-text stage; studies not in English, Portuguese, French or Spanish were translated to English using Google Translate. Studies were only excluded if the translation was unclear.

Result screening and selection

Deduplication was performed on EndNote 20, and then Covidence, where screening was undertaken. Given the high number of identified studies, initial screening was performed by title to exclude clearly irrelevant results, followed by abstract. Eligibility was confirmed in full-text review. Screening was performed by two reviewers independently with discrepancies resolved by consensus.

Data extraction and quality assessment

Data were extracted from included studies using a pre-defined data extraction sheet designed on Microsoft Excel, including the following parameters: publication details (doi, authors, title, year published), study details (design, scope, data source, sample size, location(s) of study, country income-level classification, population, sampling methods, funding, conflicts of interest), outcome of interest details (date span of data in pre-COVID and COVID periods, use of controls, vaccines included, outcome title and outcome units), results for each outcome of interest, methods of analysis and conclusions. Outcomes of interest included number of vaccines administered pre- and during COVID-19 pandemic; vaccine coverage—defined as the number of individuals receiving a certain vaccine as a percentage of the target population for that vaccine in a specific time-period—pre- and during COVID-19 pandemic; and proportional or percentage change in either outcome. Where available, outcomes pre- and during COVID-19 pandemic were extracted per smallest unit of time available, usually per month. Where data were only available in graphical format, WebPlotDigitizer 4.5 (16) was used for extraction.

Studies underwent quality and bias assessment using National Heart, Lung and Blood Institute (NHLBI) checklist for observational studies (17). Data from 8 randomly selected studies (20% of total) were extracted by two reviewers. Given that all data extracted was identical, the remaining extractions were performed by a single reviewer. Bias assessments were performed fully by two reviewers and discrepancies resolved by consensus.

Data synthesis and analysis

As there are no universally-accepted guidelines for conducting systematic reviews and meta-analyses of proportional changes, a guide published in BMC Medical Research Methodology (18), the Cochrane Handbook for Systematic Reviews of Interventions (19) and COSMOS-E guidelines (20) were consulted and adapted as appropriate.

Although a meta-analysis was planned it was not performed because studies were found to have substantial methodological variation, including in the vaccines studied, scope of data and locations. Furthermore, only a minority of studies reported uncertainty levels and other data required for meta-analysis. Instead, studies were summarized using medians and interquartile ranges (IQRs). The outcome unit was mean relative percentage change between levels of vaccination pre-COVID-19 pandemic (from January 2015 to February 2020) and during the pandemic (April 2020 to December 2021). Where percentage changes were not reported, these were calculated using pre-pandemic and pandemic values. Timelines for each study varied according to availability of data (Supplementary Figure S2). March 2020 was excluded from studies that reported data per month as this was considered a transition point.

Subgroup analyses by timing of vaccination (birth or afterwards), individual routine vaccine, WHO world region and income-level were performed. Results were also subdivided by decline during the first 3-months of the pandemic (April-June 2020) and the remainder of the pandemic, to identify potential recovery. The data extraction sheet on Microsoft Excel was used to determine which studies could be included in each subgroup.

Registration

This systematic review was registered on PROSPERO (CRD42021286386) and followed PRISMA 2020 guidelines (Supplementary Tables S3, S4) (21, 22).

Protocol changes

Amendments to chosen databases were instituted after consultation with an expert librarian. This included the removal of Web of Science, as this had significant overlap with Scopus and the addition of MedRxiv for pre-prints.

Results

Following the screening of 7,705 studies, 39 were included in the review (Figure 1).

All studies were cross-sectional, utilizing data from health records (Table 1). Most reported levels of administered

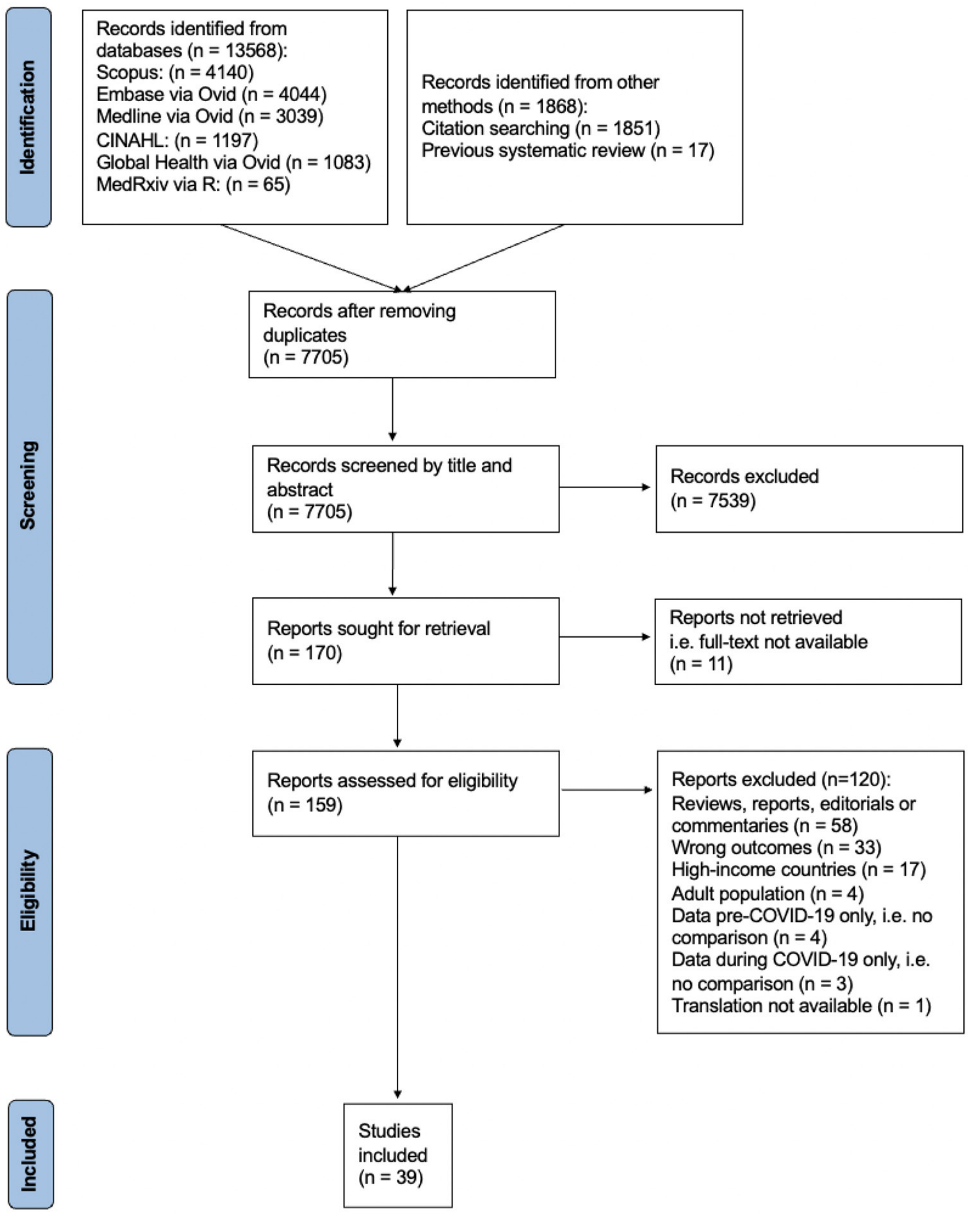

FIGURE 1
PRISMA flow diagram summarizing identification, screening, exclusion, and inclusion of studies (see Supplementary Figure 1 for detailed PRISMA 2020 flow diagram).

vaccines (n = 29) and the remainder reported vaccine coverage. Studies spanned 6 WHO regions unevenly, with Africa (53.8%) being the most common. Additionally, several countries appear repeatedly in different studies (Supplementary Table S2). Most studies reported national-level data (n = 17) or data from multiple health centers or regions (n = 11); the remainder were single-center studies and one survey-based study with unclear scope. Data were available for all WHO universally recommended vaccines apart from HPV, with levels of pentavalent or DTP (n = 33), MCV (n = 27) and BCG (n = 20) vaccines most frequently reported.

Timelines varied across studies (Supplementary Figure S2), with the median timespan being January 2019 (IQR: December 2017–July 2019) to September 2020 (IQR: June 2020–November 2020).

Overall, the quality of most studies was moderate; few studies considered confounders such as seasonality and

TABLE 1 Summary of study characteristics for studies reporting changes to vaccination levels ($n = 39$).

		All identified studies	
		Number of studies (%)	Study references
Study design	Cross sectional	39 (100.0)	(23–61)
WHO world region	African Region (AFR)	21 (53.8)	(23, 25, 26, 28–31, 33, 35, 37, 39, 40, 42, 46, 47, 52–55, 59, 61)
	Region of the Americas (AMR)	11 (28.2)	(24, 34–36, 38, 48, 51, 54, 57, 58, 60)
	Eastern Mediterranean Region (EMR)	8 (20.5)	(27, 32, 45, 49, 50, 53, 54, 56)
	South-East Asian Region (SEAR)	3 (7.7)	(43, 44, 54)
	Western Pacific Region (WPR)	1 (2.6)	(54)
	European Region (EUR)	1 (2.6)	(41)
Income level	Low-income countries (LICs)	14 (35.9)	(23, 25, 29, 31, 35, 37, 39, 42, 45–47, 49, 53, 61)
	Lower-middle-income countries (lower-MICs)	17 (43.6)	(26–30, 32, 33, 35, 43, 44, 46, 50, 52, 53, 55, 56, 59)
	Upper-middle-income countries (upper-MICs)	13 (33.3)	(24, 29, 34, 36, 38, 40, 41, 46, 48, 51, 57, 58, 60)
Scope of data	Multinational	1 (2.6)	(54)
	National	17 (43.6)	(24, 25, 28, 29, 34, 36, 38, 45, 46, 48, 51–53, 55, 57, 58, 61)
	Multicenter (national)	11 (28.2)	(23, 26, 27, 32, 35, 39–42, 49, 56)
	Single center (national)	9 (23.1)	(30, 31, 33, 37, 43, 44, 50, 59, 60)
	Unclear/NA	1 (2.6)	(47)
Data source	Health records/database (at government or local authority level)	25 (64.1)	(23–29, 32, 34, 36, 38–41, 45, 48, 49, 51–53, 55–58, 61)
	Health records/database (at hospital or medical center level)	9 (23.1)	(30, 31, 33, 42–44, 50, 59, 60)
	NGO records	2 (5.1)	(46, 54)
	Survey	1 (2.6)	(47)
	Unclear	2 (5.1)	(35, 37)
Vaccines	Pentavalent or Diphtheria-Tetanus-Pertussis vaccine (DTP)	33 (84.6)	(23–36, 38, 39, 41–46, 48–50, 52–55, 57, 58, 60, 61)
	Measles-containing vaccine (MCV)	27 (69.2)	(25–36, 38, 40–44, 46, 48, 50–52, 54, 57, 60, 61)
	Bacillus Calmette-Guérin vaccine (BCG)	20 (51.3)	(24, 26, 30–32, 34, 35, 38, 39, 41, 43, 44, 46, 48, 50, 52, 53, 57, 58, 61)
	Pneumococcal vaccine	12 (30.8)	(24–26, 31, 32, 34, 35, 38, 39, 48, 58, 61)
	Rotavirus vaccine	11 (28.2)	(24, 31, 32, 34, 35, 38, 43, 44, 48, 50, 61)
	Polio vaccine (any, including unspecified)	14 (35.9)	(24, 26, 31, 32, 34, 35, 39, 41, 43, 44, 48, 50, 57, 61)
	Oral polio vaccine (OPV)	9 (23.1)	(26, 31, 32, 39, 41, 43, 44, 50, 61)
	Inactivated poliovirus vaccine (IPV)	7 (17.9)	(26, 31, 43, 44, 48, 57, 61)
	Hepatitis B vaccine	9 (23.1)	(24, 26, 34, 41, 43, 44, 48, 50, 57)
	Multiple vaccines (i.e., reporting two or more vaccines combined)	11 (28.2)	(30, 32, 33, 37, 42, 43, 47, 51, 52, 56, 59)
Extracted outcomes	**Vaccine administration**	**29 (74.4)**	(23, 24, 27, 30–33, 35–40, 42–46, 49–56, 59–61)
	Observed values	12 (30.8)	(24, 30, 31, 33, 37, 45, 46, 51, 56, 59–61)
	Mean values	10 (25.6)	(23, 32, 38, 40, 42, 44, 49, 50, 52, 55)
	Percentage difference	9 (23.1)	(27, 30, 32, 36, 37, 40, 43, 50, 54)
	Adjusted percentage difference	3 (7.7)	(35, 51, 53)
	Other	2 (5.1)	(36, 39)
	Vaccine coverage	**10 (25.6)**	(25, 26, 28, 29, 34, 41, 47, 48, 57, 58)
	Observed values	7 (17.9)	(25, 28, 29, 47, 48, 57, 58)
	Mean values	2 (5.1)	(26, 34)
	Percentage difference	3 (7.7)	(29, 41, 47)
Comparison timeline	Same months*	23 (69.0)	(23–25, 29–31, 34, 37, 41–43, 45–49, 54, 55, 57–61)
	Different months	16 (41.0)	(26–28, 32, 33, 35, 36, 38–40, 44, 50–53, 56)

See Supplementary Table B2.1 for individually reported study characteristics. The bold values indicate the different ways of reporting vaccine administration or vaccine coverage.
*Yearly coverage assumed to be same months, unless otherwise stated.

population changes, and most did not report total population of the study or participation rates (Figure 2).

The overall median relative percentage change was −10.8% (IQR −27.6%, −1.4%) (Figure 3). This value was calculated using 331 observations, representing 45 countries (Table 2). The decline in studies reporting numbers of vaccines administered (−13.2%, IQR −44.7%, −2.0%) was greater than those reporting vaccination coverage (−3.5%, IQR −15.7%, 0.0%).

The median decline was greater in upper-middle income countries (MICs) (−14.3%, IQR −24.3%, −2.4%) and lower-MICs (−18.0%, IQR −48.6%, −4.1%) than LICs (−3.1%, IQR −12.8%, 2.9%) (Figure 4). There were 19 (70.4%) LICs represented in this analysis, compared to 12 (21.8%) and 14 (25.5%) upper-MICs and lower-MICs, respectively.

The WHO world regions showing the greatest declines were WPR (−41.0%; IQR −42.3%, −39.7%), EMR (−34.5%, IQR −51.4%, −19.1%) and SEAR (−28.6%, IQR −53.6%, −18.4%). Regions showing the least declines were EUR (−1.9%, IQR −2.4%, −1.2%), followed by AFR (−4.0%, IQR −14.1%, 2.2%). However, whilst 35 countries from the AFR region were included in this analysis, the remaining regions had 6 or fewer represented countries [excluding Shet et al. (54)]. The study by Shet et al. (54) is an observational study summarizing global WHO vaccination coverage data which was included in the analysis for AFR, AMR, EMR, SEAR and WPR regions.

Vaccines administered at birth showed a median decline of −11.8% (IQR −27.7%, −3.5%) and vaccines after birth a decline of −8.2% (IQR −28.8%, −0.6%). Vaccines showing the greatest degrees of decline were polio vaccines (−16.6%, IQR −50.9%, −3.9%) and rotavirus vaccines (−22.4%, IQR −45.2%, −6.9%). Those showing the least declines were PCV (−4.7%, IQR −31.1%, 0.8%), followed by MCV (−5.2%, IQR −21.2%, 1.7%) and DTP or pentavalent vaccines (−7.4%, IQR −23.9%, −0.1%).

Declines during the first three months of the pandemic, that is April to June 2020, were greater (−8.1%, IQR −35.1%, −1.4%) than declines during the remainder of the pandemic relative to baseline, for time periods available (−3.9, −13.0, 11.4%).

Discussion

Overall, a median decline of over 10% was seen in routine childhood vaccination in LMICs. Most countries represented in the analysis were from the WHO African region. Drops were greatest for vaccines given at birth, and in MICs. The drop in the first 3 months of the pandemic appears greater than later in the pandemic, suggesting a degree of recovery, although declines persist.

The decline in vaccination coverage corroborates findings from a previous systematic review which narratively synthesized evidence from LMICs and HICs in early 2021 (62), and the three WHO Pulse Surveys (2, 4, 5), all of which identified global disruptions to routine vaccination programs. The second Pulse Survey categorized results by income-level, also demonstrating that a greater proportion of MICs reported disruptions than LICs (4). Reasons for this are unclear, but maybe a consequence of publication bias, particularly as fewer MICs are represented in WHO data, and this study, than LICs. Alternative reasons to be explored include differences in stringency of COVID-19 measures, support from non-governmental organizations, such as the Global Alliance for Vaccines and Immunization (GAVI), and degrees of urbanization, particularly if these areas are found to have been more affected than rural areas.

This study found evidence that the median decline in vaccination during the first 3 months of 2020 was greater than the decline in the remainder of that year. This suggests there may have been some recovery in vaccination levels since the start of the pandemic, but declines persist. This corroborates findings from the third Pulse Survey; 53% of countries that participated in all three survey rounds reported disruptions to immunizations, compared to 56% in the first round, suggesting little improvement (5). By contrast, literature from England (63), France (64), Sweden (65), Japan (66) and the United States (67) suggests vaccination is recovering in these HICs, although not always returning to pre-pandemic levels. Data from these studies are from 2020; more recent data are needed for definitive conclusions on recovery. One study from Sierra Leone has since published data on vaccination declines until March 2021 by quarter. This dynamic analysis showed that despite improvements in vaccination levels in every quarter, most vaccines continued to show declines of over 10% by March 2021 (68). If recovery is greater in HICs than LMICs, these findings raise concern over potential widening of global inequalities in vaccination (13).

Given WHO recommendations to continue vaccination during the pandemic (69, 70), disruptions to maternal health services may explain part of the observed decline in vaccines delivered at birth. Observational studies from Bangladesh (71) and Nepal (72) have shown reductions in institutional deliveries of 10–20% and over 50%, respectively, during the first 3 months of the pandemic. By the end of 2021, 26% of countries still reported a decline in facility-based births to the WHO (5). The BCG vaccine was also thoroughly investigated for its use against COVID-19 (73), which may have led to temporary shortages in its supply, as was reported in Japan (74, 75). It is possible, however, that the finding that vaccines delivered in hospital soon after birth fell more than vaccines given in primary care later in infancy, is a result of the way data are collected and reported, or a function of the different studies included in this review.

The reasons behind disruptions to vaccinations are likely multifactorial. WHO findings suggest that 76% of reasons underlying disruptions to health-services stem from disruptions to healthcare service provision (5). A multinational study of IMPRINT members also identified fear of COVID-19 as a reason for delayed vaccination (76). Reasons for disruption are likely

NHLBI assessment: cross-sectional studies

Studies	1) Clear objectives	2) Clear population	3) Participation rate	4) Recruitment	5) Sample size/power/effect estimates	6) Exposure measurement before outcomes	7) Timeframe	8) Levels of exposure	9) Clear exposure	10) Exposure measurements	11) Clear outcomes	12) Blinding	13) Loss to follow-up	14) Controlling confounders	Overall score
Abdoulaye et al. (2021)	+	+	?	NA	+	NA	+	NA	+	NA	+	NA	?	−	M
Alves et al. (2021)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	+	G
Atim et al. (2021)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Babatunde et al. (2022)	+	+	?	NA	NA	NA	+	NA	+	NA	+	NA	?	−	M
Baloch et al. (2021)	+	+	?	NA	−	NA	−	NA	+	NA	+	NA	?	−	M
Barasa et al. (2021)	+	+	?	NA	+	NA	+	NA	+	NA	+	NA	?	−	M
Bello et al. (2021)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Bimpong et al. (2021)	+	+	+	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Buonsenso et al. (2020)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Chandir et al. (2020)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Chelo et al. (2021)	+	+	NA	NA	NA	NA	+	NA	+	NA	+	NA	NA	+	G
Colome-Hidalgo et al. (2021)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	+	G
Connolly et al. (2022)	+	+	?	NA	+	NA	+	NA	+	NA	+	NA	?	+	G
Doubova et al. (2021)	+	+	+	NA	+	NA	+	NA	+	NA	+	NA	?	+	G
Hategeka et al. (2021)	+	+	?	NA	+	NA	+	NA	+	NA	+	NA	?	+	G
Jensen et al. (2021)	+	+	+	NA	+	NA	+	NA	+	NA	+	NA	?	−	M
Kara et al. (2021)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Kassie et al. (2021)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Khan et al. (2021)	+	+	+	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Kinikar et al. (2021)	+	+	NA	NA	NA	NA	−	NA	+	NA	+	NA	NA	−	M
Kotiso et al. (2022)	+	+	−	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Masresha et al. (2020)	+	+	+	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Miretu et al. (2021)	+	+	+	NA	+	NA	+	NA	+	NA	+	NA	NA	+	M
Moreno-Montoya et al. (2022)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	+	G
das Neves Martins Pires et al. (2021)	+	+	?	NA	+	NA	+	NA	+	NA	+	NA	?	−	M
Oladeji et al. (2020)	+	+	?	NA	+	NA	+	NA	+	NA	+	NA	?	−	M
Rahman et al. (2021)	+	+	+	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Santos et al. (2021)	+	+	?	NA	NA	NA	+	NA	+	NA	+	NA	NA	+	G
Sato et al. (2021)	+	+	NA	NA	NA	NA	+	NA	+	NA	+	NA	NA	−	M
Shapira et al. (2021)	+	+	+	NA	+	NA	+	NA	+	NA	+	NA	?	+	G
Shet et al. (2022)	+	+	−	NA	−	NA	+	NA	+	NA	+	NA	+	+	G
Shikuku et al. (2021)	+	+	?	NA	+	NA	+	NA	+	NA	+	NA	?	−	M
Siddiqi et al. (2021)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
da Silva et al. (2021)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Silveira et al. (2021)a	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	+	G
Silveira et al. (2021)b	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Sow et al. (2020)	+	+	?	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Torres et al. (2021)	+	+	+	NA	−	NA	+	NA	+	NA	+	NA	?	−	M
Wanyana et al. (2021)	+	+	?	NA	+	NA	+	NA	+	NA	+	NA	?	+	M

FIGURE 2
NHLBI assessments for included studies [Overall scores: good (G), moderate (M), poor (P)].

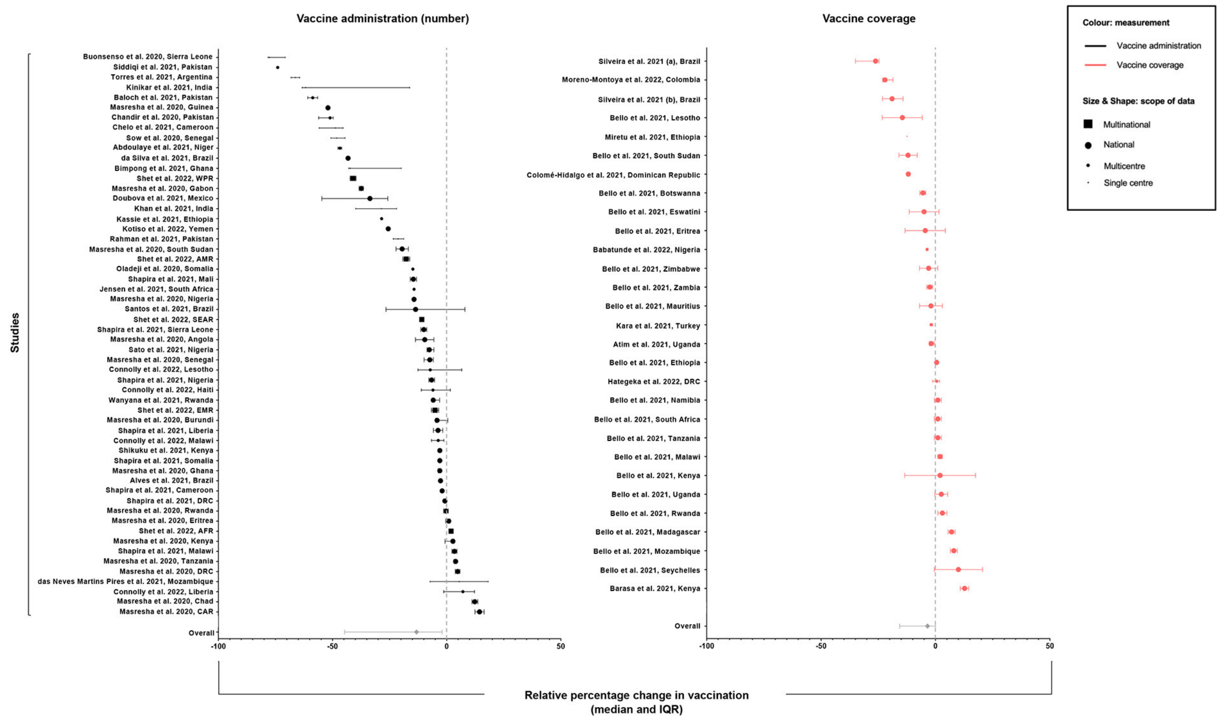

FIGURE 3
Median relative percentage change (±IQR) in vaccination coverage or number of vaccines administered per study and overall across all studies.

to vary according to each country's experience of the pandemic, including public health messaging and lockdown measures.

Vaccine hesitancy may also have contributed to declines in vaccination. Although vaccine hesitancy existed prior to COVID-19, hesitancy may have been exacerbated by the pandemic. A Norwegian study investigated factors associated with vaccine hesitancy during the COVID-19 pandemic and found that the greatest predictors of hesitancy were perceived risks of vaccinations and preference for natural immunity (77). Trust for information shared by health officials appeared to reduce risk of hesitancy (77). However, in instances where health professionals are themselves unsure of vaccine safety—as happened with COVID-19 vaccination—and share this publicly, such as through social media, trust in healthcare professionals might instead increase hesitancy. Similarly, government messaging discouraging vaccination, as was seen in Brazil with regards to COVID-19 vaccination (78), also has potential to translate into hesitancy across other vaccines.

Declines in routine childhood vaccination raise concern over future morbidity and mortality of vaccine-preventable diseases. Prior to the pandemic, many LMICs already had rates of vaccination coverage below the levels necessary to eliminate these diseases or achieve herd immunity (11). Such setbacks bring nations further away from achieving these targets. A modeling study predicted that an 18.5% decline in routine child vaccinations would result in a 10% increase in severely malnourished children, with declines in WHO universally recommended vaccines independently responsible for ~15 thousand additional deaths every three months (6). An older modeling study investigating the impact of falls in BCG coverage estimated that a 10% annual decline in BCG coverage worldwide could lead to over 11,700 tuberculosis deaths in children up to 15 years old (79).

It is not the first time that a disease outbreak has impacted healthcare. A systematic review found a decline in children's health services, including over 20% in pentavalent vaccinations, during the West Africa Ebola outbreak in 2014–2016 (80). Given its high transmissibility (81), the risk of measles outbreaks following declines in vaccination is particularly concerning; Guinea, Liberia and Sierra Leone all had significant rises in measles cases for up to 2 years following the Ebola outbreak (82). Vaccine-preventable disease outbreaks have already been reported during the pandemic for measles and polio (83, 84), including a polio outbreak in Malawi reported in February 2022 (85). Wild poliovirus was eliminated in Africa in 2020 (86); this outbreak brings major setbacks to polio eradication. Declines in vaccination are likely to increase the frequency and severity of these outbreaks. The fall in rotavirus vaccination is also concerning, as diarrhea has been reported as the second most common cause of death in children aged under five, excluding

TABLE 2 Median change (± interquartile range) in level of vaccination.

	Measurement	*n* (observations)	*n* (studies)	*n* (countries)*	Overall relative change [median]	Q1	Q3
	Overall	331	39	50	−10.8	−27.6	−1.4
Outcome	Number of vaccines administered	236	28	38	−13.2	−44.7	−2.0
	Vaccine coverage	96	11	23	−3.5	−15.7	0.0
WHO world region	AFR	195	20	36	−4.0	−14.1	2.2
	AMR	59	10	7	−17.9	−24.3	−8.8
	SEAR	26	3	2	−28.6	−53.6	−18.4
	EMR	39	7	4	−34.5	−51.4	−19.1
	WPR	2	1	1	−41.0	−42.3	−39.7
	EUR	10	1	1	−1.9	−2.4	−1.2
Income level*	LIC	124	10	19	−3.1	−12.8	2.9
	Lower-MIC	130	16	14	−18.0	−48.6	−4.1
	Upper-MIC	67	12	12	−14.3	−24.3	−2.4
Vaccine age group	Birth	37	19	19	−11.8	−27.7	−3.5
	After birth (up to 2 years)	269	33	50	−8.2	−28.6	−0.4
Individual vaccines	BCG	27	16	18	−9.9	−23.0	−3.1
	Hep B	10	8	7	−7.5	−16.6	−1.6
	Polio	48	13	14	−16.6	−50.9	−3.9
	OPV	23	9	7	−28.6	−53.2	−6.0
	IPV	9	8	7	−26.2	−53.6	−21.7
	DTP/Penta	101	31	50	−7.4	−23.9	−0.1
	Rota	22	11	11	−22.4	−45.2	−6.9
	PCV	26	13	13	−4.7	−31.1	0.8
	MCV	80	27	46	−5.2	−21.2	1.7
Timeline	April to June 2020	91	19	28	−8.1	−35.1	−1.4
	June 2020 onwards	75	10	15	−3.9	−13	11.4

AFR, African Region; AMR, Region of the Americas; SEAR, South-East Asian Region; EMR, Eastern Mediterranean Region; WPR, Western Pacific Region; EUR, European Region; LIC low-income country; lower-MIC, lower-middle-income country; upper-MIC, upper-middle-income country; BCG, Bacillus Calmette-Guérin vaccine; Hep B, Hepatitis B vaccine; OPV, oral polio vaccine; IPV, inactivated polio vaccine; DTP, diphtheria, tetanus and pertussis vaccine; Penta, pentavalent vaccine; Rota, rotavirus vaccine; PCV, pneumococcal conjugate vaccine; MCV, measles-containing vaccine.

*Shet et al. (54) not included income level analysis as this was a multinational study, reporting a single value per region. It was counted as a single country as the countries included in this study are not specified.

neonates, globally (87)—with rotavirus being the most common cause of severe or fatal diarrhea (88).

Furthermore, declines in surveillance and treatment have also been observed; over half of African countries reported reductions to suspected measles cases and lab specimens in 2020 (89). Whilst lockdown measures including school closures may have reduced transmission, considering the increasing trend in suspected measles cases between 2017 and 2019, declines are likely consequences of under-reporting (89). The combination of declines in vaccination with reduced healthcare-seeking behavior and less robust surveillance raise concern over increased prevalence, transmission, and severity of infections.

Efforts to recover lost vaccinations, such as catch-up programs, should be prioritized. Additionally, it is vital for nations to invest in public health campaigns encouraging attendance to essential health-services, including vaccinations. National investigations exploring factors disrupting vaccination programs and the extent of disruption for individual vaccines should also be performed, to ensure targeted approaches to catch-up programs. There may also be regional differences to investigate (77). These data would enable the prioritization of populations and vaccines with the highest level of disruption and risk of transmission. Greater understanding would also enable the development of guidance to prevent similar disruptions in future pandemics.

There are several limitations that should be acknowledged. First, given the substantial methodological heterogeneity between studies and missing participation rates for most

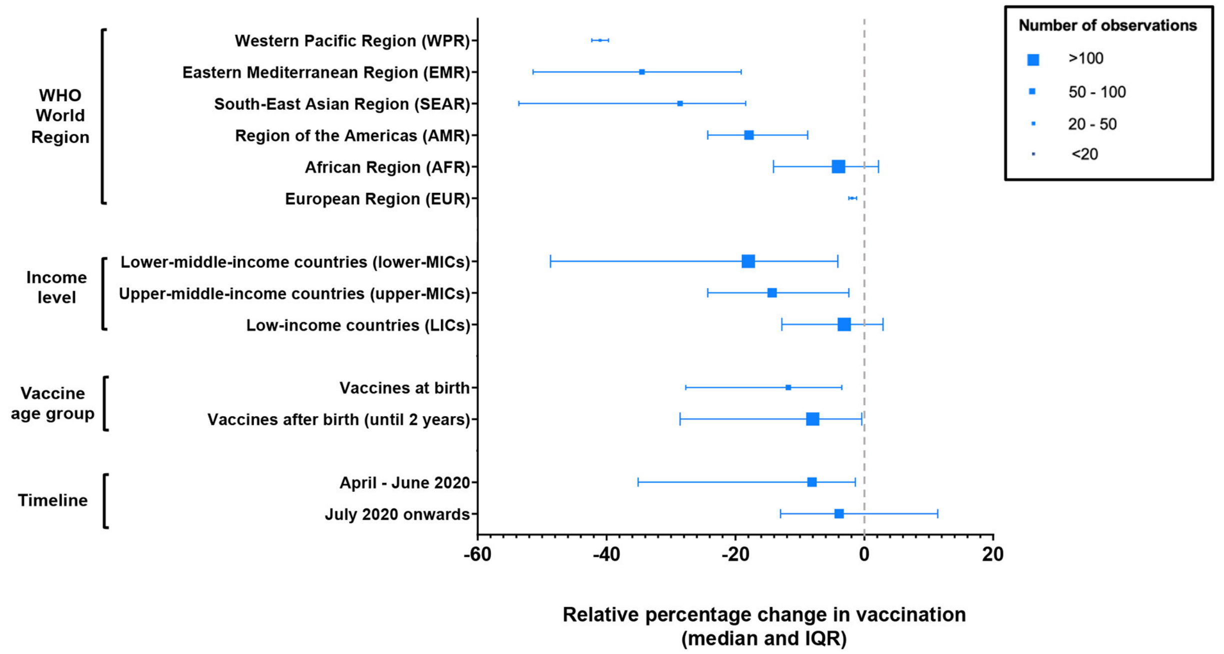

FIGURE 4
Median relative percentage change (±IQR) in vaccination by WHO world region, income level and vaccine age group.

studies, a meta-analysis was not performed. The analysis is descriptive, and measures of effect must be interpreted with caution. In addition, there is lack of representation from several world regions, with most studies reporting data from African countries. Similarly, there is low representation of MICs. Furthermore, available data is mainly from 2020; more recent data is required to establish reliable conclusions. These data limitations emphasize the need for recent national-level data from more countries and per vaccine, to improve the generalizability of findings and inform more meaningful analyses, respectively. Moreover, studies measuring levels of vaccine administration and coverage were included and assumed equal; however, this assumes that there is no change in population from pre-pandemic to pandemic time-periods. Most studies also did not account for confounders such as seasonality or secular trends. Finally, this study did not explore reasons behind disruptions to vaccination, including the potential impact of vaccination hesitancy during the COVID-19 pandemic.

Overall, this study found a drop in routine childhood vaccination in LMICs during the COVID-19 pandemic, with some evidence of recovery in 2020. To avoid increases in child mortality due to the resurgence of vaccine-preventable diseases, LMICs must now focus on recovery of lost vaccination through catch-up programs and strong public health messaging to encourage attendance to health services for routine vaccinations.

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

AC, JS, and EW designed the study and protocol. AC conducted first round of study screening, data extraction, and appraisal, conducted data analysis, and wrote the first draft of the manuscript. LR conducted second round of study screening, data extraction, and appraisal. JS and EW supervised the work. All authors provided critical feedback that helped shape the research, discussed results and contributed to the final version 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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.979769/full#supplementary-material

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Neurological Involvement in Multisystem Inflammatory Syndrome in Children: Clinical, Electroencephalographic and Magnetic Resonance Imaging Peculiarities and Therapeutic Implications. An Italian Single-Center Experience

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Objective: To describe neurological involvement in multisystem inflammatory syndrome in children (MIS-C) and to evaluate whether neurological manifestations are related to the degree of multiorgan involvement and inflammation.

Methods: The authors conducted a retrospective analysis of clinical, electroencephalographic (EEG), neuroradiological (MRI), and CSF parameters in 62 children with MIS-C (45 M, age 8 months—17 years, mean age 9 years) hospitalized between October 1, 2020 and March 31, 2022.

Results: Neurological involvement was documented in 58/62 (93.5%) patients. Altered mental status was observed in 29 (46.7%), focal neurological signs in 22 (35.4%), and non-specific symptoms in 54 (87%). EEG was performed in 26/62 children: 20 showed EEG slowing, diffuse or predominantly over the posterior regions. Ten patients underwent brain MRI: three showed a cytotoxic lesion of the corpus callosum. CSF analysis, performed in six patients, was normal. On the basis of the clinical and EEG findings, two profiles of neurological involvement were identified: 16/62 (26%) patients presented encephalitis with rapid-onset encephalopathy, focal neurological signs, and EEG slowing; 42/62 (68%) showed mild neurological involvement with mild or non-specific neurological signs. All patients received intravenous immunoglobulin and methylprednisolone (MTP), low-molecular-weight heparin, and therapeutic-dose anticoagulant treatment. Children with severe encephalopathy received intravenous

MTP at 30 mg/kg/day for 3 days, obtaining rapid clinical and EEG improvement. Neurological assessment at discharge was normal in all cases. Children with encephalitis were younger than those without (median age 5 and 10 years, respectively); no differences between the two groups were found in the other parameters: comorbidities, fever, number of organs and systems involved, shock, hospitalization, pediatric intensive care unit admission, non-invasive ventilation, inotropic support, laboratory data.

Conclusion: Neurological involvement in MIS-C is frequent but not serious in most cases: around two thirds of the affected children had mild and short-lasting symptoms. It seems to be related to age, but not to the degree of multiorgan involvement and inflammation. In children with acute immune-mediated encephalitis, the clinical picture was dominated by encephalopathy that disappeared with immunomodulatory therapy. Neurological assessment allowed timely diagnosis and treatment.

Keywords: COVID-19, SARS-CoV-2, multisystem inflammatory syndrome in children (MIS-C), acute immune-mediated encephalitis in children, neurological involvement in MIS-C, cytotoxic lesion of the corpus callosum (CLOCC), therapy of MIS-C

INTRODUCTION

Although the primary target of SARS-CoV-2 is the respiratory system, symptoms of nervous system involvement are so frequent in infected patients that some of them—ageusia and anosmia—are considered pathognomonic of COVID-19. The central nervous system (CNS) damage occurring in this setting may be due to direct infection of brain vascular endothelial cells or of the olfactory nerve, or indirect infection resulting from para or postinfectious inflammation, triggered by cytokine storm effects on blood-brain barrier (BBB) permeability (1, 2). Different neurobiological processes and mechanisms may underlie the link between SARS-Cov-2 and COVID-19 in the brain. These pathophysiological mechanisms lead to specific clinical pictures and neurological signs and symptoms that appear in sequence, although they sometimes overlap considerably. The first neurological sign is loss of smell or taste due to the SARS-Cov-2 infection of the epithelial cells of the nasal and oral mucosa, and to retrograde transport from the nasal mucosa to the brain, in the presence of a low and controlled cytokine storm. The next neurological symptoms, corresponding to stage two of neuroCOVID (from the second week after the onset of symptoms), reflect the activation of a robust immune response characterized by high cytokine, ferritin, C-reactive protein, and D-dimer levels, a hypercoagulable state that could result in strokes, and a heightened immune response, which also causes cerebral vasculitis. Finally, the third stage (from the fourth week after the onset of symptoms) includes damage to the BBB and infiltration of cytokines, blood components and viral particles into the brain parenchyma, possibly leading to delirium, encephalopathy and seizures (2).

In adults, neurological involvement is reported in around 30–40% of patients, and encephalopathy, induced by hypoxia or systemic diseases, is common. Cerebrovascular diseases are recognized as primary neurological complications and have been associated with a worse outcome (1). The spectrum of neurological involvement in children and adolescents, on the other hand, is still unclear, both in acute COVID-19 and in multisystem inflammatory syndrome (MIS-C), the severe hyperinflammatory disease that has been documented in some pediatric patients who have been exposed to SARS-CoV-2 (3–5). Shock, which many older MIS-C patients experience, can also be a factor in CNS involvement (6).

Although children are largely spared the severe acute effects of SARS-CoV-2 infection, MIS-C, albeit rare, is a severe disease that affects multiple organs including the CNS. Its pathophysiological mechanism is still unclear, but it is thought to be a highly complex postinfectious phenomenon resulting in hyperinflammation (7). MIS-C is underlain by a series of events very similar to those underlying the most serious neurological manifestations of SARS-CoV-2 infection described above, i.e., neuroCOVID stages two and three (2). Acute SARS-CoV-2 infection triggers a proinflammatory reaction and, in a genetically susceptible child, a delayed hyperinflammatory reaction consisting of vasculitis with augmented levels of lymphocyte T-helper 17 and T-helper 1 mediators, and a cytokine storm, including massive release of inflammatory mediators and exaggerated activation of the immune system leading to BBB damage (1). MIS-C was first described in April 2020 in Europe, but it is now reported and documented worldwide (8). Its true incidence is unknown. A recent US paper reported an adjusted estimated incidence of 1–10 cases per 1,000,000 people per month (9).

To date, the largest published study dealing with neurological involvement in children with SARS-CoV-2 infection is a retrospective study of a population of 1,695 patients; all were younger than 21 years and were hospitalized for MIS-C (in 616 cases) or acute COVID-19, between March and December 2020. Of these patients, 365 (22%) developed neurological complications (3). The vast majority showed transient symptoms, while 12% had a severe clinical presentation, which could consist of focal CNS disease (acute ischemic or hemorrhagic stroke, cerebral venous sinus thrombosis, or focal cerebral arteriopathy) or widespread CNS involvement with severe encephalopathy (CNS infection, acute disseminated encephalomyelitis, encephalopathy with white matter and corpus callosum lesions, or acute fulminant cerebral edema), or peripheral nervous system disorders (Guillain-Barré syndrome and variants). Although the mechanisms underlying the CNS damage were diverse, inflammation was found to be more serious in patients who developed severe neurological complications. Approximately one in four patients with neurological involvement presented altered awareness or confusion. The distribution of other symptoms was age related: seizures and status epilepticus were most commonly seen in younger patients, whereas anosmia and/or ageusia, headache, and fatigue/weakness were most commonly found in older patients. In these patients, severe sequelae were not rare: 26% of patients with neurological involvement died and 40% survived with a new neurological deficit.

Sa et al. in a retrospective review, reported neurological involvement in 9/75 children with MIS-C (12%). Two children developed cerebrovascular disease, and seven presented encephalopathy, in one case associated with hippocampal and splenium of corpus callosum changes. One child with extensive stroke died, and of the surviving eight children, half presented neurological sequelae at the 3-month follow up. Children with neurological symptoms were found to have significantly higher systemic inflammatory markers than children without. MIS-C-associated neurological involvement seems to be linked to a systemic para or postinfectious immune-mediated phenomenon with a distinct immunophenotype characterized by high levels of interleukin activation (10, 11).

Our research team also previously described acute encephalitis in a series of seven children with MIS-C. These patients displayed rapid-onset encephalopathy with drowsiness, irritability, mood deflection, focal neurological signs, and specific EEG abnormalities. MRI and CSF were normal. In all cases, the clinical picture rapidly improved with intravenous immunoglobulin therapy (IV IG) and high-dose intravenous (IV) methylprednisolone (MTP), and EEG normalized within 2 weeks of the neurological recovery. The severity and duration of the EEG abnormalities was proportional to the extent of the neurological involvement (5).

Abel et al., in 2020, reported the case of a previously healthy 2-year-old child with reversible encephalopathy with EEG slowing and bilateral thalamic lesions. He was successfully treated with IV steroids and IVIG, and discharged after 15 days on oral steroids, with mild residual weakness requiring physical therapy (4).

Hilado et al. recently reported the cases of three children with SARS-CoV-2 antibodies (but no multisystem involvement) who presented postinfectious autoimmune-mediated encephalitis and showed a good outcome after high-dose IV MTP treatment (12).

Overall, the currently available data show that children with MIS-C may present various neurological complications, some with a severe prognosis, and suggest that the spectrum of neurological involvement in this syndrome could be wider and more complex than is currently thought. Furthermore, since the clinical picture of MIS-C tends to be dominated, in particular, by systemic and cardiac complications, it is reasonable to think that signs of neurological involvement may be missed in many cases. Indeed, it seems likely that patients with mild and non-specific neurological symptoms are not adequately investigated, while neurological signs and symptoms appearing in those with multiorgan failure may be ignored, misunderstood, or underestimated.

Conversely, in our hospital neurological assessment has recently become an integral part of the multidisciplinary workup and management protocol applied in children admitted with a definite diagnosis of MIS-C. In the present study, we set out to describe neurological involvement in patients with MIS-C, characterizing its profile and severity in order to define the characteristics of subjects with more severe pictures, warranting a more aggressive immunomodulatory therapy, and to evaluate whether neurological involvement is related to the degree of multiorgan involvement and the inflammatory state.

MATERIALS AND METHODS

Patients

The study includes all children and adolescents (aged $\leq$ 18 years) consecutively hospitalized at the Pediatric Department of Vittore Buzzi Children's Hospital, a tertiary referral pediatric hospital in Milan, between October 1, 2020 and March 31, 2022, with a diagnosis of MIS-C meeting the relevant WHO criteria and American College of Rheumatology recommendations (10). Children with mimicking conditions (Kawasaki Disease, Toxic Shock Syndrome, Bacterial Sepsy, Macrophage Activation Syndrome, Myocarditis) were excluded.

For all patients the following data were recorded:

- general demographic and clinical data, comorbidities.
- clinical presentation: duration of fever, presence of organ and system involvement (neurological, cardiological, abdominal, respiratory, renal, mucocutaneous), shock.
- duration of hospitalization.
- pediatric intensive care unit (PICU) admission, non-invasive ventilation support (NIV), inotropic support.
- laboratory data: levels of white blood cells, neutrophils, lymphocytes, platelets, hemoglobin, C-reactive protein, ferritin, D-dimer, N-terminal proB-type natriuretic peptide (NTproBNP), and troponin T (high sensitivity).

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Vittore Buzzi Hospital (Protocol n. 2021/ST/004). All participants or their legal guardians were asked for and gave their written consent after being informed about the nature of the study.

Neurological Clinical and Instrumental Workup

In our hospital, neurological clinical assessment is part of the diagnostic workup of children diagnosed with MIS-C. It is currently carried out both at admission and during the hospital stay, in accordance with our previously reported assessment protocol, also described below (4). Children who experienced shock had stable hemodynamic conditions when undergoing neurological assessment. **Figure 1** shows our patient management algorithm. Clinical and instrumental data are collected in a dedicated database.

Neurological Clinical Assessment

The clinical assessment is carried out by a child neurologist in all children with a confirmed diagnosis at hospital admission. Signs and clinical symptoms are classified as:

- *signs of altered mental status* (altered state of consciousness, irritability or agitation, behavioral changes, i.e., emotional lability/impulsivity, mood deflection/anxiety);

- *focal neurological signs* (abnormal eye movements, facial asymmetries, gait disturbances, hemiparesis/hemiplegia, flaccid paralysis, dyskinesia, myoclonias, changes in speech, memory deficits, visual/auditory hallucinations, seizures, rigor nucalis, photophobia, muscle tone alterations, abnormal reflexes);

- *non-specific symptoms* (apathy, lack of appetite, asthenia, changes in the sleep/wake rhythm, headache, limb or trunk pain, paresthesia/anesthesia).

EEG is performed, in both wakefulness and sleep, in subjects presenting signs and symptoms suggestive of CNS involvement, i.e., altered mental status and neurological signs. EEG abnormalities are classified as focal or diffuse according to the characteristics of the background activity slowing or the presence and localization of epileptiform changes and periodic and rhythmic patterns.

CSF analysis (including SARS-CoV-2 PCR and neurotropic viral PCR, isoelectrofocusing) is performed in subjects with severe encephalopathy.

Brain MRI is performed in subjects with severe encephalopathy.

Profiles of neurological involvement were identified on the basis of clinical and EEG findings. Patients were divided into two groups accordingly:

Encephalitis, defined according to the International Encephalitis Consortium (13), comprising two subgroups:

- severe encephalopathy: patients who presented altered mental status + three or more focal neurological signs + diffuse EEG abnormalities;
- moderate encephalopathy: patients with altered mental status + one or two focal neurological signs + focal EEG abnormalities;

Mild neurological involvement, comprising two subgroups:

- mild clinical involvement: patients with mild signs of altered mental status or one or two focal neurological signs.
- non-specific neurological signs: patients with only non-specific neurological findings.

Therapy

All the patients were treated according to our internal protocol (14). The rationale of the therapy is to counter the hyperimmune response that characterizes the disease. Accordingly, the cardinal treatment consisted of IVIG 2 g/kg and IV MTP 2 mg/kg for 5 days. In the presence of significant oxygen requirement, mild organ injury, and/or moderately reduced left ventricular ejection fraction (LVEF), MTP 10 mg/kg for 1 day then 2 mg/kg for 5 days was given before tapering over a period of 2 weeks. In patients needing respiratory or inotropic support, in the presence of moderate to severe organ damage, and in children with encephalitis with severe encephalopathy, we used a high MTP dose (30 mg/kg) for 3 days followed by 2 mg/kg for 5 days before tapering over a period of 2 weeks.

Anti-thrombotic prophylaxis was started in all patients > 12 years old, and was considered in those < 12 years old if the D-dimer level was high (>5 times the upper normal value) or if there was at least one known risk factor for thromboembolism. Anticoagulation therapy was prescribed in the presence of thrombosis or severe left ventricular (LV) dysfunction. Once the D-dimer level fell or LV function normalized, heparin was replaced with low-dose aspirin for 3–4 weeks.

Statistical Analysis

Quantitative values are described as the mean and standard deviation (SD), or the median and interquartile range if not normally distributed (Shapiro–Wilk test). Qualitative variables are described as counts and percentages. Comparisons between groups were made with a chi-square test or Fisher's exact test for qualitative variables, and with a *t*-test or Mann–Whitney test for quantitative data.

RESULTS

General and Non-neurological Data

Demographics and clinical characteristics, comorbidities, clinical presentation, and laboratory data are reported in **Table 1**. The sample consisted of 62 patients (45 M, 72.5%; age 8 months—17 years, mean age 9 years). No preexisting major common systemic comorbidities were recorded. Sixteen patients (25.8%) were overweight; none were obese. None of the patients had congenital heart disease or preexisting cardiovascular disease.

Nine (14.5%) patients had neurological comorbidities (epilepsy, neuromuscular disease, febrile convulsions, cerebral palsy, neurodevelopmental disorder, severe prematurity), while 8 patients (12.9%) had a previous history of immunological diseases (allergies, autoimmune thyroiditis, arthritis, dermatitis). Fever was present in all the patients, with a median duration of 7 days at diagnosis. Laboratory testing (**Table 1**) showed elevated inflammatory markers (C-reactive protein, fibrinogen, ferritin, D-dimer levels), neutrophilia with lymphopenia, and increased cardiac biomarkers. In 33 children (53.2%), more than two organs were involved, excluding the CNS. All 62 patients had positive IgG serology for the virus, and were treated with IVIG at the time of diagnosis, with a median delay of 5 ± 2 days from the onset of symptoms. Steroid (IV MTP) treatment was added in 58 patients (93.5%): 9 (14.5%) received the highest dose, 13 (21%) the intermediate dose, and 36 (58%) the lowest dose, as defined by our protocol. Low-molecular-weight heparin was prescribed in 62 patients (100%), of whom 12 (19.3%) received therapeutic-dose anticoagulant treatment. All the

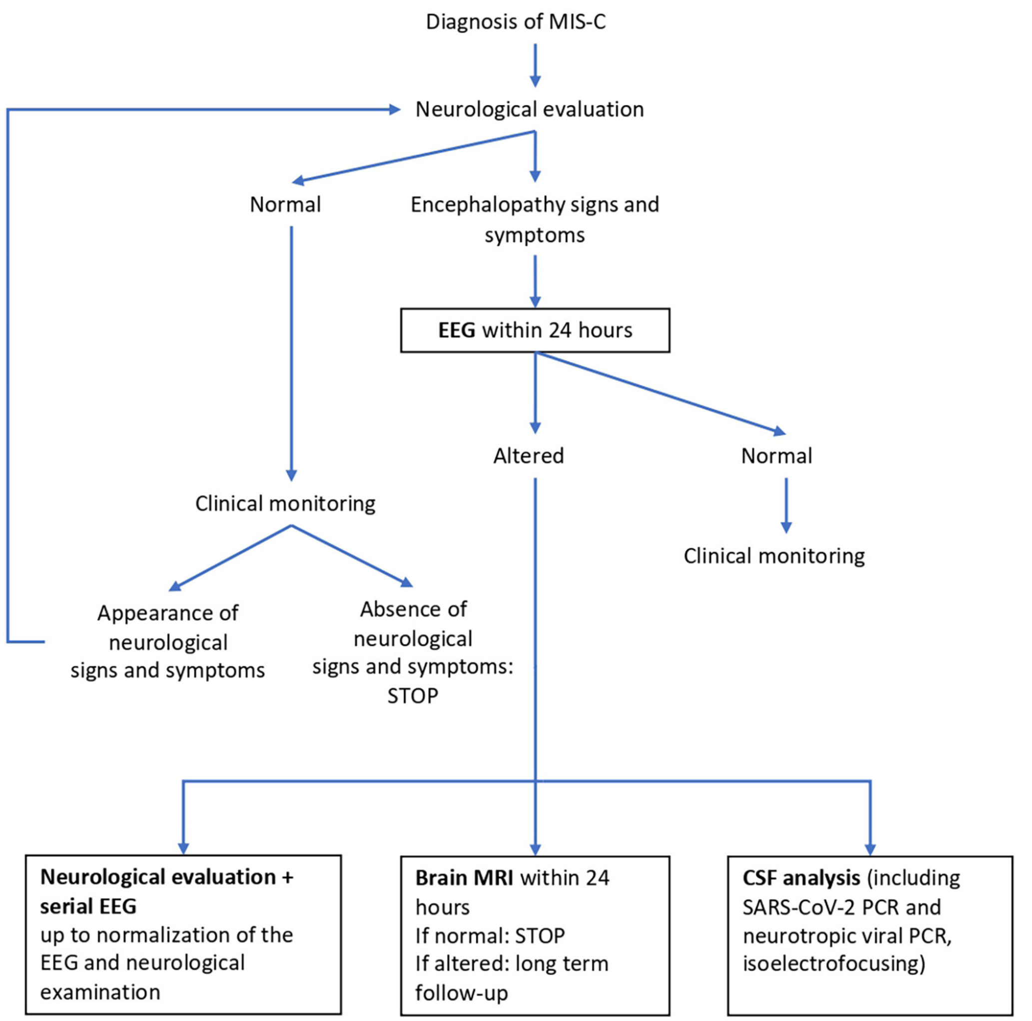

FIGURE 1 | Neurological management algorithm. EEG, electroencephalography; MRI, magnetic resonance imaging; CSF, cerebro spinal fluid.

patients were discharged under treatment with low-dose aspirin. Thirty-six patients (58%) were admitted to the PICU. No patients required intubation and mechanical ventilation, while 15 (24.2%) needed NIV. Hospitalization for MIS-C lasted an average of 12 days (7–26 days).

Neurological Clinical and Instrumental Workup

Neurological Clinical Assessment

Neurological involvement was documented in 58/62 (93.5%) patients. **Table 2** shows the neurological findings, both in the entire sample and by severity of neurological involvement.

Signs of altered mental status were observed in 29 patients (46.7%), of variable severity and in different combinations. Irritability or/agitation was observed in 18 patients (29%), and altered state of consciousness in 16 (25.8%). With regard to behavioral changes, emotional lability/impulsivity was seen in 10 patients (16.1%) and mood deflection/anxiety (e.g., inconsolable crying) in nine (14.5%).

Focal neurological signs were observed in 22 patients (35.4%), in different combinations. Changes in speech were reported in 13 children (20.9%), gait disturbances in eight (12.9%), photophobia in eight (12.9%), abnormal eye movements in three (4.8%), neck stiffness in three (4.8%), muscle tone alterations in two (3.2%), memory impairment in two (3.2%), visual/auditory hallucinations in two (3.2%), and abnormal reflexes in two (3.2%); facial asymmetries, dyskinesia, and seizures were each observed in one patient (1.6%). Hemiparesis and flaccid paralysis were not observed.

Non-specific symptoms were reported in 54/62 patients (87%), in different combinations. headache in 34 (54.8%), asthenia in 26 (41.9%), lack of appetite in 12 (19.3%), apathy in 11 (17.7%), limb or trunk pain in 11 (17.7%), sleep/wake rhythm changes in three (4.8%), and anesthesia or paresthesia in one (1.6%).

Electroencephalographic

Electroencephalographic (EEG) was performed in 26/62 children (42%): 20/62 (32.2%) showed abnormalities, particularly

TABLE 1 | Characteristics of 62 patients (age < 18 years) hospitalized for MIS-C.

		All	Encefalopathy	Mild/No neurological involvement	*P*-value (<0.05)
Patient number, n (%)		62 (100)	16 (25.8)	46 (74.2)	
Age (y), median (range)		9 (0.8–17)	5 (2–10)	10 (0.8–17)	0.00048
Gender, n (%)					
	Male, n (%)	45 (72.5)	11 (68.75)	34 (73.9)	0.74
	Female, n (%)	17 (27.5)	5 (31.25)	12 (26.1)	0.74
Ethnicity, n (%)					
	Caucasian, n (%)	45 (72.5)	13 (81.25)	32 (69.6)	0.51
	African, n (%)	6 (9.7)	2 (12.5)	4 (8.7)	0.64
	Asian, n (%)	5 (8.1)	1 (6.25)	4 (8.7)	1
	Hispanic, n (%)	6 (9.7)	0 (0)	6 (13)	0.32
Risk factors for neurological involvement					
	Pre-existing neurological disorders (*), n (%)	9 (14.5)	3 (18.75)	6 (13)	0.68
	Pre-existing immunological disorders (**), n (%)	8 (12.9)	4 (25)	4 (8.7)	0.18
	Overweight, n (%)	16 (25.8)	3 (18.75)	13 (28.25)	0.73
Inflammation					
	Serology positive, n (%)	62 (100)	16 (100)	46 (100)	1
	Positive RT-PCR, n (%)	62 (100)	16 (100)	46 (100)	1
	Fever, n (%)	62 (100)	16 (100)	46 (100)	1
	Fever duration (days), median (range)	7 (2–14)	7 (4–14)	7 (2–14)	0.61
Organs/systems involved					
	Neurological involvement, n (%)	58 (93.5)	16 (100)	42 (91.3)	0.56
	Cardiological involvement, n (%)	19 (30.65)	5 (31.25)	14 (30.4)	1
	Abdominal involvement, n (%)	52 (83.9)	13 (81.25)	39 (84.8)	0.7
	Respiratory involvement, n (%)	41 (66.1)	13 (81.25)	28 (60.9)	0.22
	Acute kidney injury, n (%)	0 (0)	0 (0)	0 (0)	1
	Mucocutaneous involvement, n (%)	46 (74.2)	11 (68.75)	35 (76.1)	0.74
	2 organs/systems involved, n (%)	29 (46.8)	6 (37.5)	23 (50)	0.56
	> 2 organs/systems involved, n (%)	33 (53.2)	10 (62.5)	23 (50)	0.56
	Shock, n (%)	10 (16.1)	2 (12.5)	8 (17.4)	1
Hospitalization					
	Duration of hospitalization (days), median (range)	12 (7–26)	13 (9–20)	12 (7–26)	0.66
	PICU admission, n (%)	36 (58)	7 (43.75)	29 (63)	0.24
	PICU stay (days), median (range)	2 (0–12)	1 (0–12)	2.5 (0–9)	0.92
	NIV, n (%)	15 (24.2)	2 (12.5)	13 (28.25)	0.31
	NIV stay (days), median (range)	0 (0–6)	0 (0–6)	0 (0–6)	0.67
	Inotropic support, n (%)	16 (25.8)	5 (31.25)	11 (23.9)	0.74
	Therapeutic-dose anticoagulation, n (%)	12 (19.3)	4 (25)	8 (17.3)	0.65
Laboratory data					
	WBC (10^3/mmc), median (range)	8,685 (2,226–33,500)	8,990 (3,420–33,500)	8,400 (2,226–30,850)	0.99
	N (10^3/mmc), median (range)	6,660 (1,520–27,805)	7,255 (1,810–27,805)	6,580 (1,520–27,010)	0.25
	L (10^3/mmc), median (range)	800 (230–8,610)	995 (230–4,310)	780 (280–8,610)	0.3
	PLT (10^3/mmc), median (range)	168 (27–398)	181 (75–339)	162.5 (27–398)	0.78
	Hb (g/dl), median (range)	11.2 (7.5–14.6)	10.95 (8.2–14.1)	11.4 (7.5–14.6)	0.71
	PCR (mg/l), median (range)	168.05 (18.6–456)	170 (24.3–265)	165.65 (18.6–456)	0.15
	Ferritin (mcg/l), median (range)	505.5 (96–5,389)	430 (221–2,245)	606 (96–5,389)	0.18
	D-Dimer (mcg/l), median (range)	2,795 (347–25,385)	3,808 (1,114–23,000)	2,777 (347–25,385)	0.46
	NT-Pro BNP (ng/l), median (range)	3757.5 (73–35,000)	3,406 (73–35,000)	3757.5 (167–35,000)	0.4
	Tnt (ng/l), median (range)	34.5 (2–1,342)	14 (3–820)	44.5 (2–1,342)	0.23

**Epilepsy, neuromuscular disease, cerebral palsy, extreme prematurity (24 weeks), febrile seizures, psychomotor delay, specific learning disabilities, language disorders. **Autoimmune thyroiditis, autoimmune arthritis, autoimmune dermatitis, allergy. PICU, pediatric intensive care unit admission; NIV, non-invasive ventilation; WBC, white blood cells; N, neutrophils; L, lymphocytes; PLTs, platelets; Hb, hemoglobin; CRP, C-reactive protein; NT-ProBNP, amino-terminal fragment of the brain natriuretic peptide; TnT, troponin T.*

TABLE 2 | Neurological presentation/involvement and therapy of 62 patients (age < 18 years) hospitalized for MIS-C.

			Total n 62 (100)	Severe n 7 (11.3)	Moderate n 9 (14.5)	Milld n 17 (27.4)	Non-specific n 25 (40.3)	No neurological symptoms n 4 (6.5)
Neurological symptoms	Signs of altered mental status	1. Altered state of consciousness	16 (25.8)	5 (71.4)	6 (66.6)	5 (29.4)	0 (0)	0 (0)
		2. Irritability/agitation	18 (29)	6 (85.7)	8 (88.8)	4 (23.5)	0 (0)	0 (0)
		3. Behavioral changes	10 (161)	5 (71.4)	2 (22.2)	3 (17.6)	0 (0)	0 (0)
		4. Mood deflection/anxiety	9 (14.5)	2 (28.5)	1 (11.1)	6 (35.2)	0 (0)	0 (0)
	Focal signs	5. Abnormalities of eye movements	3 (4.8)	1 (14.2)	0 (0)	2 (11.7)	0 (0)	0 (0)
		6. Facial asymmetries	1 (1.6)	0 (0)	0 (0)	1 (5.8)	0 (0)	0 (0)
		7. Gait disturbance	8 (12.9)	4 (57.1)	4 (44.4)	0 (0)	0 (0)	0 (0)
		8. Hemiparesis/hemiplegia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
		9. Flaccid paralysis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
		10. Dyskinesia	1 (1.6)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)
		11. Myoclonias	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
		12. Speech alterations	13 (20.9)	5 (71.4)	4 (44.4)	3 (17.6)	1 (4)	0 (0)
		13. Memory deficit	2 (3.2)	1 (14.2)	0 (0)	0 (0)	1 (4)	0 (0)
		14. Visual/auditory hallucinations	2 (3.2)	1 (14.2)	0 (0)	1 (5.8)	0 (0)	0 (0)
		15. Seizures	1 (1.6)	0 (0)	1 (11.1)	0 (0)	0 (0)	0 (0)
		16. Neck stiffness	3 (4.8)	1 (14.2)	1 (11.1)	0 (0)	1 (4)	0 (0)
		17. Photophobia	8 (12.9)	2 (28.5)	2 (22.2)	3 (17.6)	1 (4)	0 (0)
		18. Altered muscle tone	2 (3.2)	1 (14.2)	0 (0)	1 (5.8)	0 (0)	0 (0)
		19. Abnormal reflexes	2 (3.2)	1 (14.2)	0 (0)	0 (0)	1 (4)	0 (0)
	Non-specific symptoms	20. Apathy	11 (17.7)	5 (71.4)	2 (22.2)	1 (5.8)	3 (12)	0 (0)
		21. Lack of appetite	12 (19.3)	2 (28.5)	1 (11.1)	5 (29.4)	4 (16)	0 (0)
		22 Asthenia	26 (41.9)	4 (57.1)	2 (22.2)	6 (35.2)	14 (56)	0 (0)
		23. Changes in sleep/wake rhythm	3 (4.8)	1 (14.2)	0 (0)	1 (5.8)	1 (4)	0 (0)
		24. Headache	34 (54.8)	3 (42.8)	4 (44.4)	10 (58.8)	17 (68)	0 (0)
		25. Limb or trunk pain	11 (17.7)	3 (42.8)	2 (22.2)	3 (17.6)	3 (12)	0 (0)
		26. Paresthesias/anesthesia	1 (1.6)	0 (0)	0 (0)	1 (5.8)	0 (0)	0 (0)
EEG		Focal delta slow activity	13 (20.9)	4 (57.1)	5 (55.5)	4 (23.5)	0 (0)	0 (0)
		Diffuse delta slow activity	7 (11.3)	3 (42.8)	3 (33.4)	1 (5.8)	0 (0)	0 (0)
		Focal epileptic abnormalities in sleep	15 (24.1)	7 (100)	6 (66.6)	2 (11.7)	0 (0)	0 (0)
		Normal	6 (9.7)	0 (0)	0 (0)	2 (11.7)	4 (12)	0 (0)
		Not performed	36 (58)	0 (0)	1 (11.1)	10 (58.8)	21 (84)	4 (100)
MRI		Altered	3 (4.8)	3 (42.8)	0 (0)	0 (0)	0 (0)	0 (0)
		Normal	7 (11.3)	2 (28.5)	4 (44.4)	1 (5.8)	0 (0)	0 (0)
		Not performed	52 (83.8)	2 (28.5)	5 (55.5)	16 (94.1)	25 (100)	4 (100)
CSF		Altered	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
		Normal	6 (9.5)	6 (85.7)	0 (0)	0 (0)	0 (0)	0 (0)
		Not performed	56 (90.5)	5 (71.4)	6 (66.6)	17 (100)	24 (96)	4 (100)
Steroid treatment		No	4 (6.5)	0 (0)	0 (0)	1 (5.8)	1 (4)	2 (50)
		2 mg/kg	36 (58)	1 (14.2)	5 (55.5)	13 (76.4)	18 (72)	1 (25)
		10 mg/kg	13 (21)	0 (0)	2 (22.2)	5 (29.4)	5 (20)	1 (25)
		30 mg/kg	9 (14.5)	6 (85.7)	2 (22.2)	0 (0)	1 (4)	0 (0)

EEG, electroencephalography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

high-amplitude delta slow activity, which was diffuse in seven patients (11.3%) and observed predominantly over the posterior regions in the other 13 (20.9%). During sleep, posterior delta biphasic complexes and focal bilateral anterior theta rhythmic discharges were detected in 15 patients (24.1%).

Magnetic Resonance Imaging

Ten patients underwent brain Magnetic Resonance Imaging (MRI). In three (4.8%), a median, oval-shaped cytotoxic lesion was detected in the splenium of corpus callosum. In all cases, the cytotoxic lesion of the corpus callosum (CLOCC) was characterized by T2-weighted hyperintensity and restricted diffusion on diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps. Follow-up MRI examination (after 1 week in one patient and 2 weeks in the other two) showed complete resolution of the signal abnormality. No other alteration was detected.

Cerebro Spinal Fluid

Cerebro Spinal Fluid (CSF) analysis was performed in six patients (9.5%). All the examinations were normal. SARS-CoV-2 was not detected.

Neurological Profiles

The distribution of neurological signs and symptoms according to the severity of neurological involvement is described in **Figure 2**.

Encephalitis

This group comprised 16 children: seven with severe and nine with moderate encephalopathy.

The children with severe encephalopathy (7/62, 11.3%) displayed both focal and diffuse neurological signs. Within this subgroup, we observed severe irritability (85.7%), mood deflection (28.5%), and drowsiness (71.4%), variably associated with apathy (71.4%), headache (42.8%), meningism (14.2%), photophobia (28.5%), oculomotor apraxia (14.2%), gait disorder (57.1%), pain (42.8%), and slow, "whiny" and repetitive speech with reduced verbal output and preserved comprehension (71.4%). One patient presented a generalized tonic-clonic seizure during fever. Wake EEG at the onset of the neurological symptoms was dominated by high-amplitude delta slow activity, diffuse (42.8%) or recorded predominantly over the posterior regions (57.1%). During sleep, posterior delta biphasic complexes and focal bilateral anterior theta rhythmic discharges were detected. When encephalitis was confirmed, these children received treatment with high-dose MTP. The symptoms peaked in 2–3 days and thereafter showed a dramatic improvement. EEG usually improved markedly by 10 days, with progressive reorganization of background activity. A normal EEG was usually recorded between 15 and 24 days from the start of steroid therapy. In three of the seven patients in this subgroup, brain MRI documented CLOCCs; in the others, it was normal. CSF analysis was carried out in 6/7 children, giving normal results. **Figures 3**, **4** show the clinical and EEG changes recorded over time in two representative patients with focal (**Figure 3**) and diffuse EEG alterations (**Figure 4**).

The children with moderate encephalopathy (9/62, 14.5%) showed mild symptoms of diffuse encephalopathy, namely mild irritability (88.8%), drowsiness (66.6%), mood deflection (11.1%), and headache (44.4%). Within this subgroup, EEG documented focal (55.5%) or diffuse delta waves (33.3%), high-amplitude biphasic delta waves in sleep, and/or focal spikes. All these patients recovered within 5–8 days from the start of steroid therapy, and the EEG performed between days 15 and 21 was normal. Brain MRI was performed in three of the children with moderate encephalopathy and was normal in all of them. None underwent CSF analysis.

Mild Neurological Involvement

This group comprised 42 children: 17 with mild clinical involvement and 25 with non-specific neurological signs.

In the subgroup of children with mild clinical involvement (17/62, 27.4%), we observed mild mood deflection and anxiety (35.2%), mild irritability (23.5%), drowsiness (29.4%), headache (58.8%), and asthenia (35.2%).

Among the children with non-specific neurological signs (25/62, 40.3%), the main complaints were asthenia (56%), limb or trunk pain (12%), headache (68%), usually worse at the peak of fever, apathy (12%), lack of appetite (16%), sleep/wake rhythm changes (4%), and mild photophobia (4%).

Systemic Dysfunction and Its Relationship With Neurological Profiles

Table 2 sets out the data on systemic dysfunction in these patients, namely the number of systems involved, the rates of cardiac involvement and of PICU admission, laboratory data and steroid therapy doses. The data are presented both for the entire sample and by severity of neurological involvement.

In 62.5% (10/16) of the patients with encephalitis, and in 50% (23/46) of those with either mild or no neurological involvement, more than two organs or systems were affected, excluding the neurological system.

Cardiac involvement (LVFE $< 45\%$) was documented in 31.25% (5/16) of the children with encephalitis and in 30.4% (14/46 patients) of those with either mild or no neurological involvement. Respiratory involvement was observed in 66.1% (44/62) and abdominal involvement in 83.9% (52/62), with no statistically significant difference between the two severity groups. No patient showed acute kidney injury (AKI).

Seven of the 16 patients (43.75%) with encephalitis and 29/46 (63%) of those with either mild or no neurological involvement were admitted to the PICU. Shock was reported in 16.1% (10/62); again, no statistical difference was found between the two groups.

Laboratory data (**Table 1**) showed elevated inflammatory markers (C-reactive protein, fibrinogen, ferritin, D-dimer), neutrophilia with lymphopenia, normal platelet counts and hemoglobin levels, and increased cardiac biomarkers in both groups.

No statistically significant differences in demographic data, comorbidities, organ or system involvement, and hospitalization or laboratory data were found between the two comparison groups. Only patient age differed. In fact, patients with encephalitis reported a lower median age compared with the other group (5 years vs. 10 years, $p = 0.00048$).

DISCUSSION

This study describes the spectrum of neurological involvement in a sample of 62 children with MIS-C admitted to a single tertiary pediatric department between October 1, 2020 and March 31, 2022.

Neurological signs and symptoms were present in 93.5% of the patients. Headache, of varying duration and severity,

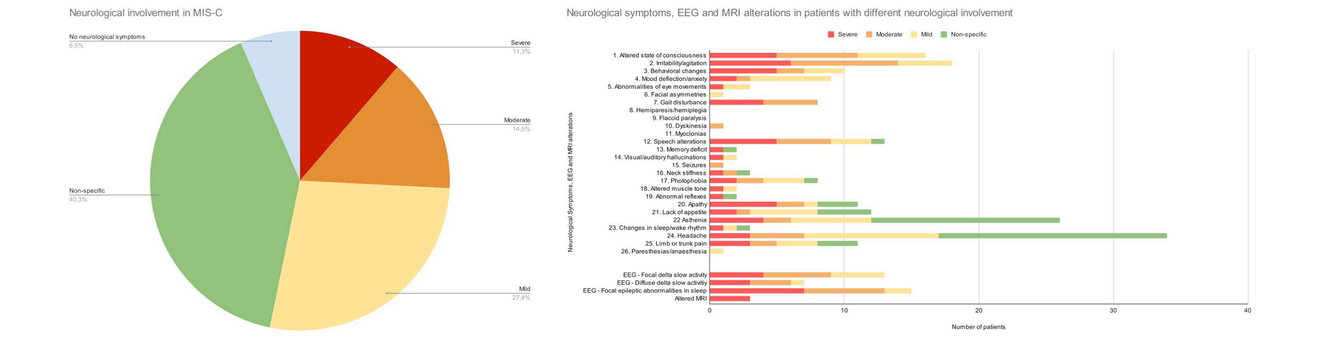

FIGURE 2 | Distribution of neurological involvement in MIS-C. Neurological symptoms and EEG and MRI alterations in patients with different profiles of neurological involvement.

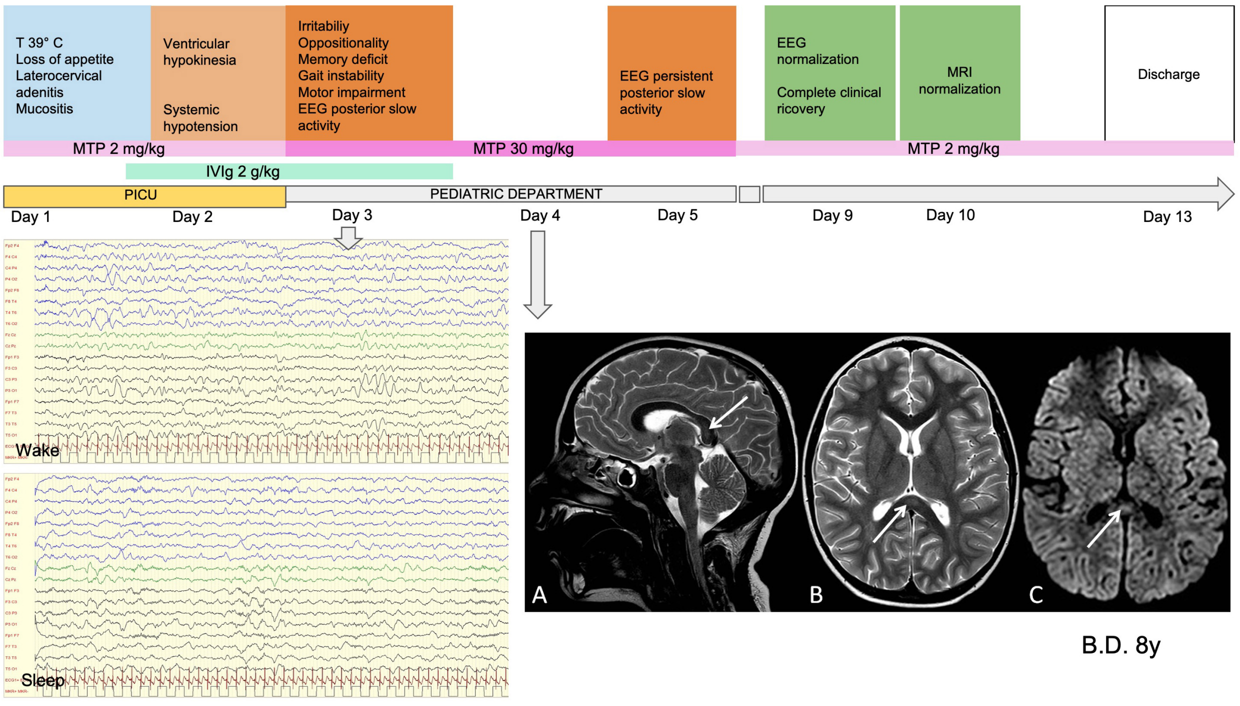

FIGURE 3 | Clinical, MRI and EEG findings in representative patients with focal EEG alterations. Male, 8 years old. MISC presentation characterized by fever (T 39°C), systemic symptoms, ventricular hypokinesia and neurological symptoms (irritability, oppositionality, memory deficit gait instability, motor impairment). WBC 16460 (10^3/mmc) (N 14579, L 1030); PLTs 152 (10^3/mmc); Hb 10.1 (g/dL); CRP 189.6 (mg/l); Ferritin B29 (mcg/l); D-dimer 1114 (mcg/l); NT-ProBNP 15979 (ng/l); TnT 28 (ng/l). On day 1 he was given Mg (2 g/kg for 2 days) and on day 2 was started on high-dose MTP (30 mg/kg for 3 days). MRI performed on day 4 **(A)**. Sagittal, **(B)** Axial T2-weighted images show slight focal median hyperintense lesion in the splenium of corpus callosum (arrows). **(C)** Axial diffusion-weighted image shows reduction of proton diffusivity at the site of the lesion (arrow). EEG performed on day 3 **(D)**. High-amplitude delta slow activity prevalent in the posterior regions **(E)**. Slow activity during sleep with preserved spindles. Clinical and EEG normalization was observed on day 7 and normalization of MRI on day 9. CK, creatine kinase; WBC, white blood cells; N, neutrophils; L, lLymphocytes; PLTs, platelets; Hb, hemoglobin; CRP, C-reactive protein; NT-ProBNP, amino-terminal fragment of the brain natriuretic peptide; TnT, troponin T; IVlg, intravenous immunoglobulin; MTP, methylprednisolone; MRI, magnetic resonance imaging; CC, corpus callosum; EEG, electroencephalography; PICU, pediatric intensive care unit admission.

was the most commonly reported symptom, occurring in over half of the subjects, followed by asthenia. Although in themselves and if present in isolation these symptoms are poorly specific and not indicative of neurological involvement, we found that they were rarely isolated; for this reason, we believe they should be considered red flags of possible neurological involvement, and therefore that their presence should prompt a more detailed evaluation of the clinical picture. Approximately half of the sample showed clear signs of altered mental status, mainly drowsiness and irritability, associated with apathy and mood and behavioral changes. Overall, these disturbances, severe and pervasive in most cases, made the

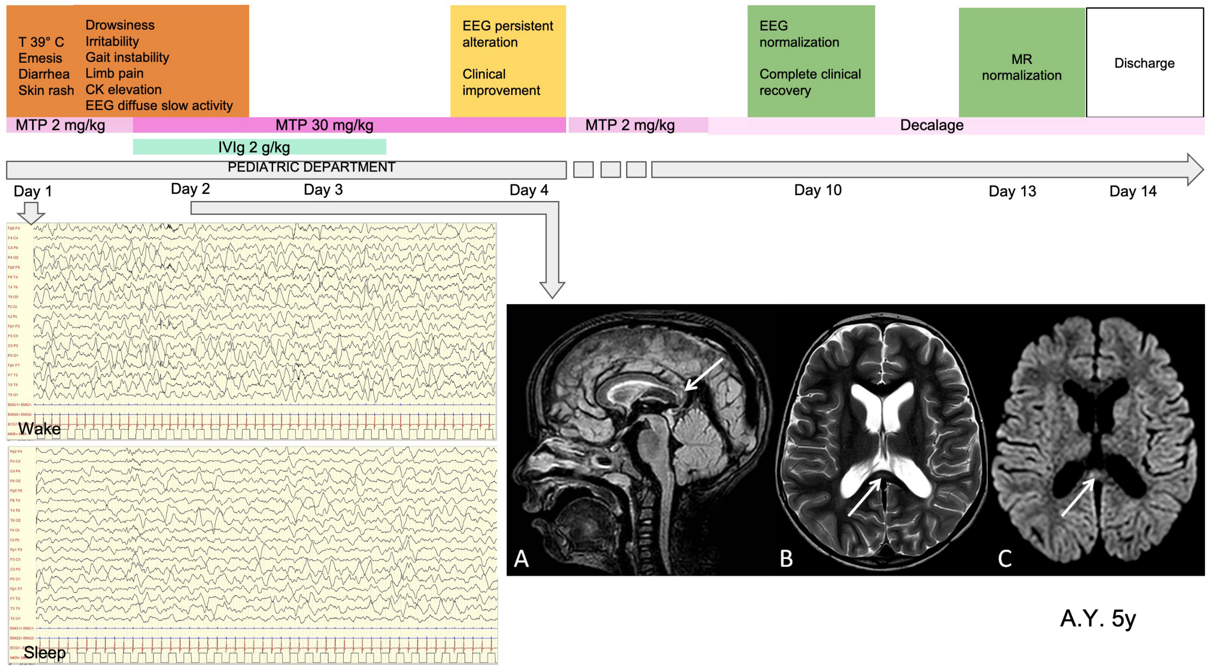

FIGURE 4 | Clinical, MRI and EEG findings in a representative patient with diffuse EEG alterations. Male, 5 years old. MISC presentation characterized by fever (T 39°C), gastrointestinal involvement, skin rash, neurological symptoms (drowsiness, irritability, gait instability, limb pain) and CKelevation. Laboratory data at onset WBC 3420 (10^3/mmc) (N 1810, L 1470); PLTs 224 (10^3/mmc); Hb 11.9 (g/dL); CRP 33 (mg/l); ferritin 829 (mcg/l); D-dimer 12077 (mcg/l); NT-ProBNP 1982 (ng/l); TnT 820 (ng/l). On day 1 he was given IVIg (2g/kg for 2 days) and on day high-dose steroid treatment was started (MTP 30 mg/kg for 3 days). MRI performed on day 2 **(A)**. Sagittal FLAIR image, **(B)** Axial T2-weighted images show slight focal median hyperintense lesion in the splenium of corpus callosum (arrows). Parenchymal signal abnormality and thickness reduction can be observed in the peritrigonal white matter on the left side in **(B)**. **(C)** Axial diffusion- weighted image shows reduction of proton diffusivity at the site of the CC lesion (arrow). EEG performed on day 1 **(D)**. Diffuse high-amplitude delta slow activity **(E)**. Loss of organization of sleep activity, with high-amplitude delta slow waves. Clinical and EEG normalization was observed on day 10 and normalization of MRI on day 13. CK, creatine kinase; WBC, white blood cells; N, neutrophils; L, lymphocytes; PLTs, platelets; Hb, hemoglobin; CRP, C-reactive protein; NT-ProBNP, amino-terminal fragment of the brain natriuretic peptide; TnT, troponin T; IVIg, intravenous immunoglobulin; MTP, methylprednisolone; MRI, magnetic resonance imaging; CC, corpus callosum; EEG, electroencephalography; PICU, pediatric intensive care unit admission.

children "unrecognizable" to their parents. Parents reported that their children would swing between states of apathy-drowsiness and fits of anger and irritability, for no apparent reason. With the exception of speech and gait abnormalities, observed in around a fifth and a sixth of the children, respectively, focal neurological signs were observed in very few children. No child showed acute motor deficits or signs of peripheral nervous system involvement. Just one had a generalized seizure during fever.

The incidence of neurological involvement in our sample was found to be much higher than the rates of up to around 50% reported in the literature (3, 4, 15, 16). This difference is very likely due to the fact that the patients in the present study were all assessed, at admission or shortly afterward, by a child neurologist who was able to detect and evaluate even mild neurological signs and symptoms, and it suggests that specialist assessment of neurological aspects should be routinely included in the workup of patients with MIS-C.

Although very frequent, the neurological involvement observed in our sample was not serious in most cases: around two thirds of the affected children had mild and short-lasting symptoms. This is in line with the findings of Larovere et al., who reported transient symptoms in 88% of their subjects with neurological involvement (17).

In children with encephalitis, the clinical picture was dominated by encephalopathy and EEG abnormalities very similar to those previously reported in the first cases we observed (4). Indeed, in the present study, too, the EEG recordings showed well-defined characteristics, confirming that EEG plays a valuable role in the diagnosis of encephalitis in children with MIS-C and altered mental status. At the onset of the neurological symptoms, EEG typically showed absence of physiological organization, particularly on awake recordings, which were dominated by high-amplitude delta slow activity, diffuse or predominant over the posterior regions. During sleep, posterior delta biphasic complexes and focal bilateral anterior theta rhythmic discharges were detected. The symptoms peaked in 2 or 3 days and showed a dramatic improvement after high-dose MTP treatment. Neurological assessment at discharge was usually normal. EEG background activity improved from the first week, and normalized within 2 or 3 weeks.

Among the patients with encephalitis, three showed diffuse abnormal T2-weighted hyperintensity and restricted diffusion involving the white matter and genu or splenium of corpus callosum on MRI. CLOCCs have already been described as a potential neuroradiological presentation of SARS-CoV-2 infection in adults (18, 19) and, in the context of inflammatory multisystem syndrome, temporally associated with SARS-CoV-2 exposure in children (20). Our cases with callosal lesions expand the series already described and confirm that CLOCCs could be a neurological complication of SARS-CoV-2 exposure in children. In the literature, CLOCCs are reported to be secondary lesions associated with different entities, including infections, all sharing specific features: high levels of cytokines and extracellular glutamate (21). It has been hypothesized that the corpus callosum shows selective vulnerability to cytokine storms due to its high density of cytokine and glutamate receptors (21); a cytokine storm seems to be the cause of the callosal neuron and microglia dysfunction that allows T cells to breach the BBB, causing inflammation and intramyelinic edema (22). The rapid resolution of the neuroradiological picture observed in our cases supports this hypothesis and suggests that immunotherapy can play a key role in the treatment of this condition.

The children with encephalitis (median age 5 years) were younger than those with mild or no neurological impairment (median age 10 years), an aspect that points to a possible, and as yet undescribed, age dependence of the neurological clinical pictures associated with MIS-C. Although neurological involvement (sterile meningoencephalitis) has been reported in in Kawasaki disease, which mainly affects preschool-age children and shows a known clinical overlap with MISC in very young children, we found the neurological phenotype in this latter group to be more severe and more complex than what has been described in patients with Kawasaki disease (23). Indeed, while greater severity of MIS-C has been described in children > 5 years of age, to date no age differences have been reported in the literature with regard to neurological involvement (24).

The other demographic data analyzed — sex and ethnicity — showed no significant differences. In comparison with literature data (25), our sample showed significantly increased frequency of comorbid neurological or immune system disorders. This might be due to the fact that our diagnostic protocol, being designed with a view to multidisciplinary management of these patients, allowed us to collect a larger and broader body of data than are provided by the retrospective studies present in the literature (25). In our study, the presence of these comorbidities was not associated with a significantly increased risk of developing neurological complications, but this observation needs to be verified over time in larger samples.

The severity of systemic involvement and the number of organs and systems (including cardiac and gastrointestinal) affected, as well as the hospitalization rates and patterns of laboratory data, were found to be similar in children with severe neurological involvement compared with what was observed in children with mild or no neurological involvement. In other words, encephalitis can be documented even in children with moderate changes in inflammatory indices and without severe systemic involvement, including cardiac involvement. This observation is in contrast to what has thus far been reported in the literature, in which more severe neurological involvement was associated with more extreme inflammation. Overall, our data support the need for neurological assessment of children with MIS-C (especially those younger than 10 years), regardless of the degree of cardiac involvement and of alteration of the inflammatory indices. It seems, in fact, that neurological involvement can be independent of cardiac and systemic involvement. Clarification, over time, of the reasons for this dissociation will allow the development of better-targeted diagnostic and therapeutic protocols.

In this regard, it should also be emphasized, in line with what has already been reported in the literature (3), that the most frequent symptoms — headache, asthenia, signs of altered mental status — are not particularly specific, and can certainly also have non-neurological causes. However, our experience and careful clinical evaluations have shown us that they rarely occur in isolation and seem to be a very sensitive indicator of more serious neurological involvement.

The findings here reported confirm, in a larger sample, what we have already observed in a previous, smaller case series, namely that children with MIS-C may present postinfectious autoimmune-mediated encephalitis that, probably the expression of immune system overactivation and of a cytokine storm, disappears in response to immunomodulatory therapy (5). They also confirm that these clinical pictures, if diagnosed and treated promptly, regress without leaving neurological sequelae (5). Clinical pictures similar to these have been described in the literature in children with SARS-CoV-2 infection, both with (MIS-C) and without multiple organ involvement: in these cases, too, the effectiveness of high-dose steroid therapy was emphasized (4, 12). However, this observation does not exclude the possibility of future sequelae. Long-term follow-up is therefore needed to evaluate effects of the infection on cognition and development.

To conclude, it is worth reflecting on the therapeutic implications of our observations in these patients.

Generally speaking, while the onset of MISC observed in our study resembled the onset symptoms described in cases reported in the literature, the clinical evolution of our patients was found to be relatively favorable (17). Early multidisciplinary diagnosis and the immediate use of immunomodulatory and anticoagulant therapies, as well as the inotropic support given to patients with severe cardiac dysfunction or with capillary leaks, certainly played a role in preventing other organ damage, such as AKI (26).

Even though our patients were hospitalized, on average, for longer than cases reported in the literature—12 days vs. 5 days (25)—the duration of their PICU stays was in line with what has been reported in other series. Our patients' longer overall stays in the pediatric department were not linked to slower resolution of the symptoms, but rather to a deliberate policy choice on the part of our institution, which, in view of possible pandemic-related difficulties in ensuring adequate home observation, preferred to keep post-acute patients monitored in a protected environment for longer. We cannot exclude the possibility that this prolonged observation reduced the risk of some complications in the post-acute phase.

Systemic aspects apart, this approach probably also affected the overall neurological outcome. In fact, none of the children in our study displayed any of the other clinical pictures falling within the broad spectrum of severe neurological manifestations related to SARS-CoV-2 infection and MIS-C reported in the literature, and associated with worse long-term outcomes, namely ischemic or hemorrhagic stroke, demyelination, acute fulminant cerebral edema, and Guillain-Barré syndrome (3, 10). Indeed, it seems likely that the use of IVIG and steroids (administered at variable doses, according to severity) led to rapid resolution of the encephalitic symptoms, and that low-molecular-weight heparin and therapeutic-dose anticoagulant treatment reduced the risk of thromboembolic complications. This hypothesis, if confirmed in larger populations of patients, could strengthen the argument for the implementation of a more aggressive and broad-spectrum therapeutic approach in children with MIS-C.

CONCLUSION

Neurological involvement in children with MIS-C is frequent but not serious in most cases: the majority of affected children had mild and short-lasting symptoms. A quarter of the children showed acute immune-mediated encephalitis with rapid-onset encephalopathy, focal neurological signs, and EEG slowing. This clinical picture disappeared with immunomodulatory therapy. The severity of the neurological picture seemed to be related to age, but not to the degree of multiorgan involvement and inflammation. Neurological assessment allowed timely diagnosis and treatment.

This study demonstrates the importance of including neurological evaluation in the diagnostic workup of MIS-C, regardless of clinical presentation, organ involvement, comorbidities, inflammatory indices, and laboratory data; this applies particularly in children younger than 10 years. In our sample we observed a favorable outcome in all cases, which can probably be linked to the prompt steroid and IVIG treatment administered in all patients.

MILAN MIS-C STUDY GROUP

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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 Comitato etico Milano Area 1. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SMB had full access to all the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and acquisition of clinical data. SMB and SM contributed to the conception, design, and acquisition of clinical data. LS, PC, ARD, and AG contributed to acquisition, analysis, interpretation of neurological data, and acquisition of clinical data. LL, AV, SM contributed to acquisition, analysis, interpretation of cardiological data, and acquisition of clinical data. CD contributed to acquisition, analysis, interpretation of neuroradiological data, and acquisition of clinical data. SMB, LS, PC, ARD, CD, and SM contributed to drafting of the manuscript and acquisition of clinical data. SMB, SM, and PV contributed to critical revision of the manuscript for important intellectual content and acquisition of clinical data. PC and LL contributed to statistical analysis and acquisition of clinical data. Milan MIS-C Study Group contributed to acquisition of clinical data. All authors contributed to the article and approved the submitted version.

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Pediatric neurosurgery AC-after COVID-19: What has really changed? A review of the literature

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The COVID-19 outbreak has dramatically changed the organization of Pediatric Neurosurgery all over the world. The departments involved developed similar plans to maintain emergency surgeries without reducing clinical activities. The Association of Pediatric Neurosurgeons wrote different memoranda to detail the surgical procedures not to be postponed with special attention given to high-risk pathology for COVID-19 contamination, like trans-naso-sphenoidal surgery. On this basis, we have conducted a complete literature review focusing on many topics: hospital organization, patients and parents screening, surgical indication criteria, outpatient clinic and teleconsultation, telematic conference and meeting, fellowship and training, and virtual multidisciplinary meeting.

KEYWORDS

COVID-19, pediatric neurosurgery, hospital organization, surgical indications, perioperative complications, virtual meetings

Introduction

Coronavirus disease (COVID-19) is an infectious respiratory disease that may cause a severe respiratory illness and is still threatening humanity globally. Since the first patients were infected in China in December 2019, it has been studied deeply by scientists from all the world. COVID-19 is caused by a new coronavirus of the Coronaviridae family (SARS-CoV-2). The virus structure is related to other viruses responsible for severe acute respiratory syndrome (SARS) (1). Due to COVID-19's long incubation period, high infection rate, and a variety of manifestations mainly affecting the respiratory function, but also with neurological symptoms in some cases, this infection has an unpredictable course and represents an unprecedented challenge to the modern health care system and society (2).

The rapid spread of the pandemic meant the global medical community faced both practical and ethical challenges that required an urgent response to adapt the way healthcare was provided. This was true for all the medical disciplines and also for the neurosurgery community (3). The literature has demonstrated that children affected by COVID develop a less severe form of infection compared to adults (4).

However, fatal cases have already been described in some countries, such as the US, the UK, France, and Belgium. The mortality has been estimated around 0.08% among the pediatric population (5). Although COVID-19 in children may be milder, pediatric patients may need hospital medical support and continuous assistance. Furthermore, even if they are affected by COVID-19, they still require the same surgical and non-surgical assistance they needed before (6). Due to the consistent need for pediatric neurosurgical care (trauma, tumors, malformation, etc.) and the new request of COVID-19 treatment, the role of pediatric neurosurgical care in global public health has changed considerably. In fact, healthcare providers, hospitals, and, most importantly, neurosurgeons from all around the world have had to change their mind regarding their protocols. The clinical needs of patients affected by neurosurgical conditions now need to be balanced with the new restrictions and limitations that hospitals face due to the Covid pandemic. The aim of this study was to evaluate the level of evidence and new guidelines established in the world to face the new needs deriving from COVID-19 and neurosurgical pathologies.

Results

We conducted a comprehensive literature search on Pubmed for publications including "COVID-19," "Neurosurgery," and "Pediatric population" as key words. Out of 18 papers, seven articles met the inclusion criteria. One of the main challenges faced in the article selection was related to the reliability of the supporting data, which were mostly obtained from reports that emerged early during the pandemic, and how the COVID-19 pandemic impacted on the pediatric neurosurgical population, which was less explored compared to the adult one. The inclusion parameters were based on the wide diversity of study methodologies, quality of publication, statistical approaches, sample sizes, population characteristics, and geographic and timing parameters. Therefore, 11 articles were excluded because of some limitations of the result's stratification, or the investigation's inaccuracy around surgical procedures and coding diagnosis. Some articles were not included because the results, as many studies related to perioperative complications, for example, were coming from pediatric patients with a general diagnosis of upper respiratory tract infections who did not specifically test positive for COVID-19. Others were excluded because they were investigated more on the anesthesiologic aspects and the pre/post-operative care rather than the actual neurosurgical intervention. The review of the seven articles selected showed different specific topics, such as the trend of neurosurgical operative volumes and solutions to manage the rate of underdiagnosis and the increased length of waiting lists (Table 1). Indications for neurosurgical procedures were analyzed, stratified by timing, and then divided into four main classes in order to have reliable decisional criteria. The studies on perioperative complications and incidence of anesthetic complications in COVID-19 positive children showed higher rates compared to the controls. Many multistep strategies in the pre-operative, anesthesia induction, extubation, and post-operative phases were hence developed to limit the increased risk of viral transmission.

Regarding hospital organizations, the focus was on different polices and customized strategies to limit COVID-19 spread, such as protocols to minimize contacts, screening, adequate equipment, and update training of the personnel. Thanks to many improvements and innovations in telemedicine, teleconsultation, and other different online solutions, outpatients' clinics and follow ups, conferences, and multidisciplinary meetings do not need to be postponed. Finally, online meetings created a more "off-campus" experience to guarantee the adequate training and professional education of residents and fellows without increasing the number of contacts and face-to-face interactions.

Discussion

The COVID-19 pandemic has considerably altered many aspects of neurosurgery. More papers have been published concerning adult settings, while pediatric reports are still few. We tried to review different topics including surgical indication criteria, hospital organization, perioperative complications and care, patients and parents screening, outpatient clinic and teleconsultation, telematic conference and meeting, virtual multidisciplinary meeting, and fellowship and training.

Neurosurgical operative volume

Dave et al. described how numbers of neurosurgical operations lowered during the COVID-19 pandemic in 2020 and 2021 (7). The decrease in surgeries involved different subcategories but epilepsy, non-traumatic spine, and trauma were the most affected ones. They also recorded a decrease in shunt operations. The reduction in volumes could be due to different health-seeking behavior (people tried to avoid hospitals), underdiagnosis, and decrease in trauma cases related to the reduction in activities and quarantine.

Another factor is online education since absence seizures and changes in behavior indicative of shunt failure may be principally noticed in academic settings or during interactions with other people. Moreover, the shift of hospital resources toward medical specialties contributed to the postponement of some elective surgeries. In 2020 and 2021, the decrease in COVID-19 cases was accompanied by an increase in neurosurgical referrals and operations due to the long waiting lists for elective surgeries. However, institutions have now updated their policies and vaccines

TABLE 1 Summary of the most important topics affected by COVID-19 pandemic.

Topic	Issue	Solution	Paper (Author)
Decreased neurosurgical operative volumes (especially in the categories of epilepsy, spine, trauma, and shunt)	- Fear-related changes in health-seeking behavior and decreased consultation lead to underdiagnosis - Increased length of waiting list due to the postponement of elective surgeries and the increase in neurosurgical referrals	Clinical and academics institution updated their policy to permit in-person interactions and tried to decrease, together with vaccines, the rate of underdiagnosis which could precipitating even longer waiting lists for elective surgeries and the dependent volume of neurosurgical operations	Trends in United States Pediatric Neurosurgical Practice during the COVID-19 Pandemic (7)
Surgical indications	Decisional criteria in pediatric patients requiring urgent neurosurgical intervention and resulting positive to PCR test for SARS-CoV-2	Classification of neurosurgical procedures stratified by timing into 4 classes ranging from emergent and urgent procedures (class I) to neurosurgical conditions able to delay treatment more than 1–2 months (class IV)	Urgent Neurosurgical Interventions in the COVID-19-Positive Pediatric Population (8)
Perioperative complications and care	The incidence and severity of anesthetic complications in children with severe acute respiratory syndrome coronavirus 2 is unknown	1. Perianesthetic respiratory complications have higher rates in children with non -severe SARS-CoV-2 infection as compared to matched controls although severe morbidity was rare and there was no mortality 2. The incidence of complications for children with non-severe SARS-CoV-2 infection is similar to the one reported for an upper respiratory tract infection.	Anesthetic Complications Associated With Severe Acute Respiratory Syndrome Coronavirus 2 in Pediatric Patients (9)
	Increased risk of viral transmission to other patients and care providers due the high asymptomatic carrier rate in the pediatric population	1. Minimize crying in the pre-operation (premedication, non-pharmacologic anxiolysis...) 2. IV induction (consider RSI, minimize Bag Mask Ventilation) 3. Prevent coughing during extubation (deep extubation to with adjuncts) 4. Recover in Negative Pressure Isolation Room or in the Operating Room in the post-operation	Unique Challenges in Pediatric Anesthesia Created by COVID-19 (10)
Hospital organization	Policies and stratiegies to limit Covid-19 spread during surgical operations and patients stay at the hospital	1. Supply of adequate equipment 2. Proper training of the healthcare personnel 3. Effective protocols to minimize contact in the operating rooms 4. Patients and parents screening	Urgent Neurosurgical Interventions in the COVID-19-Positive Pediatric Population (8)

(Continued)

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TABLE 1 (Continued)

Topic	Issue	Solution	Paper (Author)
Outpatient clinic and patients follow up	Minimize traffic into the facility of patients and family members who may be COVID-19 positive and face-to-face interaction with staff and clinic personnel	Telemedicine and teleconsultation with improvements in training, billing, and credentialing for both telephone and video-based clinic visits	Editorial. Pediatric Neurosurgery along with Children's Hospitals' Innovations Are Rapid and Uniform in Response to the COVID-19 Pandemic (3)
Conference and multidisciplinary meeting	Decrease face-to-face interaction with staff and personnel to limit the potential spread of the virus	1.Daily morning report, educational and subspecialty conferences are conducted electronically by telephone or video conference 2. Daily telephone call or video conference led by service chiefs, to keep their entire teams updated on the rapidly evolving information on the pandemic	Editorial. Pediatric Neurosurgery along with Children's Hospitals' Innovations Are Rapid and Uniform in Response to the COVID-19 Pandemic (3)
Fellowship and training	Decrease face-to-face interaction with colleagues and personnel to limit the potential spread of the virus	More opportunities for "off-campus" work and telerotation	Editorial. Pediatric Neurosurgery along with Children's Hospitals' Innovations Are Rapid and Uniform in Response to the COVID-19 Pandemic (3)

The main issues, the related solutions, and the paper which described the topics are presented.

are becoming more widespread even among children, so the rebound of surgeries and referrals is less evident in 2022.

Surgical indication criteria

Despite the overall reduction in surgical interventions, differently from other neurosurgical subspecialties, most pediatric neurosurgical cases are emergent or urgent because delayed operations can impede cognitive development. Therefore, institutions all over the world tried to adapt and develop protocols to guide healthcare personnel in their daily practice. Lang et al. conducted a retrospective study including pediatric patients who required urgent neurosurgical intervention and had a positive PCR test for COVID-19 (8). They stratified neurosurgical procedures based on the timing of the need for intervention and detailed all the challenges in dealing with COVID-19-positive patients who also needed urgent surgery. The procedures that could not be postponed included CSF diversion of hydrocephalus or hygromas, evacuation of hematomas/hemorrhages, stabilization of unstable fractures, and tumor resection. All these interventions could be safely performed without additional risks or worsening sequelae for the patients.

Lang et al. also described how the equipment should be adequate and the healthcare personnel must be properly trained to prevent the diffusion of the virus and to avoid complications for the patients (8). For example, premedication with midazolam before surgery has the potential benefit of minimizing crying or coughing by the infected child, thereby reducing the risk of aerosolization of COVID-19 viral particle. For the same purpose, complete muscle relaxation with intravenous neuromuscular blockade was utilized. To reduce air leakage, they used a cuffed orotracheal tube. No additional personnel were present at the induction of anesthesia to minimize the number of contacts and the waste of protective devices; the surgical team entered the room only after the patient was on mechanical ventilation. To minimize door opening, walkie-talkies or phones were used for communication with people outside the room. Movements from the rooms were limited as much as possible and visitors were not allowed. In the series by Lang and colleagues, no patient experienced worsening of COVID-19 related symptoms that required targeted therapy, apart from supportive care (8). They demonstrated that pre-, peri-, and post-operative care of COVID-19-positive patients requiring urgent neurosurgical intervention can be performed without delay, increased complications, or involved personnel infection if defined protocols are applied. This record is very important as young children are still not vaccinated and new variant strains of COVID-19 have become predominant.

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Perioperative complications and care

Saynhalath et al. stated that pediatric patients with non-severe COVID-19 infections are at higher risk of developing perianesthetic respiratory complications such as laryngospasm, bronchospasm, hypoxemia, or postoperative supplemental oxygen requirements compared with uninfected patients (9). This is particularly true in patients with previous pulmonary conditions (e.g., bronchopulmonary dysplasia or respiratory distress in premature babies). However, infected children did not show increased risk of non-respiratory complications or mortality and their perianesthetic complication rates are lower compared to adults. These findings were consistent with other reports in literature which also suggested measures to minimize complications and diffusion of the virus (10). For example, the use of intravenous drugs for induction of anesthesia has been demonstrated to lower the rates of perioperative respiratory adverse events compared to inhalation induction.

Hospital organization and telemedicine

Screening before individuals were allowed to enter the hospital facility was implemented for patients, parents, and healthcare personnel. The COVID-19 pandemic also impacted on other aspects of neurosurgical practice, such as outpatient clinics (3). In order to minimize traffic of patients and family members into the facility, and face-to-face interaction, institutions focused on the improvement and expansion of telemedicine. Both telephone and video-based visits were conducted with success, limiting in-person appointments to those deemed as urgent and absolutely necessary. Optimization of this process allowed full clinic schedules to be maintained even in a situation of restricted in-person contact. Neuroradiological studies were limited to those deemed really necessary.

Online meetings, education, and working

The same principle of employing electronical technologies was applied to the daily morning report, education, and subspecialty conferences and journal clubs (3). Meetings and handovers were conducted by telephone or video conference. Moreover, in most hospitals, administrative and research staff mainly worked from home. With the reduction of surgical and clinical activities, even medical staff was reduced to an essential core (3). This also helped to always have someone available in case of infection of healthcare personnel. Resident pediatric neurosurgery rotations and students' internships were limited and they were encouraged to focus on research activities (3).

A summary of the most important topics affected by the COVID-19 pandemic are presented in Table 1 and Figure 1.

Meyer children hospital's experience and comparisons

Most of the previously discussed topics give a realistic idea of the measures and strategies undertaken at the Meyer Children's Hospital in Florence during the Covid-19 pandemic. Many similarities were also found comparing the specific guidelines adopted by our hospital and the Giannina Gaslini Children's Hospital in Genoa (11).

One of the main priorities was related to the classification of surgical indications and criteria. This necessity, shared by the two Italian hospitals as well as by the American ones (8), has been approached with a communal principle to stratify the neurosurgical procedures by timing, for a total of four classes (8) and five classes (11).

Concerning the perioperative complications and the anesthetic challenges, the principal precautions taken at our hospital were related to the reduction of aerosol and bag mask ventilation in favor of intravenous drugs administration, and the development of strategies to minimize the virus spread with patient's crying (pre-operation) and coughing (post-operation), in line with the indications proposed by Gai et al. (10).

The same restrictions concerning visitors, patient's assistance, and personnel in the operating room described above were applied in our hospital. For patients' and parents' admission, a nasopharyngeal swab must be performed within 48 h.

Both personnel and visitors had to be monitored with routine screening and wear adequate PPE, as comprehensively studied by Ballestero et al. (1).

Another very challenging aspect that had to be faced was related to the education of residents and fellows and, as described by Weiner et al., the development of online opportunities and "off-campus" solutions represented the key factor (3). At Meyer Children's Hospital, face-to-face lectures and multidisciplinary reunions were substituted with online meetings and video conferences. We also had direct proof that telemedicine represents a valid alternative for outpatient clinics and patient follow up, in order to reduce face-to-face interactions and high numbers of visitors to the hospital.

In conclusion, we are prone to state a remarkable homogeneity in the guidelines adopted by hospitals in Europe, South America, Canada, and the USA.

Conclusion

The above-described topics are only part of the profound change produced by the COVID-19 pandemic to pediatric neurosurgery.

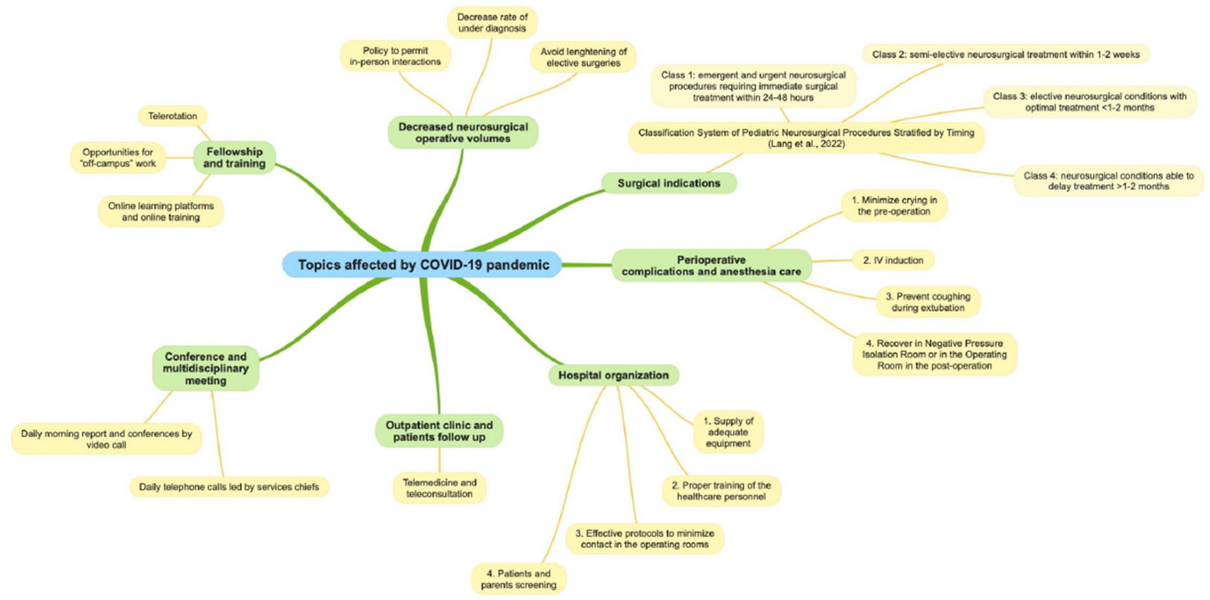

FIGURE 1
Summary of the most important topics affected by COVID-19 pandemic and related solutions.

The aim of this study was firstly to evaluate the level of evidence and new guidelines proposed by up-to-date literature. In the second instance, we compared our hospital's experience with the strategies undertaken to face COVID-19 by different healthcare systems all over the world, in order to offer an innovative point of view on the current pediatric neurosurgical trends.

Although epidemiological data look more promising now and the availability of the vaccine even for the youngest children is helping us deal with this challenging battle against the virus, the advent of new very contagious variants continuously creates new obstacles. For these reasons, we believe that further studies and research will be necessary.

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

FG conceived the study. AN, SP, and CS collected and re-examined the data and wrote the manuscript. FG, AD, and ML reviewed and revised 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.

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The parental psychological distress caused by separation from their critically ill child during the COVID-19 pandemic: A tale of two cities

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Introduction: A child's critical illness is a stressful event for the entire family, causing significant emotional distress among parents and changes to family functioning. The Severe Acute Respiratory Syndrome-Related Coronavirus 2 (SARS-CoV-2) pandemic has abruptly caused modifications in visitation policies of Pediatric Intensive Care Units (PICUs) in many countries. We hypothesized that caregivers with no or severely restricted access to PICUs would demonstrate increased psychological distress as compared to those who had limitless access (LA) to PICUs.

Methods: Sociodemographic variables, levels of psychological distress, ratings of family functioning, and ability to cope with stressful events were collected with an online survey in a group of caregivers after their child's hospitalization. Ratings of psychological distress were compared between caregivers with no/severely restricted (NA) and with LA to PICUs.

Results: Measures of depression, anxiety, and global severity index (GSI) of psychological distress were significantly higher in NA caregivers as compared to LA. Among demographic characteristics of the sample, only gender influenced the severity of psychological symptoms: women showed an increased score on levels of somatization, depression, anxiety, and GSI. Avoidant coping style positively correlated with measures of depression. Univariate General Linear Model (GLM) analyses of the effects of sex, age, visitation policies of PICUs, and score of avoidant coping strategies on measures of psychological distress confirmed a significant univariate effect of no access to PICUs on parents' psychopathological scores.

Conclusion: Restrictions imposed on visitation policies in PICU during the pandemic negatively impacted families' psychological wellbeing. A balance between the safety of patients, families, and health care professionals and meeting the needs of families is of utmost importance.

KEYWORDS

PICU visitation policies, COVID-19, psychological distress, caregivers, separation

Introduction

A child's critical illness is a stressful event for the entire family, causing significant emotional distress among parents and changes to family functioning (1), which can lead to symptoms of Acute Stress Disorder (ASD), Post-Traumatic Stress (PTSS), and Post-Traumatic Stress Disorder (PTSD) (2–4).

Partnerships between families and the health care team are essential in pediatrics where children are often unable to self-report symptoms or treatment preferences due to their developmental stage or health status. Open visitation policies in Pediatric Intensive Care Units (PICUs) are the heart of Patient-Centered and Family-Centered care (PFCC), which is the scenario where there is a mutually beneficial partnership among patients, families, and providers, and the importance of the family in the patient's life is recognized and valorized (5). The PFCC has been demonstrated to improve outcomes of patients, families, and health care providers. It can be effective in decreasing anxiety, sedative dose requirements, delirium, mechanical ventilation, and sedation duration, and it is significantly related to early mobility and reduced ICU length of stay (5, 6).

The pandemic of Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) has abruptly caused modifications in visitation policies of PICUs across the globe (7), mainly necessitated by the scarcity of personal protective equipment (PPE) and the complexity involved in implementing protocols for the admission of family members.

Although it has been defined as ethical to limit visitation in the interests of public health during times of pandemic (8), the separation of a person from critically ill relative can be a source of stress (9, 10), which is particularly increased in the case of a hospitalized child with his parents (11).

The aim of the present study was to compare self-reported psychological distress between parents of children admitted to a PICU with no modification to visitation policy during the COVID-19 outbreak (and limitless parental presence) with parents of children admitted to a PICU with restricted visit access (from no presence allowed to access restricted to 1 h a day).

Materials and methods

Participants

The present is an observational, cross-sectional cohort study. After institutional review board (IRB) approval (2021/ST/005), the parents of children admitted to two PICUs for longer than 24 h during the period March–December 2020 were enrolled in the study. Parents of children whose outcome was death were not enrolled.

The two PICUs are located, respectively, in Milano, Italy (Vittore Buzzi Children's Hospital) and Lisbon, Portugal (Centro Hospitalar Universitário Lisboa Norte).

The Italian PICU did not allow the entrance of families of admitted patients during the year 2020 up to October and allowed restricted access (1 h a day) during November and December 2020.

The Portuguese PICU did not change its visiting policy during the first year of the pandemic and allowed limitless presence at the bedside, as before the pandemic.

Parents of children who were admitted to both PICUs during the given period were contacted at the beginning of 2021 and agreed to participate in the study. The questionnaires were hosted on an online platform (*SurveyMonkey*®). Informed consent was obtained from all participants, and the IRB approved the study in accordance with the principles in the Declaration of Helsinki.

Data collection and analyses

In the group of participants, sociodemographic data, levels of psychological distress, characteristics of family functioning, and coping skills were collected following their child's hospitalization in the PICUs.

Patients' clinical severity at admission to PICU was assessed with pediatric risk of mortality (PRISM) II (12).

Caregivers were asked to retrospectively evaluate their psychological distress using the self-report questionnaire Brief Symptom Inventory-18 (13) (BSI-18), an 18-item questionnaire that assesses three psychological symptoms (somatization, anxiety, and depression) and provides a global index of distress (global severity index; GSI) based on the number and intensity of the symptoms endorsed by the respondent.

Caregivers' family functioning was assessed with the Family Assessment Device (FAD), identifying six dimensions of family functioning (14): (1) problem solving, the family's ability to resolve problems at a level that maintains effective family functioning; (2) communication, which is defined as the exchange of information among family members; (3) roles, which evaluate established patterns of behavior for handling a set of family functions that include provision of resources, providing nurturance and support, and supporting personal development; (4) affective responsiveness, which assesses the extent to which individual family members can experience appropriate effect over a range of stimuli; (5) affective involvement, which is concerned with the extent to which family members are interested in and place value on each other's activities and concerns; and (6) behavior control, which assesses how a family expresses and maintains standards for the behavior of its members.

The Brief-Coping Orientation to Problems Experienced (COPE) inventory (15, 16)was administered to measure caregivers' effective and ineffective ways to cope with stressful circumstances. This scale can identify three coping styles:

1. Problem-focused coping, which is characterized by active coping, informational support, planning, and positive reframing.
2. Emotion-focused coping, relying on venting, emotional support, humor, acceptance, self-blame, and religion, and
3. Avoidant coping that includes strategies, such as self-distraction, denial, substance use, and behavioral disengagement.

Student's t-tests exploring the effects of sex and visitation policies of PICUs on parents' symptoms severity were performed. Pearson's correlation analysis was conducted to test the correlation between age, years of education, economic status, family functioning scores, personal ability to cope with stressful events, and psychopathology scores. To account for the multiple covarying variables, we also tested the effect of predictors on the current psychopathological status (self-report scores) by modeling the influences of the predictors on the outcomes in the context of the General Linear Model (GLM) and calculating the statistical significance of the effect of the single independent factors on the dependent variables by parametric estimates of predictor variables (least squares method). Analyses of univariate effects were performed by using a commercially available software package (StatSoft Statistica 12, Tulsa, OK, United States) and following standard computational procedures (17, 18).

Results

In total, 78 families in Lisbon and 20 families in Milano were contacted. Forty-three parents (N = 43) were agreed to participate in the study: 19 caregivers from Italy had no or severely restricted access to PICUs (NA group), while 24 parents from Portugal had maintained limitless access (LA group). The study was carried out 2–9 months after the child's hospitalization; this time frame was homogeneous in both groups.

Demographic and psychological characteristics of the whole sample and the two subsamples are resumed in **Table 1**.

In total, 49% of caregivers were aged between 26 and 40 years old and 51% were between 41 and 60: 53% of them were married, 17% were separated or divorced, and 30% were single.

TABLE 1 Demographic and psychological characteristics of the whole group and subgroups.

	All (N = 43)	NA (N = 19)	LA (N = 24)	χ/T	p
Sex (M/F)	9/34	1/18	8/16	5.04	0.02*
PRISM II	5.34 ± 4.28	3.60 ± 2.47	6.65 ± 4.91	−2.19	0.03*
BSI–Somatization	6.90 ± 5.32	8.31 ± 6.23	5.79 ± 4.28	1.57	0.12
BSI–Anxiety	14.27 ± 5.27	16.78 ± 4.76	12.29 ± 4.86	3.03	0.004*
BSI–Depression	12.39 ± 6.01	15.26 ± 5.63	10.12 ± 5.39	3.04	0.004*
BSI–Global severity index	33.58 ± 14.91	40.36 ± 15.03	28.20 ± 12.69	2.87	0.006*
FAD–Problem solving	1.94 ± 0.32	1.90 ± 0.35	1.97 ± 0.29	−0.70	0.48
FAD–Communication	2.22 ± 0.38	2.05 ± 0.38	2.35 ± 0.33	−2.55	0.01*
FAD–Roles	2.33 ± 0.38	2.28 ± 0.38	2.38 ± 0.39	−0.76	0.45
FAD–Affective responsiveness	2.12 ± 0.51	1.96 ± 0.40	2.25 ± 0.55	−1.8	0.07
FAD–Affective involvement	2.77 ± 0.33	2.78 ± 0.28	2.77 ± 0.38	0.04	0.96
FAD–Behavioral control	2 ± 0.35	2 ± 0.39	2 ± 0.32	0.08	0.93
FAD–Global functioning	1.89 ± 0.46	1.79 ± 0.36	1.98 ± 0.51	−1.25	0.21
Brief COPE–Problem-focused therapy	1.91 ± 0.34	1.93 ± 0.33	1.90 ± 0.36	0.29	0.77
Brief COPE–Emotion focused therapy	1.66 ± 0.42	1.61 ± 0.48	1.69 ± 0.37	−0.57	0.56
Brief COPE–Avoidant coping	0.82 ± 0.38	0.78 ± 0.33	0.85 ± 0.41	−0.52	0.60

Caregivers self-rated their symptoms on the Brief Symptom Inventory-18 (BSI-18), also yielding mean scores for somatization, anxiety and depression; their family functioning at Family Assessment Device (FAD) providing mean scores for the following measures: problem solving, communication, roles, affective responsiveness, affective involvement, behavior control, global functioning and their ability to cope for stress with The Brief-COPE (Coping Orientation to Problems Experienced) inventory. Data are means ± standard deviations and χ squared, T-test statistics and relative p-values. Significant differences are marked with an asterisk (*).

Concerning their educational level, 5% of parents reported to have a primary school diploma, 32% of parents reported to have a secondary school diploma, 23% of parents reported to have a high school diploma, 28% of parents reported to have a Bachelor's Degree, 7% of parents reported to have a Master's Degree, and 5% of parents reported to have a first-level Specializing Master. A full-time job was reported by 70% of respondents, 21% had a part-time job, 5% were housewives, and 4% were unemployed. Regarding annual income, 28% of respondents had an average salary lower than 8,000€, 21% of respondents had an average salary between 8,000€ and 15,000€, 37% of respondents had an average salary between 15,000€ and 28,000€, 12% of respondents had an average salary between 28,000€ and 55,000€, and only 2% had higher than 75,000€.

Brief Symptom Inventory measures of depression, anxiety, and GSI of psychological distress were significantly higher in NA caregivers as compared to LA ($t = 3.04$, $p = 0.004$; $t = 3.03$, $p = 0.004$; and $t = 2.87$, $p = 0.006$, respectively).

Among demographic characteristics of the samples, only gender influenced the severity of psychological symptoms: women showed an increased score on levels of somatization, depression, anxiety, and GSI ($t = 2.05$, $p = 0.04$; $t = 2.55$, $p = 0.01$; $t = 2.44$, $p = 0.01$; and $t = 2.66$, $p = 0.01$, respectively). No significant effect of age, education, average annual income or marital status, or child's clinical prognosis on measures of parents' psychological distress was found.

Among dimensions of family functioning, affective responsiveness was found to inversely correlate with anxiety score ($R = -0.34$, $p = 0.03$), but no other dimension was associated with symptomatology. Avoidant coping style positively correlated with measures of depression ($R = 0.37$, $p = 0.02$) and GSI ($R = 0.35$, $p = 0.03$).

Univariate GLM analyses of the effects of sex, visitation policies of PICUs, scores of affective responsiveness, and avoidant coping strategies on measures of psychological distress confirmed a significant univariate effect of visitation policies of PICUs (anxiety: $\beta = 0.38$, $F = 5.83$, $p = 0.021$; depression: $\beta = 0.39$, $F = 6.75$, $p = 0.014$; GSI: $\beta = 0.37$, $F = 5.79$, $p = 0.022$), avoidant coping style (somatization: $\beta = 0.43$, $F = 5.96$, $p = 0.024$; depression: $\beta = 0.57$, $F = 14.48$, $p = 0.006$; GSI: $\beta = 0.55$, $F = 13.05$, $p = 0.01$), but none of the other predictors (Tables 2, 3).

Discussion

To our knowledge, this is the first study directly comparing parental psychological distress between parents who have been denied access to the bedside during their child's PICU stay and parents who did not experience separation from their child during PICU stay, during the COVID-19 pandemic period.

TABLE 2 Correlations between measures of family functioning at Family Assessment Device (FAD) and ability to cope with stress at the Brief-COPE (Coping Orientation to Problems Experienced) inventory and measures of psychological distress at the Brief Symptom Inventory-18 (BSI-18).

	FAD–Problem solving	FAD–Communication	FAD-Roles	FAD-Affective responsiveness	FAD–Affective involvement	FAD–Behavioral control	FAD – Global functioning	Brief COPE–Problem-focused therapy	Brief COPE–Emotion focused therapy	Brief COPE–Avoidant coping
BSI–Somatization	$R = 0.08$	$R = 0.098$	$R = 0.087$	$R = -0.085$	$R = -0.151$	$R = 0.254$	$R = 0.157$	$R = 0.131$	$R = -0.037$	$R = 0.35$
	$p = 0.629$	$p = 0.557$	$p = 0.603$	$p = 0.609$	$p = 0.362$	$p = 0.123$	$p = 0.345$	$p = 0.439$	$p = 0.827$	$p = 0.136$
BSI–Anxiety	$R = -0.008$	$R = -0.199$	$R = -0.083$	$R = -0.341$	$R = -0.226$	$R = 0.052$	$R = -0.124$	$R = 0.073$	$R = 0.088$	$R = 0.374$
	$p = 0.958$	$p = 0.229$	$p = 0.619$	$p = 0.032$*	$p = 0.171$	$p = 0.756$	$p = 0.456$	$p = 0.667$	$p = 0.603$	$p = 0.021$*
BSI–Depression	$R = 0.02$	$R = -0.205$	$R = -0.096$	$R = -0.307$	$R = -0.101$	$R = -0.017$	$R = -0.165$	$R = -0.076$	$R = -0.091$	$R = 0.284$
	$p = 0.904$	$p = 0.216$	$p = 0.564$	$p = 0.061$	$p = 0.543$	$p = 0.915$	$p = 0.320$	$p = 0.654$	$p = 0.590$	$p = 0.093$
BSI–Global severity index	$R = 0.032$	$R = -0.118$	$R = -0.036$	$R = -0.225$	$R = -0.179$	$R = 0.103$	$R = -0.053$	$R = 0.047$	$R = -0.009$	$R = 0.354$
	$p = 0.849$	$p = 0.481$	$p = 0.826$	$p = 0.173$	$p = 0.280$	$p = 0.535$	$p = 0.752$	$p = 0.780$	$p = 0.954$	$p = 0.031$*

Data are R Pearson correlation coefficients and relative p-values. Significant correlations are marked with an asterisk (*).

TABLE 3 Univariate GLM analyses of the effects of sex, visitation policies of PICU's, scores of affective responsiveness, and avoidant coping strategies on measures of psychological distress.

	Sex	PICU's policy	FAD–Affective responsiveness	Brief COPE–Avoidant coping
BSI–Somatization	$F = 0.83$ $\beta = 0.159$ $p = 0.369$	$F = 0.845$ $\beta = 0.163$ $p = 0.364$	$F = 1.288$ $\beta = -0.213$ $p = 0.265$	$F = 5.967$* $\beta = 0.438$ $p = 0.02$
BSI–Anxiety	$F = 2.416$ $\beta = 0.236$ $p = 0.13$	$F = 5.832$* $\beta = 0.381$ $p = 0.021$	$F = 2.258$ $\beta = -0.441$ $p = 0.113$	$F = 2.241$ $\beta = 0.475$ $p = 0.423$
BSI–Depression	$F = 1.906$ $\beta = 0.202$ $p = 0.177$	$F = 6.758$* $\beta = 0.397$ $p = 0.014$	$F = 1.334$ $\beta = -0.363$ $p = 0.376$	$F = 14.485$* $\beta = 0.572$ $p = 0.006$
BSI–Global severity index	$F = 2.207$ $\beta = 0.22$ $p = 0.147$	$F = 7.712$* $\beta = 0.40$ $p = 0.009$	$F = 1.563$ $\beta = -0.37$ $p = 0.243$	$F = 13.051$* $\beta = 0.55$ $p = 0.001$

Data are *F*-tests, beta coefficients, and relative *p*-values. Significant tests are marked with an asterisk (*).

The results show a correlation between separation and parents' psychological wellbeing: those who have been separated from their children during the pandemic show higher scores in anxiety, depression, and GSI, which is the sum of nine symptom dimensions: somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism.

The experience of having a child admitted to a PICU is an extremely stressful one, with long-time repercussions, as easily understandable and objectively demonstrated by previous studies (4, 19, 20). During this experience, both the child (patient) and caregivers become vulnerable due to the uncertainties generated by the illness and the hospitalization. Coping with this new situation requires adaptation to it, and in this process, there is a potential role for health care workers to provide a more comfortable environment. The possibility for parents to be at the bedside without time restrictions had become obvious in a great part of the world before the COVID-19 pandemic that has abruptly changed this scenario (7). Its benefits—communication, collaboration, and support—show their effect on all the figures involved: the child who is critically ill, the family, and the health care workers. In 2020, a qualitative descriptive study was conducted at an Australian quaternary hospital to explore the care and communication experienced by family members of ICU patients during this time. The severe visiting restrictions introduced in the ICU during the pandemic to limit the spread of infection and protect patients and staff members have been reported to cause significant psychological and social impacts on families. Patient care and involvement in decision-making were appeared to be unchanged, but communication with staff was felt to be lacking (21).

The experience of not being allowed at the bedside, close to the child, adds on the opposite another stress to parents, as shown by our results. Similar results have been demonstrated by researchers in relatives of adult patients admitted with COVID-19 (9) but we believe family presence is inalienable and undeniable when the patient is a child, especially if the child is critically ill. In a potential and dramatic scenario, the patients could die without having their families with them, and a family could lose their child without being present. Although the initial intention is a good one (avoidance of community spread of pathogens), the results of a restricted visitation policy cause a too severe burden on the different actors involved that cannot be acceptable (22).

It is interesting to note that this psychological distress is not strictly related to the patient's clinical prognosis/gravity (through the PRISM II index): Portuguese parents, though their children were on average more severely ill than the Italian ones, showed better results, as if the event of critical illness/PICU admission was the cause of stress *per se*, rather than the real clinical severity. In addition, this could be explained by better communication with nurses and doctors when the presence at the bedside of the child is guaranteed and a better understanding of the patient's conditions and procedures a child is undergoing (23).

Among parents, women showed higher scores in some of the investigated points, namely, somatization, depression, and anxiety; although it is beyond our scope to interrogate the causes of this difference, this is a recognized scenario (24–26). However, our results suggested that a restricted visitation policy could impact the severity of anxiety, depression, and GSI scores regardless of the gender of the participants, which lacked significant effect in the models.

The severity of anxiety was found to inversely correlate with affective responsiveness in the family context. Anxiety is characterized by a condition of diffuse arousal following the perception of a real or imagined threat. This future-oriented, self-focusing emotion, when it reaches maladaptive levels, can consume a great number of attentional resources and lead to the feelings of helplessness and withdrawal. Therefore, it is no surprise that deficiencies in emotional awareness and affective responsiveness over a range of different stimuli are likely to associate with anxiety feelings.

The use of avoidant coping strategies to deal with stressful events did not differ in the two samples and was associated with a higher level of psychological distress.

Communication between health care workers and families has changed means, during the COVID pandemic, with the new strategies being implemented, such as video conferences, but the results in terms of satisfaction are never as satisfying as in person (27) and could lead to potential inequalities (28, 29) between families.

Potential limitations

We acknowledge there are a few limitations to our study, mainly concerning the temporal distance of the Questionnaires' administration to parents in relation to the PICU stay of their child. A previous study (19) evaluating the trajectories of parental distress up to 12 months after the experience of admission of a child to PICU showed three types of reactions—persistent low distress, persistent moderate-high distress, and high distress with recovery—but the pattern of distress did not rise over time. Based on this too, we believe that it is not likely that the participants in our study could be of over-reporting symptoms, although we cannot rule it out; the possibility, however, resides homogeneously in both groups along with the same time gap being present in both groups.

Another limitation that could be addressed is that the two study groups are from two different countries, but these two countries are similar in terms of geographical position, language, culture, and religion; and the feelings a parent experiences toward the child are universal.

Strengths

The main strength of the study resides in the very well-detailed scales that were administered to the parents, which cover different aspects of the potential responses to psychological distress and of the different mechanisms of coping. Although we feared that the questionnaires could have been time consuming and tiring for "lay" persons, all parents were enthusiastic about their participation in the study and did not report fatigue in completing the questionnaires.

Conclusion

Separation from a critically ill child during the most acute phase of the disease, that is, during PICU stay, has detrimental effects on parents in terms of psychological distress symptoms. The results of this study reinforce the need to develop strategies to allow the presence of parents during PICU admission, even in times of pandemic or other exceptional circumstances. The lessons learned from COVID-19 can be useful in future pandemics.

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 Milano Area 1, protocol no. 2021/ST/005. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AC and EM: study design and conceptualization. FA, ET, FI, SF, and EZ: data collection. EM: data analysis. AC, EM, and FA: manuscript writing. All authors 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.

Publisher's note

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Taking the rights of children with complex conditions seriously: New ethics challenges arisen during the COVID-19 pandemic

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Introduction

Children with complex care conditions (CCCs) and their families have always been a fragile population, at high risk of marginalisation and social exclusion, even prior to the outbreak of the COVID-19 pandemic. Few studies have explored in detail the impact of the pandemic on CCCs, and there are no shared guidelines on how to tackle the specific ethical dilemmas posed by the COVID-19 predicament. Both healthcare professionals and families improvised novel strategies to overcome the current crisis, but these tentative answers cannot be the solution in the long run.

In this article, we set out to highlight some new ethics challenges regarding CCCs arisen during the COVID-19 pandemic, referring on the one hand to the United Nations Convention on the Rights of the Child (UNCRC)[1] and on the other hand to the experience of a Paediatric Palliative Care Service of the Veneto Region (Italy), presenting and discussing three real-life cases.

Clinical ethics considerations such as those inspired by Beauchamp and Childress' principlist approach (1) must be coupled with other relevant evaluations regarding the access to education (UNCRC, art. 28) or the protection of family unity (UNCRC, art. 9), without any discrimination (UNCRC, art. 23), and with a particular attention to children with special needs (UNCRC, art. 23). Furthermore, this lines up with Amartya Sen's approach (2), who identified the social opportunities of decent healthcare and education as prerequisites for developing one's capabilities and consequently for exercising one's freedom. The growing recognition of the importance of adopting a rights-centred approach in healthcare led the World Health Organisation (WHO) Europe to develop a set of tools to assess and improve the respect of children's rights also in primary healthcare[2] (3).

1 https://www.unicef.org/child-rights-convention/convention-text-childrens-version

2 https://ec.europa.eu/info/aid-development-cooperation-fundamental-rights/your-rights-eu/eu-charter-fundamental-rights_en

Existing medical literature has shown that the COVID-19 pandemic has had a considerable impact on the paediatric healthcare settings (4–11). Social distancing and school closure, coupled with the reduction of other activities, have caused harmful psychological consequences on adolescents and the paediatric population in general (5, 6). Such negative consequences were especially heavy on CCCs, on minors with a migrant background, and with low socioeconomic status (7–10). In addition, visiting limitations during hospitalisation and reduction of elective healthcare activities have had long-term detrimental consequences (11, 12). In some specific situations, a delay in the interventions or very strict visiting policies have adversely influenced the care trajectory of these patients.

While it is important that paediatric teams take up their responsibilities to defend and promote these rights (4), it is also important to systematically collect the opinions and experiences of all parties involved (especially those of the minors and their parents) to accurately map their problems and to critically evaluate the balance that we have so far achieved between competing ethics concerns or competing rights. This seems a necessary preliminary step towards revising our priorities and better organising the services we deem essential for granting the basic rights of CCCs.

The three cases we have selected are meant to shed light on the kinds of ethics challenges we need to tackle through empirical research and philosophical reflection.

Case 1: The story of Mary—The challenge of providing humane end-of-life care to CCCs even under strict public health measures to counter the pandemic

Mary was a 3-year-old girl, affected by gangliosidosis type 1. She was hospitalised in the COVID-19 Paediatric Emergency Department (ER) 1 week before her death, due to an acute respiratory distress syndrome caused by the COVID-19 infection. Her parents were not vaccinated. Her clinical neurologic condition had been evolving over time, and at the moment of hospitalisation, she presented with a progressive neurological impairment with increasing seizures, dystonic movements, and major difficulties in oral feeding. Pain and dyspnea management was challenging at the beginning of hospitalisation, with an improvement after the optimization of the analgesic therapy. Within 48 h, Mary presented a clinical evolution towards multiorgan failure. Since death was imminent, both parents were admitted to the unit, but regulations forbid other family members to visit her. This was a source of distress for Mary's mum and dad.

The family is of Macedonian origin. Mary's parents have been living in Italy for a long time. They had always wanted to bring the little girl to Macedonia, to introduce her to the rest of their large family. Unfortunately, their daughter's health problems, combined with the fear of contagion and closed borders, made the desired family reunion impossible.

The story of Mary and her family is emblematic of the difficulties to grant the respect of the child's right to spend time with all family members, also during hospitalisation in emergency times (UNCRC, art. 9), and to receive appropriate palliative care, including timely psychological support.

The ethics challenge we have to face in this case could be summarised as follows: how to balance the need to implement public health safety measures with the moral duty to provide humane end-of-life care to CCCs and to support their families?

Case 2: The story of Federico—The challenge of granting effective educational opportunities to chronically ill patients

Federico is an 11-year-old boy, suffering from Duchenne's muscular dystrophy.

In spring 2020, Federico was in fifth grade, and due to the pandemic, the school attendance was disrupted and replaced by distance learning, which was somewhat disorganised at the beginning. After a few weeks, Federico's family was able to obtain that one educator would go to their house, but it was only for 1 h a week. All his pneumological, neurological, and cardiac follow-ups, as well as dental surgery, were postponed to a later date due to public health restrictions.

In September 2020, schools reopened for everyone but Federico. His parents were very anxious about the possibility of contagion. Furthermore, they were unconvinced to vaccinate their son and they decided not to send the boy to school. Federico always felt he had no say in the decision. Federico's school was very open to dialogue both with the boy's parents and with healthcare professionals, but at the same time it was not prepared to deal with Federico's fragile health situation during a pandemic crisis. Several meetings were held with the teaching staff to identify the best way to guarantee the boy's right to education and his desire to have social contacts while preserving his physical wellbeing.

For the first 2 months of the new school year, no educator was allowed to go to Federico's home, and only in November 2020, a home support teacher was finally assigned. He established a positive relationship with him, with good school performance. Contacts with classmates remained sporadic.

The story of Federico is emblematic of the difficulties to defend CCCs' right to give their opinion on issues affecting them (UNCRC, art. 12) and to grant CCC's right to education and social interaction even if seriously ill (UNCRC, art. 28).

The ethics challenges we have to face in this case could be summarised as follows: how to balance the understandable desire to reduce the probability of contagion in fragile patients with the crucial need to grant access to effective education and social interaction, which are instrumental in the flourishing of CCCs? How to include CCCs who are cognizant of the situation in decision-making regarding their education?

Case 3: The story of Alex—The challenge of granting access to adequate elective care for cancer patients

Alex was a 10-year-old patient with anaplastic ependymoma. He was hospitalised to receive radiotherapy (RT) in order to contain the symptoms. After 10 days, he contracted the SARS-COV2 infection in the hospital and had to be isolated (together with his mother) in the paediatric COVID-19 ward. Alex's family originates from East Africa, and his mother did not speak Italian, making communication *via* standard online devices very difficult. In the new ward, Alex did not feel comfortable: all the doctors and nurses were dressed in white, their faces masked, and their bodies completely covered by protective equipment. It was not easy for him to understand who they were and what they wanted to do on him. His mother found it even harder to understand what was happening and fell into a depression.

Since he was infected with SARS-CoV-2, Alex's RT was scheduled in the late evening, without the possibility for him to be accompanied by anyone. Consequently, he was terribly anxious and experienced a crisis of psychomotor agitation during one of the RT sessions. For this reason, the clinical staff decided to suspend the RT till the resolution of the SARS-CoV-2 infection, which lasted 20 days. Once retransferred to the standard hospitalisation unit, due to the positivity of his caregiver, he needed to be isolated again in the COVID unit for 5 more days, with a new suspension of the RT. Eventually, since he had become depressed as a result of the prolonged isolation, it was decided to send him back home. The subsequent RT sessions were organised with daily transport from his home to the hospital and back. Unfortunately, shortly afterward Alex passed away.

The story of Alex is emblematic of the difficulties to grant the right of CCCs to access treatments in a timely manner (UNCRC, art. 6), the right not to be separated from their family (UNCRC, art. 9), and the right to rest, relax, play, and take part in creative activities (UNCRC, art. 31).

The ethics challenge we have to face in this case could be summarised as follows: how to balance the necessity to reorganise and prioritise the healthcare resources during a pandemic with the importance to ensure vital access to elective care (such as cancer treatments)?

Discussion and conclusion

The ethics challenges we have presented are just a sample of the new ethics issues arisen in the care of CCCs and their families during the current COVID-19 pandemic.

While the literature has focused so far on the ethics dilemmas connected with the drastic restriction of visitation policy in acute settings (11, 12), especially during the first waves, less attention has been dedicated to the impact of the reorganisation of the healthcare services and to the repercussions of public health policies on some fundamental rights of children with complex conditions. Indeed, many CCCs have experienced a remarkable reduction in the enjoyment of basic rights, such as access to timely therapies, access to education, and the possibility to socialise, play, and take part in cultural and creative activities.

At the beginning of the pandemic, some families of CCCs reported that social isolation was perceived as a form of protection (13, 14). Later on, however, both parents of CCCs and healthcare providers were confronted with a new kind of ethics dilemmas: what is the right balance between the duty to protect and preserve health and the duty to grant children the social and cultural experiences that are essential to their flourishing and to their mental wellbeing? How can we put in place the necessary public health policies without compromising the access to therapies to particularly fragile children and families? The solutions devised by some healthcare institutions, that were able to reorganise their services in order to offer home care, are commendable and a sign of moral creativity, i.e., of the tension to constantly find new ways to interpret and implement moral values, especially in response to unprecedented situations. For instance, in the case of Alex, the healthcare team was able—alas only in his last days—to organise a daily transport from home to the hospital, in order to grant both access to needed therapy and the crucially important closeness to the family. However, more structured prevention measures and the definition of new policies require a preliminary effort to carry out research involving all stakeholders and more nuanced moral reflection. Indeed, only after such a process we could tackle the issue, for example, of how to balance the need for healthcare professionals to wear personal protective equipment and the importance not to scare already fragile and confused minors.

This is why we end this article by calling for widespread mix-methods studies on the experiences and opinions of CCCs, families, educators, and healthcare providers. Patient-reported outcomes (PROs) (15, 16) should be more integrated in clinical research as they provide information on how healthcare affects patient health and wellbeing in a patient- and family-centred approach.

Coupling ample stakeholders' involvement with frank moral discussion seems to us the best way to tackle the thorny ethics issues we have highlighted, such as the balance between the rights of the single and the community or the balance in resource allocation of our already stressed healthcare systems.

Author contributions

AZ conceived the article. AZ and AS collected and described the clinical cases and drafted the first version of the manuscript. EF thoroughly revised the article with specific attention to the ethics considerations. FB supervised this work and discussed with all the authors the clinical cases and the overview of the topic. All authors discussed, contributed, and approved the final manuscript.

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.

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COVID-19 pandemic impact on follow-up of child growth and development in Brazil

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Objectives: This study investigated the impact of the COVID-19 pandemic on the primary health care (PHC) services to follow-up the child growth and development (CGD) in Brazil.
Methods: A cross-sectional study was conducted using secondary data related visits to assess the growth and development of children up to five years between Apr-2017 to Mar-2021. Differences between monthly rate of visits (per thousand inhabitants up to five) during the pandemic (Apr-2020 to Mar-2021) and before (Apr-2017 to Mar-2020) were analyzed using paired t test and control diagrams (averages $\pm$ 1.96 standard deviation).
Results: A total of 39,599,313 visits for monitoring CGD was studied. The average monthly rate of visits dropped from 61.34 (per thousand) before the pandemic to 39.70 in the first 12 months of the pandemic ($p < 0.001$). In all states, except Rio Grande do Sul, there was a significant reduction, with differences ranging from −14.21% in São Paulo to −59.66% in Ceará. The Northeast region was the most impacted, being lower than expected in all 12 first months of pandemic.
Conclusions: The number of visits to follow-up the CGD in PHC in Brazil decreased during the first year of the COVID-19 pandemic, varying over the months and between states and regions.

KEYWORDS
COVID-19, pandemics, health services accessibility, child care, growth and development

Introduction

In February 2020, the first COVID-19 case was registered in Brazil, caused by the SARS-CoV-2 virus. Currently, in December 2021, there are more than 22 million cases and almost 616,000 deaths in the country (1). Besides the number of infected and dead people, there is the economic, social, cultural, political, and public health impact entailed by this situation.

Although the definitive impacts of the pandemic on health systems have not yet been revealed, in many countries, effects have been pointed out, with emphasis on the reduction in the use of health services for elective care, including a reduction in the rates of individual clinical care for children in primary care services (2–4). Visits to monitor the children's growth and development (CGD) were also undermined during the pandemic (5–7).

At first, both political-organizational and public health factors and individual decisions contributed to these impacts on health care services. From an individual point of view, the fear of contracting the disease may have been decisive in the intention of seeking care and, consequently, in the use of services (3, 4). From a political-organizational and public health point of view, measures to control the spread of contamination and ensure a response to the most serious cases converged to discourage the supply of routine and elective care, as well as its demand, including health care in programs focused on monitoring the CGD in primary health care services (PHC) (8, 9).

Monitoring the children's growth and development is part of one of the seven strategic axes of the National Policy for Comprehensive Child Health Care, in addition to being one of the actions that contribute to achieving global challenges such as the Sustainable Development Goals (10). In practice, it consists of periodic visits in which actions are carried out to promote health, breastfeeding, development, immunization, tracking of pathological conditions, prevention of accidents and monitoring of growth and body weight according to the children's age; and, in many situations, they favor access to diagnosis of both acute and chronic diseases.

Similar to other elective care in PHC, it is expected that services focused on monitoring the CGD has been reduced. Nevertheless, it is not yet known the size of this impact or its regional distribution after 12 months of the first case. In this sense, the objective of this study was to investigate the impact of the COVID-19 pandemic on the PHC services to follow-up the CGD in Brazil.

Methods

This is a descriptive and analytical study, with an ecological cross-sectional design, using data from the Health Information System for Primary Care (SISAB, as per its Portuguese acronym), which belongs to the Brazilian Ministry of Health. SISAB has been mandatory throughout the country since June 2015 and is part of the e-SUS Primary Care (e-SUS AB, as per its Portuguese acronym) strategy (11).

Data about the monthly number of individual visits performed to assess the growth and development of children up to five years of age in PHC services throughout Brazil in the period from April 2017 to March 2021 were considered. Data extraction took place in June 2021 in an automated manner and directly from SISAB, through the process known as web scrapping or data scrapping (12). The extraction process was carried out using Node.js software, with code in *JavaScrip*t language to access the page https://sisab.saude.gov.br, fill in the forms according to a previously defined protocol and download reports referring to problems or conditions evaluated by health professionals in each of the months included in the studied period. Data from the Federal District for April, May and June 2017 were not available in the SISAB tool, and therefore were not studied.

Descriptive analyses were performed using absolute and relative frequencies of primary health care visits. The rates of visits for to assess the growth and development were calculated for each thousand children up to five years of age considering population estimates by age groups for Brazil, regions, states, and the Federal District (13).

Differences between the average rates of visits in the pre-pandemic periods (from April 2017 to March 2020) and during the pandemic (from April 2020 to March 2021) were calculated and compared using paired *t* test at a significance level of 5%.

Monthly visit rates in the first 12 months of the pandemic, month by month, were compared using control diagrams (14). The control diagrams were designed for each State, Federal District and Country region using averages of monthly pre-pandemic visit rates ± 1.96 standard deviation. This strategy allowed analyzing if pandemic visit rates were above or below historical limits.

In order to complement the analysis by States and the Federal District, Resultant Vectors Graphs (RVG) were used. It is a technique developed with the intention of synthesizing the information from the control diagrams in just one graph. Resultant Vectors Graphs include, simultaneously, three pieces of information in the diagrams: monthly visit rate above, within or below historical limits. From the diagrams, each time the visit rate exceeded the expected upper limit, a unit vector was assigned in the growth direction of the ordinate axis; when the rate was below the expected lower limit, a vector in the decreasing direction was assigned in the decreasing direction of the ordinate axis; and when the rate was within the expected limits, a unit vector was assigned in the growth direction of the abscissa axis. Finally, after "walking through" the entire diagram, the vectors were added to generate a resultant.

It is underlined that RVG can be composed of vectors resulting from more than one control diagram, with the resultant vectors displayed in a single figure. In RVG, if the vector is in the first quadrant, it will indicate an increase in the visit rate for the studied period; if it is in the fourth quadrant, the visit rate will have been lower than expected; and if it is close to the abscissa axis, the rate will be within historical limits.

All analysis were conducted using MATLAB software, version R2021a Update 4 (9.10.0.1710957), and its Statistics and Machine Learning Toolbox.

Results

A total of 39,599,313 visits for monitoring CGD occurred between April 2017 and March 2021 were covered (**Table 1**).

TABLE 1 Number of visits before and during the pandemic, according to regions, states, and the Federal District.

Location	Number of studied visits (×1,000)[a]		
	Pre-Pandemic (Apr. 2017 – Mar. 2020)	During the pandemic (Apr. 2020 – Mar. 2021)	Total
Brazil	32,586.13 (82.29%)	7,013.18 (17.71%)	39,599.31
Mid-West	1,717.84 (81.64%)	386.29 (18.36%)	2,104.13
Distrito Federal	358.13 (79.28%)	93.59 (20.72%)	451.71
Goiás	583.12 (81.44%)	132.86 (18.56%)	715.98
Mato Grosso	484.82 (84.97%)	85.73 (15.03%)	570.54
Mato Grosso do Sul	291.77 (79.74%)	74.12 (20.26%)	365.90
Northeast	11,832.95 (86.45%)	1,854.22 (13.55%)	13,687.17
Alagoas	983.10 (86.86%)	148.68 (13.14%)	1,131.78
Bahia	2,465.78 (87.70%)	345.92 (12.30%)	2,811.70
Ceará	1,770.85 (88.12%)	238.74 (11.88%)	2,009.59
Maranhão	1,264.01 (82.56%)	266.92 (17.44%)	1,530.92
Paraíba	1,085.42 (86.96%)	162.71 (13.04%)	1,248.13
Pernambuco	2,290.60 (85.61%)	384.99 (14.39%)	2,675.60
Piauí	943.30 (86.71%)	144.55 (13.29%)	1,087.86
Rio Grande do Norte	698.58 (86.65%)	107.60 (13.35%)	806.18
Sergipe	331.30 (85.96%)	54.11 (14.04%)	385.41
North	2,880.28 (83.22%)	580.92 (16.78%)	3,461.20
Acre	77.78 (82.32%)	16.71 (17.68%)	94.49
Amapá	78.18 (82.41%)	16.69 (17.59%)	94.87
Amazonas	716.55 (81.14%)	166.54 (18.86%)	883.09
Pará	1,520.76 (83.94%)	290.90 (16.06%)	1,811.66
Rondônia	180.20 (84.96%)	31.91 (15.04%)	212.11
Roraima	72.69 (82.41%)	15.51 (17.59%)	88.21
Tocantins	234.12 (84.59%)	42.66 (15.41%)	276.78
Southeast	12,581.89 (79.75%)	3,194.09 (20.25%)	15,775.98
São Paulo	7,026.56 (77.91%)	1,992.16 (22.09%)	9,018.73
Espírito Santo	440.36 (82.52%)	93.28 (17.48%)	533.65
Minas Gerais	2,671.56 (80.42%)	650.43 (19.58%)	3,322.00
Rio de Janeiro	2,443.40 (84.21%)	458.21 (15.79%)	2,901.61
South	3,573.18 (78.17%)	997.66 (21.83%)	4,570.84
Paraná	1,339.47 (79.36%)	348.40 (20.64%)	1,687.87
Rio Grande do Sul	1,187.00 (75.00%)	395.59 (25.00%)	1,582.59
Santa Catarina	1,046.70 (80.49%)	253.67 (19.51%)	1,300.38

[a]Visits to monitor the growth and development of children up to five years of age.

The proportion of cases studied during the pandemic ranged from 13.5% in the Northeast region to 21.8% in the South region. Among the states, it ranged from 11.9% in Ceará to 25.0% in Rio Grande do Sul.

The average monthly rate of visits for monitoring children's growth and development in Brazil (per thousand children up to five years of age in the population) dropped from 61.34 before the pandemic to 39.70 in the first 12 months of the pandemic ($p < 0.001$), a drop of 35.28% (**Table 2**). In all states, except Rio Grande do Sul, there was a significant reduction in the monthly visit rate, with differences ranging from −14.21% in São Paulo to −59.66% in Ceará.

The average monthly rate of visits in the Northeast region was the most impacted, being lower than expected in the 12 months of the first year of the pandemic. In the Mid-West, Southeast and South, the average monthly rate of visits was less impacted, being below those expected for 5 months during the first 12 of the pandemic period (**Figure 1**).

Regarding monthly rates of visits for CGD by States and the Federal District, the greatest impacts were identified in those of the North region (Pará, Rondônia and Tocantins), Northeast (Alagoas, Bahia, Ceará, Paraíba, Pernambuco, Piauí, Rio Grande do Norte and Sergipe) and Mid-West (Mato Grosso do Sul), with visit rates below those expected for 11 months

TABLE 2 Differences among the average rates of visits before and during the pandemic, according to regions, states, and the Federal District.

Location	Average rates (per 1,000 inhab.)[a]		Differences among the rates	Standard error	p^b
	Pre-Pandemic (Apr. 2017–Mar. 2020)	During the pandemic (Apr. 2020–Mar. 2021)			
Brazil	61.34	39.70	−21.64 (−35%)	3.09	<0.001
Mid-West	39.58	26.29	−13.29 (−34%)	1.78	<0.001
Distrito Federal	53.58	37.86	−15.73 (−29%)	3.71	0.001
Goiás	31.56	21.47	−10.09 (−32%)	1.37	<0.001
Mato Grosso	47.70	25.20	−22.49 (−47%)	2.04	<0.001
Mato Grosso do Sul	36.99	28.18	−8.81 (−24%)	2.17	0.002
Northeast	79.16	37.37	−41.78 (−53%)	4.06	<0.001
Alagoas	106.95	49.25	−57.69 (−54%)	6.87	<0.001
Bahia	66.63	28.13	−38.50 (−58%)	3.53	<0.001
Ceará	75.14	30.31	−44.82 (−60%)	4.11	<0.001
Maranhão	59.68	37.88	−21.80 (−37%)	3.28	<0.001
Paraíba	105.98	47.46	−58.52 (−55%)	6.33	<0.001
Pernambuco	91.75	46.89	−44.86 (−49%)	5.15	<0.001
Piauí	110.13	50.77	−59.36 (−54%)	5.03	<0.001
Rio Grande do Norte	80.78	37.75	−43.03 (−53%)	3.99	<0.001
Sergipe	54.18	26.57	−27.61 (−51%)	3.97	<0.001
North	49.57	30.07	−19.50 (−39%)	3.08	<0.001
Acre	25.82	16.77	−9.05 (−35%)	1.53	<0.001
Amapá	26.87	17.37	−9.49 (−35%)	1.98	0.001
Amazonas	48.85	34.36	−14.49 (−30%)	4.47	0.008
Pará	58.57	33.79	−24.78 (−42%)	3.85	<0.001
Rondônia	35.96	18.99	−16.97 (−47%)	1.52	<0.001
Roraima	35.62	21.59	−14.03 (−39%)	2.78	<0.001
Tocantins	52.05	28.28	−23.77 (−46%)	2.37	<0.001
Southeast	60.24	46.12	−14.12 (−23%)	3.27	0.001
São Paulo	63.79	54.73	−9.06 (−14%)	3.96	0.043
Espírito Santo	42.67	27.02	−15.65 (−37%)	3.07	<0.001
Minas Gerais	55.83	40.84	−14.99 (−27%)	2.45	<0.001
Rio de Janeiro	60.29	34.00	−26.29 (−44%)	4.12	<0.001
South	50.05	41.95	−8.10 (−16%)	2.80	0.015
Paraná	47.11	36.82	−10.29 (−22%)	2.45	0.002
Rio Grande do Sul	46.23	46.66	0.43 (1%)	3.06	0.891
Santa Catarina	60.55	43.43	−17.12 (−28%)	3.22	<0.001

[a]Rate of visits to monitor the growth and development of children per thousand children up to 5 years of age in the population.
[b]Paired *t* test.

or more during the pandemic period. In Rio Grande do Sul, the smallest impact on rates was identified, with three months below expectations and three months above expectations. The Federal District, Amapá and São Paulo were also States where the rate of visits suffered less impact, showing two or three months with visits below expectations. It is worth highlighting that the most intense reductions in the number of visits were observed from April to June 2020 (**Figures 2**, **3**).

Discussion

During the 12 months of the first year of the COVID-19 pandemic, the use of PHC services to monitor the CGD was significantly lower than in previous years in Brazil. This reduction was not uniform and took place significantly in practically all regions and states.

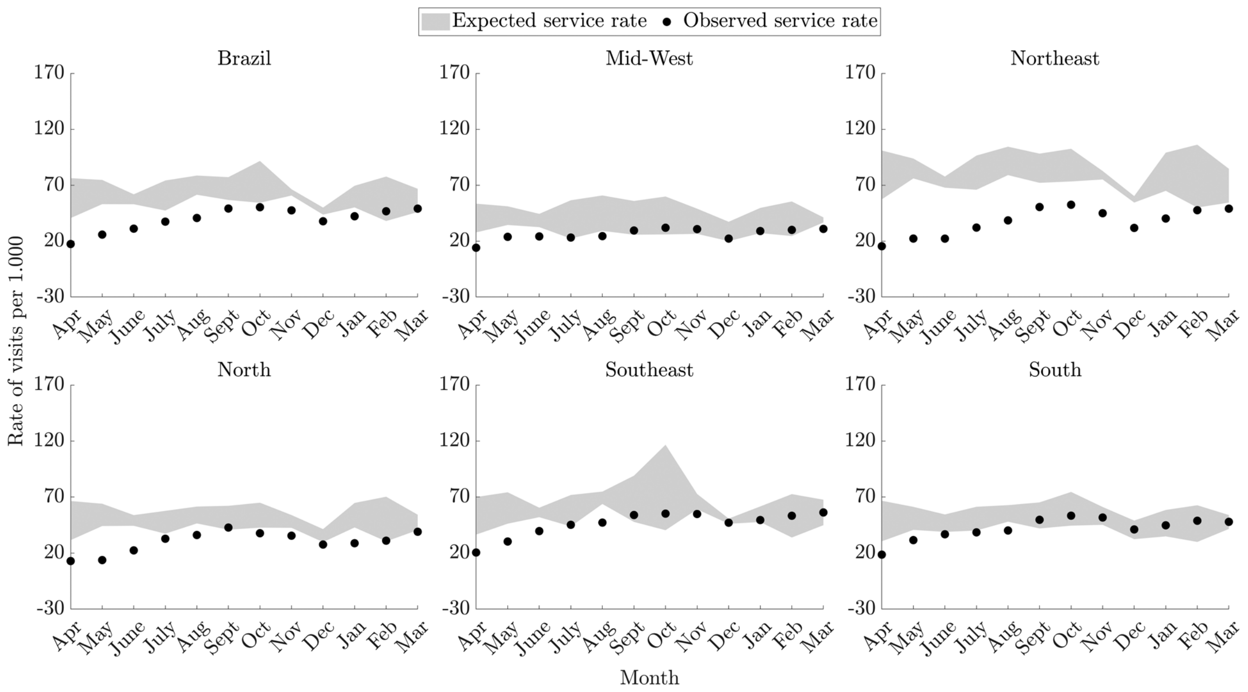

FIGURE 1
Monthly rates of visits (per thousand children up to five years of age) to monitor the growth and development of children, according to regions in primary health care services in Brazil. In gray: expected rates – pre-pandemic period (from April 2017 to March 2020); dots in black: observed rates – during the pandemic (from April 2020 to March 2021); the shaded areas indicate the average +/– 1.96 standard deviations for expected service rates.

Recognizing that some degree of reduction was expected, since the restriction of elective care was one of the measures to control the COVID-19 pandemic in Brazil, it is emphasized that our study advances by presenting important dimensions of this reduction, such as its geographic distribution, its different intensities and duration in the first year.

The average reduction in the number of visits in the first 12 months of the pandemic was similar to that found by other studies carried out with shorter periods (up to the first three months) (7, 15, 16). This is also corroborated by another study, where the reduction was more intense in the period from April to May 2020 (15). As for regional differences in the reduction of visits, it should be considered the interdependence and inseparability of political, economic, and geographic aspects among the Brazilian regions. With its large territorial extension, the regional differences and disparities in Brazil are often worsened by different forms of political-economic command and by the available health workforce. Still in this regard, a study conducted in Rwanda also identified regional differences in the reduction of visits for children during the pandemic. Nonetheless, in Brazil, the restriction measures and the installed capacity of health services vary from region to region, and one cannot disregard the number of COVID-19 cases in each area (17).

With respect to the number of months during which the number of visits was lower than expected before recovering, in many Brazilian states, it was found that the resumption was much slower than what was observed in other countries (7, 16, 18). Thus, it can be assumed that the flexibility of measures to control the pandemic was not immediately reflected in the resumption of the number of visits for CGD in Brazil. In places where resumption was faster, hybrid services, that is, face-to-face and virtual, constituted an important strategy (19).

Regular visits for monitoring children's growth and development, strongly recommended from the early 1980s as a Public Policy, were of great importance for the reduction of infant mortality in the country (20). In this sense, it can be assumed that the identified reduction in the number of visits may determine negative impacts on mortality indicators (21). Furthermore, these impacts may increase the already worrying regional inequalities in the mortality rates of children less than 5 years of age, since the North and Northeast regions persist with the highest rates in the country (20).

The reduction in these primary health care visits represent a barrier to diagnosing problems with child development and to carrying out early interventions when necessary. This occurs in a scenario in which the COVID-19 pandemic itself carries the potential to profoundly affect the development of children

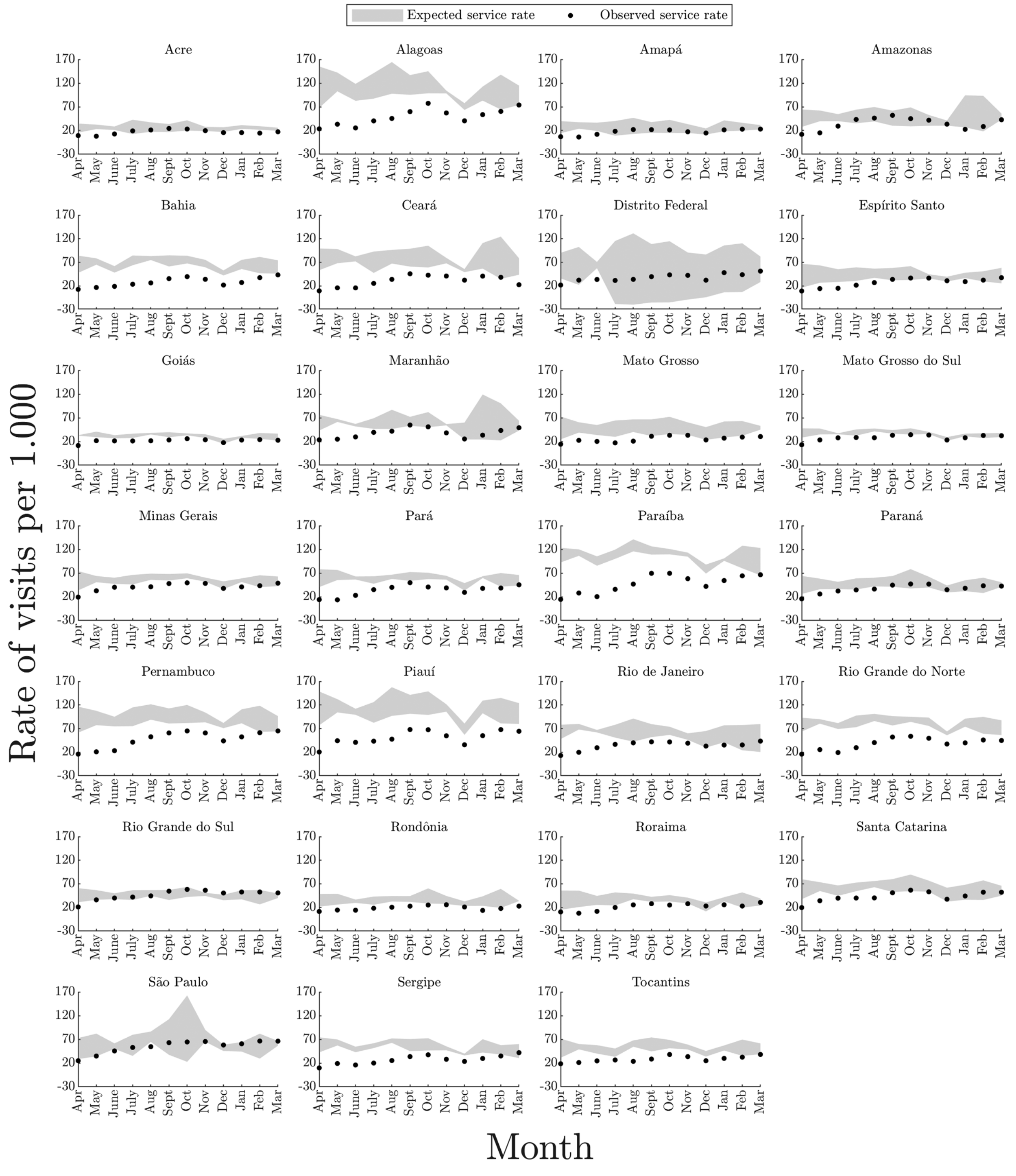

FIGURE 2
Monthly rates of visits performed in primary health care services, per thousand children up to five years of age, to monitor the growth and development of children, according to states and the Federal District in Brazil. In gray: expected rates – pre-pandemic period (from April 2017 to March 2020); dots in black: observed rates – during the pandemic (from April 2020 to March 2021); the shaded areas indicate the average +/– 1.96 standard deviations for expected service rates.

(6, 22). With the reduction, there could also be an increase in food insecurity, resulting in more cases of malnutrition and obesity (23, 24).

It is also necessary to consider that, for monitoring children's growth and development, the visits represent an opportunity for regular health care of children with chronic

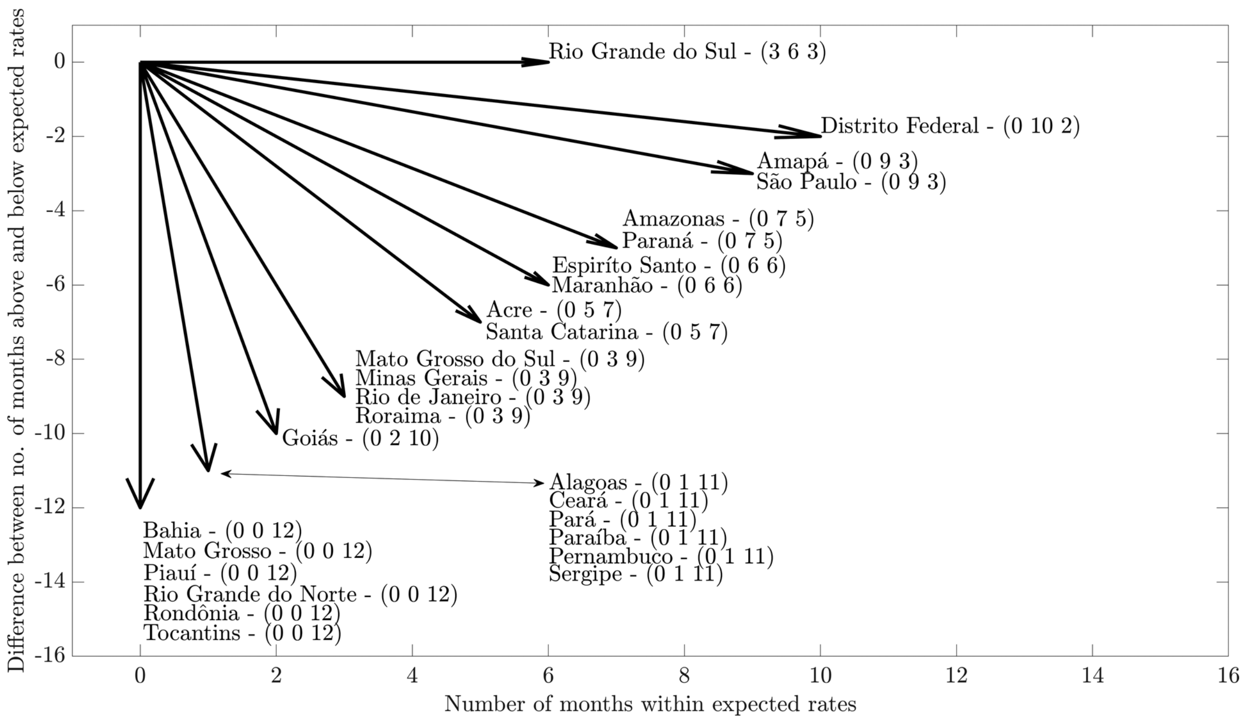

FIGURE 3
Resultant vectors obtained from the control diagrams of monthly rates of visits performed in primary health care services in Brazil, per thousand children up to five years of age, during the pandemic (from April 2020 to March 2021) compared to pre-pandemic period (from April 2017 to March 2020), according to states and the Federal District. Numbers in parenthesis represents number of months above, within and below expected rates, respectively.

conditions. Accordingly, it is assumed that interruptions in monitoring may weaken the care of children with chronic conditions, since regular visits to health professionals allow the early identification of conditions that undermine care (25).

The context of the pandemic and the measures imposed by the health recommendations imposed new determinants and health conditions on children, with emphasis on the effects on mental health, longer exposure to screens and electronic games (26–28). With such a significant decline in monitoring of children, many of the unhealthy and risky conditions may not have received the care they would require. It is also important to highlight the increase in cases of violence against children during the pandemic, which, in a context of reduced access to regular visits, may not have been diagnosed, since an important part of the cases are diagnosed during routine visits not motivated by the acts themselves (29).

Among the lessons that can be drawn from the obtained results, there is the need for the Brazilian Unified Health System to be prepared to guarantee non-face-to-face monitoring when in a context that precludes physical proximity between children and PHC professionals. In general, the use of Telehealth was an important strategy to overcome the barriers of social distancing imposed by the pandemic and to favor children's access to routine care in many scenarios (30). However, in Brazil, it requires more investments in technological and human infrastructure for its implementation (29). In this pandemic, it is a fact that virtual services have gained an important boost and may have come to stay. It is now also necessary to take care of the training of professionals with a view to guaranteeing distance care and the development of safe strategies for childcare examinations, with emphasis on anthropometric measurements.

Among the limitations of this study, it is highlighted the inherent nature of research with secondary data, such as the fact that the analyzed data were not collected specifically to answer the research question. It should also be highlighted the fact that the analyses were carried out with data aggregated by States, Regions, and country, which does not allow for an assessment of any differences among municipalities. New studies that assess the impact of the pandemic at the level of municipal health systems will be important because many decisions during the pandemic were decentralized to municipalities. New studies that consider the fact of analyzing the impacts on CGD from the perspective of socioeconomic differences will also be important, since the regional differences found in our study may have influenced these inequalities (19).

In conclusion, the COVID-19 pandemic appears to have represented a barrier in relation to access to visits in the scope of monitoring the growth and development of children less than 5 years of age in PHC services in Brazil, with geographically and temporally unequal impacts. Although the restriction of elective care in PHC was considered necessary to minimize the risk of transmission of COVID-19, the impact of these restrictions on children's health may be long-lasting. The resumption of services related to CGD by PHC professionals is an urgent need. For this purpose, it is recommended to reduce barriers to these primary health care visits and to adopt innovative solutions with the use of technologies.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://sisab.saude.gov.br/paginas/acessoRestrito/relatorio/estado/saude/RelSauProducao.xhtml.

Ethical statement

As this is a study that uses data in the public domain, with unrestricted access and without identifying individuals, the appreciation was waived by the Research Ethics Committee of the Federal University of Minas Gerais.

Author contributions

LLC: had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: LLC, EWRV, and WC: Acquisition, analysis, or interpretation of data: LLC, EWRV, EDD, NBR, and GV-M: Drafting of the manuscript: LLC, EWRV, EDD, and NBR: Critical revision of the manuscript: LLC, EWRV, EDD, NBR, GV-M, and WC: Statistical analysis of data: LLC, EWRV, and WC. 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.

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Proximity matrix indicates heterogeneity in the ability to face child malnutrition and pandemics in Brazil: An ecological study

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Background: Among the social inequalities that continue to still surpasses the basic rights of several citizens, political and environmental organizations decisively "drag" the "ghost" of hunger between different countries of the world, including Brazil. The COVID-19 pandemic has increased the difficulties encountered in fighting poverty, which has led Brazil to a worrying situation regarding its fragility in the fight against new pandemics.

Objectives: The present study aims to estimate, compare, and report the prevalence of mortality due to child malnutrition among the macro-regions of Brazil and verify possible associations with the outcome of death by COVID-19. This would identify the most fragile macro-regions in the country with the greatest need for care and investments.

Methods: The prevalence of mortality was determined using data from the federal government database (DataSus). Child malnutrition was evaluated for the period from 1996 to 2017 and COVID-19 was evaluated from February to December 2020. The (dis)similarity between deaths from malnutrition and COVID-19 was evaluated by proximity matrix.

Results: The North and Northeast regions have above average number of deaths than expected for Brazil ($p < 0.05$). A prospective analysis reveals that the distribution of the North and Northeast macro-regions exceeds the upper limit of the CI in Brazil for up to the year 2024 ($p < 0.05$). The proximity matrix demonstrated the close relationship between deaths from COVID-19 and malnutrition for the Northern region followed by the Northeast region.

Conclusions: There are discrepancies in frequencies between macro-regions. Prospective data indicate serious problems for the North and Northeast regions for the coming years. Therefore, strategies to contain the outcome of health hazards must be intensified in the macro-regions North and Northeast of the country.

KEYWORDS

social inequality, child malnutrition, COVID-19, mortality, Brazil

Background

The coronavirus disease 2019 (COVID-19), which emerged in China, has put the world in a state of public calamity. Due to the severe acute respiratory syndrome caused by the SARS-CoV-2 virus, its morbidity and mortality rate, drastic measures like social isolation were recommended as the primary way to prevent the spread of the virus. During the critical period of the pandemic, restrictive measures were put in place regarding the operation of shops, holding sporting and religious events, closing schools, universities, and companies, in addition to containing borders and limiting foreign trade (1). Shortly after the critical period of the COVID-19 pandemic, the world encountered a new challenge in the form of food and energy insecurity due to the Russia–Ukraine war (2, 3).

However, regardless of the restrictive measures and the new global order, problems such as economic crisis, hunger, and misery have been increasing in several countries worldwide, including Brazil (4, 5).

According to previous estimates by the United Nations World Food Program, hunger indices worldwide will double as a result of COVID-19. The reasons include unemployment, decreased food consumption by closed establishments, crises in agricultural production, transport and export limitations (6). Currently, these concerns are being associated with armed conflicts and the insecurity of potential new pandemics (7).

In addition, measures like quarantine, social distancing and, more recently, the economic and social aggravations, have brought social inequalities into focus, especially considering the reduction in the purchasing power of the minimum wage and the inflation evidenced in several countries (8–10).

Regarding Brazil, a middle-income country, hunger has increased significantly after the pandemic. These impacts are exacerbated by the intense social inequality observed in the country (11). Some regions of the country, such as the states in the Northeast macro-region, experience greater socioeconomic problems. Thus, generating indicators that allow pointing out the most vulnerable macro-regions to factors linked to hunger, malnutrition and related to health problems, including pandemics, becomes important to allow the generation of indicators that contribute to optimizing prevention measures to combat social vulnerability.

Thus, the objective of this study was to evaluate the retrospective and prospective distributions of infant mortality due to malnutrition and the relationship between mortality rates and the aggravations of the COVID-19 pandemic in Brazil and its macro-regions.

Materials and methods

Study design and type

An ecological observational study was carried out over a period of 22 years (1996 to 2017) for data on deaths from child malnutrition (data recorded each year), and in the year 2020 for cases of deaths from COVID-19 (data recorded daily). The Ministry of Health database (Datasus) was consulted to obtain the data. Data on mortality from severe protein-calorie malnutrition and COVID-19 were considered for this study.

Inclusion and exclusion criteria

Mortality data from severe protein-calorie malnutrition (ICD-10: E43) and from COVID-19 were included. The population of the different Brazilian macro-regions–North, Northeast, Southeast, South and Midwest–available from the database of the Ministry of Health, were evaluated. Data not validated by the Ministry of Health were not considered for this evaluation.

Data extraction

The DataSus collection *via* Tabnet, made available by the Ministry of Health on its access page (http://tabnet.datasus.gov.br), was used to obtain data on infant deaths due to malnutrition. As for the deaths caused by COVID-19, the database of the Ministry of Health was accessed through the website: https://covid.saude.gov.br. The bases were accessed between March 1st and May 25th, 2022. To obtain population data and geographic coordinates were obtained from the database of the Brazilian Institute of Geography and Statistics (IBGE).

Data processing and analysis

After accessing, the data were tabulated using the Excel program (Microsoft®). Statistical analysis was performed using Graphpad's SPSS 22.0 and Prism programs. Distribution (Kolmogorov-Smirnov with Dallal-Wilkinson-Liliefor *P*-value and Shapiro-Wilk) and variance (F test or Bartlett) were tested for all variables. Non-parametric tests were applied for comparison between groups (Mann-Whitney test and Kruskal-Wallis test), and data correlation (Spearman test). The annual mortality rates from child malnutrition between the period from 1996 to 2017 were used to optimize the linear regression model used to estimate the rates between the period from 2020 to 2025. The Euclidean distance between the variables was used to verify the (dis)similarities. To obtain the risk coefficient between the associations of mortality rates due to COVID-19 and malnutrition (shown on the map), the relative frequencies were initially determined for each variable (death from child malnutrition and COVID-19). To determine the frequencies of deaths from child malnutrition, the annual rates were added for each macro-region and then the total value (100%) was obtained by adding the frequencies for the five macro-regions, thus, the fractions for each macro-region were determined. To determine the relative frequencies of COVID-19 death rates, the same equation described above was used, however the sum for each macro-region was determined by the sum of the daily death rates. Thus, it was possible to obtain the ratio between the relative frequencies. QGIS software version 3.22.9 was used for geospatial optimization. The differences observed were considered significant when $p < 0.05$ (5%) (12).

Results

Initially, the temporal impact on the prevalence of mortality from child malnutrition in the different macro-regions during the study period (1996 to 2017) was evaluated. A total of 3,895 deaths were recorded in 22 years, distributed across different macro-regions: North ($N = 814$; 20.90%), Northeast ($N = 2005$; 51.48%), Southeast ($N = 585$; 15.02%), South ($N = 282$; 7.24%) and Midwest ($N = 209$; 5.37%). After normalizing the data by population number, per 100,000 inhabitants, the means for the period evaluated were: 0.2542 ± 0.11 (North), 0.1804 ± 0.14 (Northeast), 0.03512 ± 0.03 (Southeast), 0.04865 ± 0.05 (South) and 0.0738 ± 0.06 (Midwest).

The correlations between the prevalence of mortality per 100,000 inhabitants of the different macro-regions and the study period revealed negative and significant correlations ($p < 0.05$) for all the macro-regions (Figure 1A). The assessments of the distributions between the groups showed a heterogeneity of prevalence, pointing to high frequencies for the North and Northeast regions, followed by the Midwest, South, and Southeast regions. Both macro-regions, North and Northeast exceeded the line that shows the average distribution for Brazil in the evaluation period (0.018 ± 0.053 / 100 thousand inhabitants), which resulted in statistically significant differences between regions, $p < 0.05$ (Figure 1B).

After observing discrepancies in the distributions of mortality prevalence, as well as expressive correlations ($r^2 > 0.80$), linear regressions were used to predict prevalence for the period from 2020 to 2025.

Next, regions were compared by estimating deaths from severe malnutrition (2020 to 2025), and the cutoff of the mean and confidence interval for Brazil for estimation was inserted. The data revealed a positive correlation of 0.25, although not significant ($p = 0.63$) but with a different profile from recent years for the Northern region, previously negative correlation. The other macro-regions continued with negative correlations, but only for the Northeast region it was statistically significant ($p < 0.02$) (Figure 2A). In the comparisons of the average distributions of the prospective evaluation, two of the five macro-regions (North and Northeast) were completely above the confidence interval for the average distribution expected for Brazil; and the others followed below the confidence interval line (Figure 2B).

Prior to the investigation of the possible relationships between deaths from child malnutrition and COVID-19, average comparisons were determined between the mortality per 100,000 for the different macro-regions, with regard to the accumulated death rate and new deaths from the beginning of notifications in Brazil until the initial date of December 2020. Comparisons showed significant differences between macro-regions ($p < 0.05$): 33.42 ± 37.26 (North), 26.90 ± 32 76 (Northeast), 19.53 ± 29.92 (Southeast), 14.31 ± 21.30 (South) and 37.55 ± 41.58 (Midwest). Thus, for both comparisons, cumulative mortality and new cases followed in descending order, the Midwest, North, Northeast, Southeast, and South regions ($p < 0.05$) (Figures 3A,B).

The effect size between the prevalence of mortality from COVID-19 and child malnutrition in Brazil was evaluated after checking the averages between the relative frequencies of mortality rates for each Brazilian macro-region (Figure 4). It was possible to identify an inequality between the macro-regions. The northeast region showed the greatest association in relation to the other macro-regions (36.50%), followed by the northern region of the country (30.19). The southern region was the macro-region with the lowest association (5.37) (Figure 4).

To assess the regions critical to the impact of the association of mortality from malnutrition and COVID-19, a matrix of (dis) similarity was created, with subsequent plotting on a dendrogram (Figure 5). The evaluation revealed a link between the prevalence of mortality from malnutrition in the North and

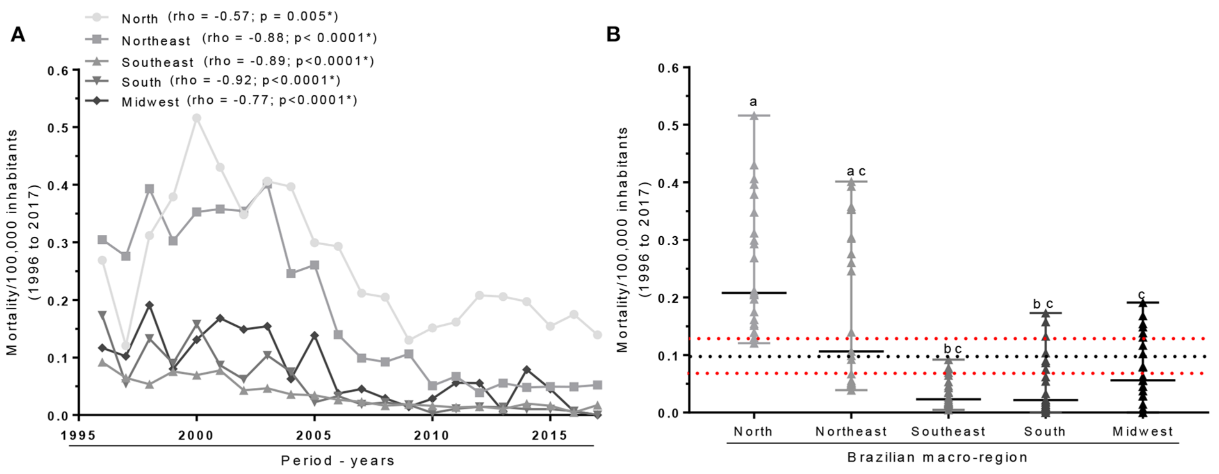

FIGURE 1
Correlation and comparison of mean distributions of the prevalence of mortality from severe child malnutrition from 1996 to 2017 for the Brazilian macro-regions. **(A)** Temporal correlation between mortality per 100,000 inhabitants and the period of 22 years. **(B)** Comparison between the frequencies of mortality per 100,000 inhabitants for the different macro-regions. Spearman's test was used to evaluate correlations and the Kruskal-Wallis test with Dunn's multiple comparison post-test was used to compare distributions (median with range). Statistically significant differences were considered when $p < 0.05$. The * and the letters a, b, and c indicate statistically significant differences.

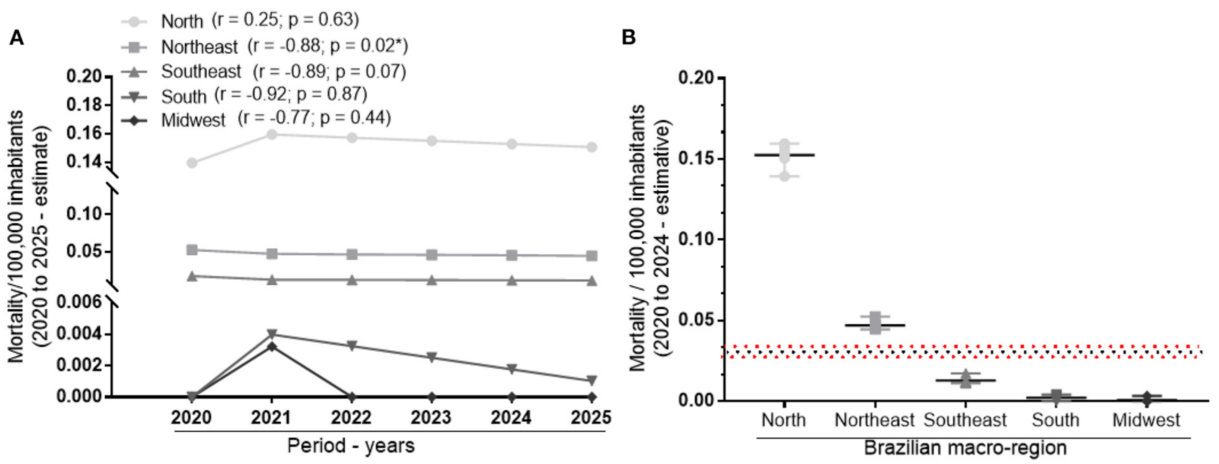

FIGURE 2
Prospective evaluation for correlation and comparison of mean distributions of the prevalence of mortality from severe child malnutrition between 2020 and 2025 for the Brazilian macro-regions. **(A)** Temporal correlation between mortality per 100,000 inhabitants and the period of six years. **(B)** Comparison between the average frequencies of mortality per 100,000 inhabitants for the different macro-regions. Spearman's test was used to evaluate correlations and the Kruskal-Wallis test with Dunn's multiple comparison post-test was used to compare distributions. Statistically significant differences were considered when $p < 0.05$. The * indicate statistically significant differences.

Northeast regions and the impacts of deaths from COVID-19, followed by the Southeast, South, and Midwest regions.

Discussion

The evaluation of data related to mortality from child malnutrition per 100,000 inhabitants in Brazil, between 1996 and 2017, allows us to observe a negative correlation of the numbers over time. That is, there was a decrease in infant deaths from protein-calorie malnutrition in all macro-regions of Brazil. Compared to the global behavior of numbers related to the prevalence of child malnutrition over time, Brazil demonstrates that it follows this reality (13). In general, child malnutrition has shown a significant decrease worldwide. However, it remains a serious public health problem, especially in developing countries, as it transcends from an individual patient issue to a reflection of the society as a whole (14).

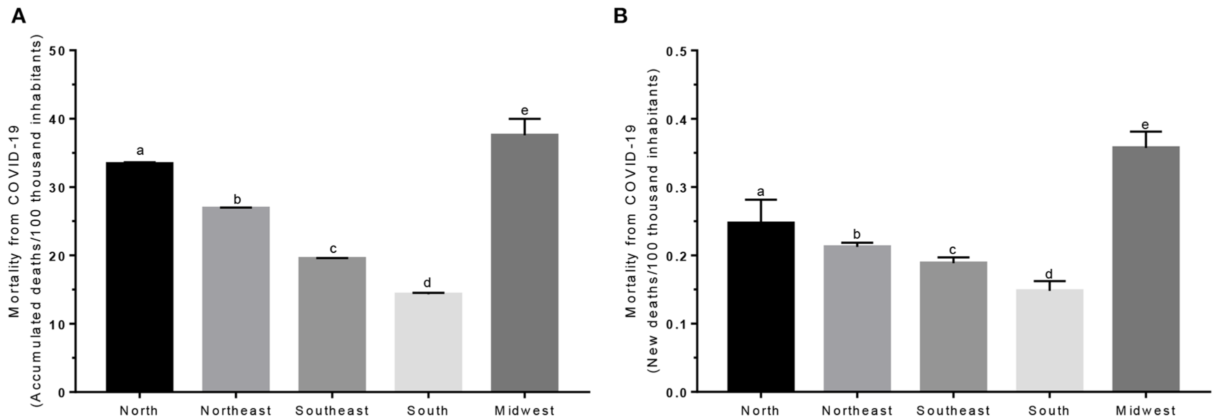

FIGURE 3
Comparison evaluation of the average distributions of mortality from COVID-19 in Brazil for the year 2020. Data were previously collected from the digital collection and made available by the Ministry of Health, for the year 2020. **(A)** Comparison of the mortality accumulated per 100,000 inhabitants, by COVID-19 to the different macro-regions. **(B)** Comparison of the mortality of new cases per 100,000 inhabitants, due to COVID-19 in the different macro-regions. The Kruskal-Wallis test with Dunn's multiple comparison post-test was used to compare the distributions. The letters a, b, c, d, and e demonstrate statistically significant differences, for $p < 0.05$.

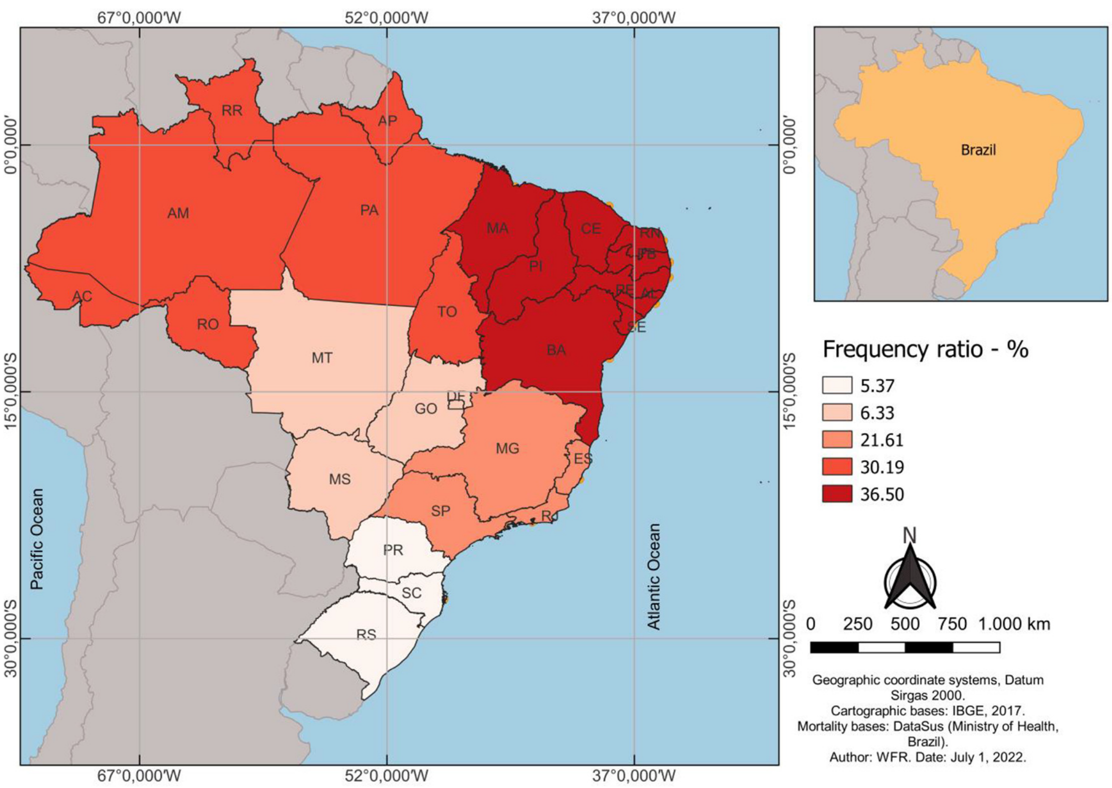

FIGURE 4
Distribution of risk frequencies for the association of the pandemic by COVID-19 and mortality rates due to malnutrition in Brazil. After obtaining the mortality rates from COVID-19 and malnutrition, the relative frequencies (%) of the rates for each macro-region of Brazil (north, northeast, southeast, south and midwest. The arithmetic mean between the relative frequencies of each macro-region was used to generate the risk frequency estimator and plotted for the federative units of each macro-region. On the map, the more intense colors show regions with greater relationships between mortality rates. The database of the Brazilian Institute of Geography and Statistics (IBGE) was consulted to obtain cartographic data. The coordinate system used was the Datum Sirgas 2000.

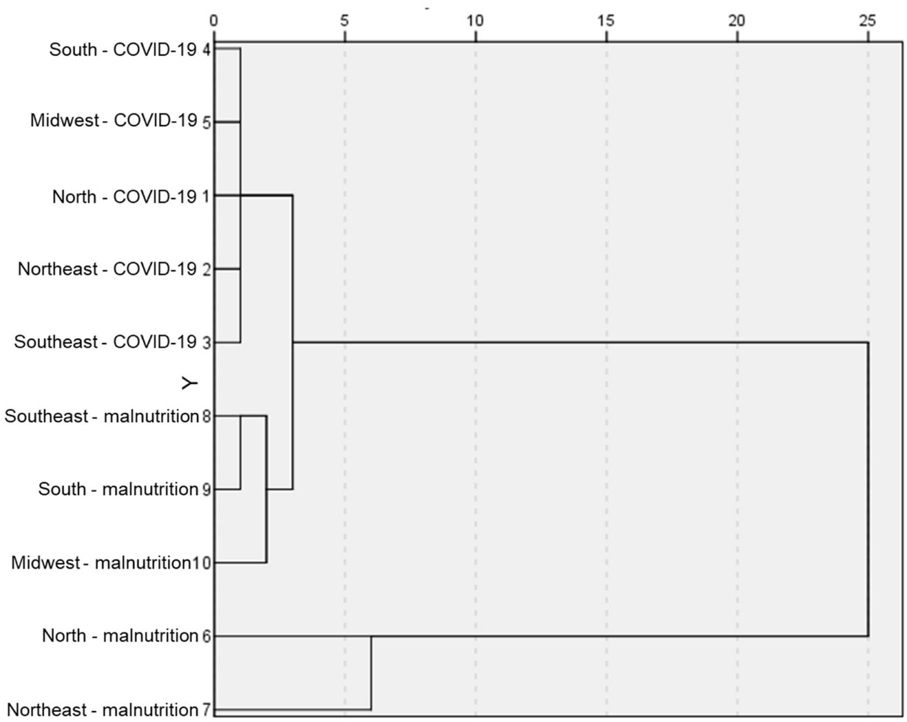

FIGURE 5
Analysis of (dis) similarity between the prevalence of mortality from malnutrition and COVID-19, in the different macro-regions of Brazil. Data were previously collecte'd from a digital collection and made available by the Ministry of Health. The (dis)similarity matrix was determined after evaluating the Euclidean distance. The dendrogram was used to assess the results.

The last decades observed a decrease in the harmful conditions associated with the effects linked to malnutrition, particularly, infant mortality from malnutrition. However, relevant indices still persist and differ according to the macro-region analyzed. Although efforts have been made to reduce the damage linked to child malnutrition, despite the heterogeneity between the macro-regions, given their different social, cultural and geographical characteristics, the discrepancy in the outcome of the disease among children from different regions can be observed (15).

By studying the behavior of each macro-region individually, it was possible to trace the average of infant deaths due to protein-calorie malnutrition between the years mentioned, in each one of them, in addition to the Brazilian average in the same period of time. Thus, the North and Northeast regions stood out with the average mortality above the upper confidence interval of the general average for the country, as well as higher numbers when compared mainly to the Southeast region. This reality reflects the conditions of social inequality in Brazil, marked by intense economic and development differences between the extreme North and South of the country (16).

In the recent Brazilian literature, social inequality has been studied in the context of mortality from COVID-19. A greater increase in cases of COVID-19 fatality was observed in the states of Ceará, Pará, and Amazonas, which is in line with the reality of mortality from child malnutrition and also more prevalent in the states of the Northeast and Northern regions (17). One of the hypotheses that explains this reality is the limited access to health by the lower-income population, especially when it comes to primary care. For example, the annual average of medical consultations in the North of the country was almost half the average in the Midwest region in 2015 (15). Additionally, the beds of intensive care units available in the public network are significantly smaller than in the private network, making macro-regions unequal and poorer, the main challenge in the control of infections that generate pandemics.

Following this perspective, when projecting mortality values from child malnutrition for up to the year 2024, based on the linear regression of previous data, it was observed that the Northern region showed a positive correlation; that is, there are no positive data regarding to a possible drop in infant death rates due to malnutrition for the next few years in this region and no indicators of worsening numbers, since the correlation is not statistically significant. A possible association with this reality can be made from the justification of inequality between the states of the region, since the proportion of health impairment of populations residing in unequal regions is greater when compared to places that follow a socioeconomic homogeneity (18).

Conversely, following the projection analysis, the other macro-regions represented by the Southeast, South, Northeast, and Midwest showed a negative correlation. The Northeast region showed a statistically significant negative prospect. However, it still ranks second in the list of regions with the highest rates of mortality from malnutrition. It is also worth mentioning that this state holds 27% of the entire Brazilian population (16) and despite being very populous, it managed to remain below the leading infant death numbers. This is mainly due to policies to improve access to education for mothers, increase in family purchasing power, access to health, and basic sanitation (19).

Furthermore, when comparing the data projections for 2020 to 2024, the average and distribution of the estimate are above the expected level for Brazil in relation to the North and Northeast, with a greater focus on the Northern region. In the coming years, despite efforts to reverse the worrying situation regarding malnutrition in the Northeast, these macro-regions will continue to witness infant death from protein-calorie malnutrition in 2024.

When considering the current pandemic situation, these surveys become more alarming. Aspects such as poverty and unemployment, which are directly related to child malnutrition, have been identified as determinants of the incidence of numerous infectious diseases, including COVID-19, in Brazil (16).

With the setback of COVID-19, the differences with regard to the socioeconomic conditions of the Brazilian regions has become more evident (20). Poorer regions have experienced more severe effects of the pandemic. This is the case for the North and Northeastern regions, especially in relation to limitations of access to formal work, health and education (16).

According to a study released on the potential impacts of the pandemic, social isolation will affect all forms of malnutrition, especially in children. Analyzing the future projections, compromised child development, education, and deficit in the formation of human capital will be the challenges of the coming decades (21).

The destabilization of the international financial market and the lack of data associated with the indexes that are predictors of inflammation, along with the lack of updated and consistent data for hunger rates in the country were the main limitations of the study. In addition, the limitations associated with the design for the ecological study, with data originating from aggregates of information, as well as the use of secondary databases, can weaken individual indicators (22).

Conclusions

Based on the retrospective and prospective analysis of child mortality data from malnutrition in Brazil, in the context of the COVID-19 pandemic, the North and Northeast regions tend to have greater negative impacts on child malnutrition due to the projections of the pandemic. These regions are arguably regions with greater vulnerabilities to face future pandemics or aggravations associated with low food demand or higher market inflation rates. It is, therefore, essential that measures be taken at the global, federal, state, and municipal levels to reverse the damage caused by the current humanitarian crisis.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: the datasets generated and/or analyzed during the current study are available in the OSF Home repository, https://osf.io/ndc52/?view_only=547f494f5bbe4cea9f5f47b0041d3b5.

Author contributions

WR, CM, CO, and AS designed the experiments. WR, CM, CO, AS, CT-d-S, and MA performed the experiments and wrote the manuscript. WR, CM, CO, and CT-d-S analyzed the data. 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.

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The effects of the SARS-CoV-2 pandemic on children and youth with special health care needs

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This article seeks to review the current knowledge of the SARS-CoV-2 virus and the health effects for children and youth with special health care needs (CYSHCN). COVID-19, an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), became a major pandemic in 2020. Recognition of the disease could be difficult, as symptoms in children are at times different than adults and can mimic other common childhood viral infections. Children with underlying medical conditions did make up a higher proportion of those hospitalized, but also were affected in other ways including loss of nursing support, missed education and rehabilitative services, and increased stress for themselves and their families, affecting mental health in this vulnerable population.

This review seeks to address what is currently known about the overall effects on CYSHCN and their families, and identify gaps in research, including the implementation of health care systems, and possible suggestions for change in the educational and community supports for this group of individuals. Ongoing analysis of large national and international data sets, as well as smaller reports based on specific congenital anomaly, genetics disease, and acquired childhood illness, and then attention to local resources and family resilience is still necessary.

KEYWORDS

COVID-19, children with disabilities, children with special health care needs, CYSHCN, pandemic

Introduction

Children and Youth with Special Health Care Needs (CYSHCN) is defined by the federal Maternal and Child Health Bureau as "those who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require health and related services of a type or amount beyond that required by children generally" (1). In the 2009/2010 National Survey of CYSHCN, approximately one in five families has at least one child with special health needs which translates into approximately 14.6 million children (1). As of July 22, 2022, more than 90.2 million COVID-19 cases and more than 1.02 million deaths have been reported, according to Johns Hopkins University (2). Among children, more than 13.9 million cases have been reported as of July 14, 2022, according to American Academy of Pediatrics data (3). Using these estimates, nearly 2.9 million CYSHCN have been ill with COVID19. But even for those that did not have the infection, major life changes have occurred related to social isolation, school closing, unavailability of in home and school nursing and therapy supports and shift to telehealth or video only visits. While the rapid shift to telehealth was amazingly effective for families with proper internet and computer or smart phone access, again underserved and vulnerable communities lack these resources. Research specific to CYSHCN has been slower than anticipated as the pandemic has evolved. Information presented is the result of both a PubMed literature search using key-words SARS-CoV-2 and CYSHCN, and well as COVID-19 and CYSHCN performed on March 31, 2022; and again July 22, 2022, reveals with the results of a recently published literature search for the effects of Sars-Cov-2 in nearly 3,000 individual adults with genetic and congenital conditions by Hromic-Jahjefendic et al.

Recognizing COVID-19 symptoms in CYSHCN

Early in the pandemic, the disease was clearly recognized to be more likely to cause death in the elderly, or those with conditions such as obesity, diabetes mellitus, or chronic pulmonary disease (COPD), as well as cause difficulty in access to ongoing medical care for those with cancer, or "non-emergency" surgical needs. Chen and colleagues report on the first 799 people with the disease who were admitted to the isolation ward of a hospital in Wuhan, China, assigned for patients with severe or critical covid-19. The authors compared the characteristics of 113 (14.4%) patients who had died thus far with those of 161 patients who recovered, finding that those who died were on average 17 years older (with no deaths among those aged under 40% and 16.8% of deaths among those aged 40–60), more likely to be male, and more likely to have a comorbidity such as hypertension, diabetes, cardiovascular disease, or chronic lung disease (4). For many this supported the hypothesis that the disease itself was mild in children. or incorrectly assumed "children don't get COVID19."

Data began to mount that children were clearly not immune to the disease and could in fact have severe outcomes. Pediatricians were faced with difficulty identifying symptoms of COVID- 19 and testing for the virus when a child was presented with many of the same complaints as other common childhood illnesses like influenza, respiratory syncytial virus, or viral rashes. Other symptoms could include emesis or diarrhea, with minimal respiratory issues. Together with sometimes vague and unrecognized symptoms, limited readily available testing resources were lacking for almost the first year of the pandemic.

While the Center for Disease Control (CDC) turned public attention to identifying at risk adults, and "flattening the curve" of rapid viral spread with use of universal personal protective equipment in hospitals and health care setting, isolation, and masking in the general population, information about COVID-19 infections in children was initially less scrutinized. Severe cases and deaths were mostly reported in the elderly, and those with chronic medical illness. Information about COVID-19 infections in children did emerge a few months later, showing that like adults, children with underlying medical conditions, or CYSHCN, were more likely to be infected. The limited supply of testing materials led to only those sickest persons presenting in emergency rooms and being considered for admission having COVID-19 or viral testing.

Businesses, schools, medical providers including Pediatricians were directed to look for respiratory symptoms and fever as screening for a clearance to participate in one's usual daily activities. But as the pandemic progressed, we discovered that many of the same symptoms could be attributed to other common childhood illnesses like Group B streptococcus pharyngitis, Influenza Type A or B, and Respiratory Syncytial Virus (RSV) bronchiolitis. For children with medical complexity with underlying intellectual disability, epilepsy, chronic respiratory concerns, feeding tube dependence and chronic constipation, it was difficult to determine if a child presenting with increased emesis and seizure frequency was in fact COVID19 or severe constipation, gastroesophageal reflux (GERD), tube malfunction or another etiology. Providers familiar with care of children with medical complexity (CMC), a subset of CYSHCN, and with the individual patient may have been in a better position to determine if the signs were more consistent with underlying medical condition, but again early on these offices lacked testing supplies. Only the sickest individuals were to be referred to the emergency rooms, and many visits were changed to virtual or telehealth only.

Parcha et al. completed an analysis of 12,306 children from the United States infected with COVID-19 from April-October 2020 in TriNetX database. Only 25.1% of children had at least one of the typical symptoms (fever, cough, or shortness of breath), and 9.9% of children had at least two typical symptoms (5). Three-fourths (74.9%) of the children did not have any of the typical COVID-19 symptoms (5). The symptoms recorded for the children included respiratory (16%), gastrointestinal (13.9%), rash (8.1%) neurological (4.8%), but also nonspecific findings such as fever, malaise, sore throat, runny nose, sneezing, fatigue (18%) (5). Only 5% required hospitalization, of whom 17.6% needed mechanical ventilation (5).

Underlying medical conditions associated with higher risk for COVID-19 infection in children and CYSHCN

Hoang et al. performed a meta-analysis/case summary of children with COVID-19, looking at 131 studies from 26 countries within the first 6 months of the pandemic. This included 7,780 children from January to May 2020, with 2,572 children from the United States and 64 (1%) of children from China. Just 20 studies ($n = 655$ individuals) reported an underlying medical condition; COVID-19 positive children who were immunosuppressed or had a history of a respiratory or cardiac condition comprised the majority (65%) (6) (**Figure 1**).

Bailey and colleagues looked at a collection of data from PedsNet, a network of 7 US pediatric health systems, comprising 6.5 million patients primarily from 11 states. This resulted in 135,794 patients younger than 25 years who were tested for SARS-CoV-2 from Jan 1-Sept 8, 2020. Testing for SARS-CoC-2 was considered the exposure, and the main outcomes collected were testing positive for infection, and then actual symptomatic illness. Demographics of the tested group were 59% white, 15% Black, 11% Hispanic, 3% Asian patients, and 5,374 (4%) had documented infection with the virus. Black, Hispanic, and Asian race/ethnicity had lower rates of testing. But they were significantly more likely to have positive test results (**Figure 2**). This data set also demonstrated that like adults, people under age 25 with underlying illness or chronic conditions, therefore likely to be considered CYSHCN, had a higher risk of positive test results at the following rates (from highest to lowest): gastrointestinal disorders, malignant disorders, endocrinologic disorders, metabolic disorders, hematologic disorders, mental health disorders, genetic disorders, musculoskeletal disorders, and cardiac disorders (7).

Most of the data we have to date is retrospective, and from large databases that may not represent all areas in terms of diversity, race and ethnicity, or socioeconomic status, and these rely on billing codes to try to tease out chronic medical conditions that existed in the patient before COVID-19 infection and those more likely to be a common complication associated with COVID-19. Studies from January 2020 through March 2021 likely reflect the Delta variant. Kompaniyets et al. completed a cross-sectional study including patients aged 18 years and younger with International Statistical Classification of Diseases, Tenth Revision, Clinical Modification code U07.1 (COVID-19) or B97.29 (other coronavirus) during an emergency department or inpatient encounter from March 2020 through January 2021, They utilized the Premier Healthcare Database Special COVID-19 Release (PHD-SR) (release date, March 15, 2021), a large, hospital-based, all-payer database which collected data from over 800 US hospitals. The study included 43,465 patients with COVID-19 aged 18 years or younger, median (interquartile range) age was 12 (4–16) years; 22,943 (52.8%) were female patients; 12,491 (28.7%) had underlying medical conditions (8).

To identify those children with medical complexity and those without from the database, the authors used the validated Pediatric Medical Complexity Algorithm (PMCA) to divide the group into those with complex chronic disease, non-complex chronic disease, or absence of chronic disease groups (9). Using the PCMA, Kompaniyets et al. concluded that the most common underlying conditions in order were asthma, neurodevelopmental disorders, anxiety and fear-related disorders, depressive disorders, and obesity. Children with cardiac and circulatory congenital anomalies, essential hypertension, and type 1 diabetes had higher risk of both hospitalization and severe illness when hospitalized. Prematurity was a risk factor for severe COVID-19 illness among children younger than 2 years. The strongest risk

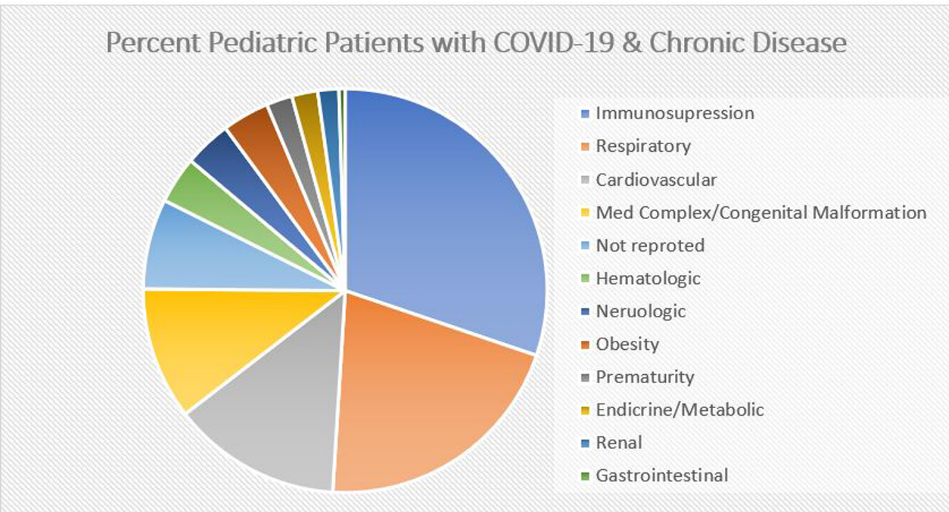
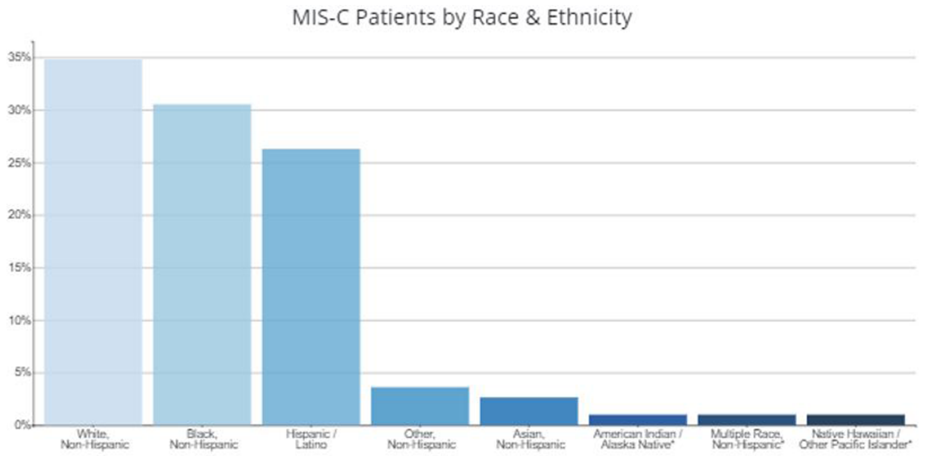


FIGURE 1
Adapted from Hoang et al. (6), demonstrates the percentage of each chronic condition reported in 655 children with COVID-19 from 20 studies.



https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance (14)

FIGURE 2
The percentage of patients with MIS-C by Race and Ethnicity reported through the local Health Departments to the CDC. The median age of patients with MIS-C was 9 years. Half of children with MIS-C were between the ages of 5 and 13 years. 53% of the reported patients with race/ethnicity information available (N=8,607) occurred in children who are Hispanic/Latino (1,919 patients) or Black, Non-Hispanic (2,618 patients).

factors for hospitalization were type 1 diabetes and obesity, however, type 1 diabetes and cardiac and circulatory congenital anomalies were the strongest risk factors for more severe illness (8). Williams et al. also did a systematic review to try to identify and describe which underlying comorbidities were associated with severe SARS-CoV-2 disease and death. The systematic review identified 1,726, of which only 28 studies fulfilled the inclusion criteria. 5,686 participants with confirmed SARS-CoV-2 infection ranging from mild to severe disease. Of these patients, only 108 pediatric patients with severe/critical illness required ventilation, and of these, medical history was available for 48 patients (10). Thirty-six of the 48 patients (75%) had documented comorbidities of which 11/48 (23%) had pre-existing cardiac disease (10). Only 17 patients died, with past medical history was reported in just 12 cases (10). Of those, 8/12 (75%) had co-morbidities (10).

All the above studies relied on data collected early in the pandemic, thus mostly reflecting the Delta variant. Delta was found to be more likely to cause serious illness in the elderly. The next wave of illness involved a series of Omicron variants that emerged in Summer/Fall 2021 in the United States. In March 2022, the American Academy of Pediatrics offered new Guidelines for Caring for Children after COVID-19 infection More children under the age of 5 years were hospitalized at the peak of Omicron 15/100,000 than during the peak of Delta, just 3/100,000. Infants less than 6 months were hospitalized at a rate of 68/100,000 during Omicron compared to 11/100,000 during Delta, or about %X (11). This did not provide more information about CYSHCN specifically.

Severe COVID-19, multisystem inflammatory syndrome in children (MIS-C) and long COVID-19 with CYSHCN

The spectrum of COVID-19 clinical manifestations is variable and fairly broad. Individuals infected with SARS-CoV-2 (those with COVID-19 disease) can present as asymptomatic or with mild symptoms such as fever, fatigue, sore throat, runny nose, and coughing. Severe COVID-19 develops in some individuals and is characterized by interstitial pneumonia, hypoxemia, and acute respiratory distress syndrome (ARDS), which may be lethal. Woodruff et al. examined the COVID-19—Associated Hospitalization Surveillance Network During March 2020 to May 2021 and identified 3,106 children hospitalized with laboratory-confirmed severe acute respiratory syndrome (ARDS) coronavirus 2 infection in 14 states. Among 2,293 children primarily admitted for COVID-19, multivariable generalized estimating equations generated adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) of the associations between demographic and medical characteristics abstracted from patient electronic medical records and severe COVID-19. Approximately 30% of hospitalized children had severe COVID-19; 0.5% died during hospitalization. Among hospitalized children aged <2 years, the following risk factors were associated with severe COVID-19: chronic lung disease, neurologic disorders, cardiovascular disease, prematurity, and airway abnormality in descending order. Among hospitalized children aged 2–17 years, feeding tube dependence, diabetes mellitus and obesity were associated with severe COVID-19. Severe COVID-19 occurred most among infants, 12 per 100,000 children overall. Hispanic children, and non-Hispanic Black children also had higher rates of severe COVID-19 (12).

It was ultimately recognized that while many children may have milder symptoms with the infection, weeks after recovering some of these children developed a hyperimmune, post-inflammatory state can lead to a Kawasaki type syndrome. This hyperimmune state was designated as multisystem inflammatory syndrome in children (MIS-C) in May 2021 with the Center for Disease publishing standard criteria for this diagnosis. MIS-C presents as high fever, and then rapid life—threatening multisystem organ failure. Persistent fever, conjunctivitis, skin rash, myocardial dysfunction, hypotension or shock and temporary development of coronary artery dilatations are common clinical complications associated with MIS-C. These features overlap with symptoms of Kawasaki disease, a febrile inflammatory and systemic vasculitis of unknown etiology that leads to coronary artery aneurysms in young children (13).

Tracking of MIS-C in the United States by the CDC indicates that at least one case has been reported from each of the 50 states and additional territories, including Puerto Rico, Guam, U.S. Virgin Islands, Washington DC. Black race/ethnicity, Hispanic/Latino and Non-Hispanic Black populations are also disproportionately affected by COVID-19. Additional studies of MIS-C are needed to learn why certain racial or ethnic groups may be disproportionately affected, and to understand other risk factors for this disease (14). Data about underlying additional special health needs in has not been fully studied, but children with hyperimmune or autoimmune states appear to be at the highest risk. Treatment recommendations are for Pediatric Intensive Care Unit (PICU) for necessary respiratory and organ supportive measures including fluid resuscitation ventilators and inotropic medications. In rare cases, extracorporeal membranous oxygenation (ECMO) has been necessary for support. Anti-inflammatory measures have included the use of IVIG and steroids. The use of other anti-inflammatory medications and the use of anti-coagulation treatments have been variable. Aspirin has commonly been used due to concerns for coronary artery involvement, and antibiotics are routinely used to treat potential sepsis while awaiting bacterial cultures. Thrombotic prophylaxis is often used given the hypercoagulable state typically associated with MIS-C (14).

The most recent study was done in April 2022 by Hromić-Jahjefendić et al. which looked at the amount of hits in PubMed using specific genetic and congenital disorders plus COVID-19 as keywords and ranking these by how many hits they found. The most common relationship that they found was with congenital heart disease and COVID-19. Other conditions that made the top five with relationship to COVID-19, in order, were Cystic Fibrosis, Autism Spectrum Disorder, Autoimmune Hemolytic Anemia, and Hemophagocytic Lymphohistocytosis. While this furthered the relationship of these diseases with COVID-19 in some way, the only disease where children were specifically mentioned was in the discussion about Autism Spectrum Disorder (ASD). Families with children with autism primarily reported behavioral/mental health issues related to disruption of routine, and lack of school supports (15).

Impact on access to medical and intervention services

Access to services for all children, and specifically CYSHCN, has typically emphasized coverage, service, timeliness, and capability. Services such as multiple specialty physician visits, school and home health nurse support, durable medical equipment such as ventilators, wheelchairs and orthotics, and increased hours of parental hands-on daily care are ubiquitous for these families. In home therapies such at Early Intervention, and school based rehabilitative services rapidly changed even disappeared for these families. Even with some areas having continued traditional in person medical clinics or where schools were open, most guardians were fearful of leaving their home and seeking evaluation in the office and emergency room, where the highest cohort of sick individuals and exposure to active disease was most prevalent. Most CYSHCN receive habilitation/rehabilitation services as a part of their school curriculum. Rather than being immune to other disparities in services, often these children and their families create a special group of marginalized citizens, with the issues of poverty or low socioeconomic status, race and ethnicity and lack of insurance. The closing of schools resulted in a lack of school-based health care and therapies in addition to education. While there has been much research due to the rapid and ease of transmission of the COVID-19 virus, many rehabilitation providers (PT (Physical Therapist), OT (Occupational Therapist), and Speech for example), moved to remote or canceled sessions all together. This created a higher burden on the families to be more participatory in the child's rehab services, and that required access to internet and electronic devices (16). Evaluations of the outcome of this rapid loss of services and then loss or slowed achievement of major milestones are difficult to measure for each individual child; however, there are some studies that show overall generalities.

According to a study by Allison et al. 42% of children with disabilities lost access to therapy services and 34% received services *via* telehealth. While there is convincing evidence promoting telehealth as a reasonable alternative if in person therapy is not available, it is still difficult to continue the same types of therapy. In this study, children were found to experience a dramatic loss of services, and therefore had a decline in functioning. This was especially true if the child was medically complex. "Children receiving a greater number of services pre-COVID-19 and having access to more technological devices pre-COVID-19 were significantly more likely to receive teletherapy" (17). Overall, virtual therapy during the pandemic was challenging and caused both slowing of new skills achievement, and for some children, setbacks in their development.

Impact on CYSHCN and their families mental health

It has been well documented that the COVID19 pandemic itself as well as the steps taken to mitigate spread has had a profound impact on the mental health of children and adolescents. School closures and stay at home mandates have caused increased isolation which increases anxiety and depression. However, CYSHCN did not appear from the pandemic unscathed by the current increase in mental and behavioral health concerns. A study done by Guller et al. surveyed 299 children and adolescent with neurodevelopmental disorders like autism spectrum disorder and intellectual disability as well as their families and asked about the child's emotional, behavioral, and sleep problems as well as their appetite changes during the pandemic. Of the parents surveyed, 44.5% stated that their child has emotional problems, 33.4% behavior problems, 65.2% had sleep problems, and 32% had appetite problems. Irritability and hyperactivity were the highest reported behaviors by these parents (18).

Another study by Montirosso et al. surveyed 1,472 families in Italy about their children with neurodevelopmental disorders, and using the parent-report Child Behavior Checklist (CBCL) which was modified to ask if their child's behavior across the original CBCL dimensions (emotional reactivity, anxiety/depression, sleep problems, somatic concerns, withdrawn behavior, attention concerns, and aggressive behavior concerns) were decreased, the same, or increased pre- to post-COVID19 across a 5 point scale (19). The surveys showed a significant increase in behavior regulation in children/adolescents compared to pre-pandemic, specifically in the anxiety/depression, attention problems, and aggressive behavior dimensions. This dysregulation is displayed in the increase in symptoms such as clinginess, inattention, and irritability (19). Another study done by Masi et al. surveyed caregivers of children with neurodevelopmental disability on their child's symptom severity and well-being. This study found that, like Montirosso's study, their children were more easily annoyed, irritable, and angry since COVID-19 and the children were having difficulty maintaining relationships. They also found that approximately 20% of caregivers reported an increase in their child's medication (20). Overall, the COVID-19 pandemic had a negative impact on CYSHCN's mental health.

The CYSHCN are not the only ones who had difficulty with coping with the COVID19 pandemic. There is also research done on the overall stress levels and mental health of the caregivers of CYSHCN. In Masi's study mentioned above, they also surveyed the caregivers about their own mental health and well-being and found that 76.1% reported that COVID-19 has had an impact. Also, 73.6% reported difficulty balancing work with childcare/family responsibilities. 43.4% of parents reported an exacerbation of an existing mental health condition (20).

Another study performed by Willner et al. compared the mental health of caregivers of children with intellectual disabilities and caregivers of children without intellectual disabilities in the UK. They found that caregivers of individuals, particularly children, with intellectual disability had a 5-fold increase in the rate of severe anxiety and a 4 to 10-fold increase in the rate of major depression, compared to parents whose children did not have intellectual disability. Factors that were found to relate to the reasons why this increase was seen include more challenging behaviors from the child, increased financial pressure, and less social support (21).

However, there are some resilience factors that have been studied that show protective effects against the mental health impacts of COVID-19. In the study cited above by Monirosso et al. factors such as a positive view of the future or hope and higher perception of self, which is described as understanding one's child and their self-limitations and working within the parents' capabilities to help themselves and their child, lead to increased resilience factors. These factors have been shown to lower their capacity to score high in anxiety and depression during the COVID pandemic (19). In another study by Yusuf et al. it was determined that the resiliency of a family/child during the pandemic relied on three factors: type of diagnosis, parenting self-efficacy, and ease in accessing schooling. This study looked at multiple domains of functioning, including nutrition and access to school. The study found that if a parent could help their child cope with the pandemic including getting them access to schooling and finding "silver lining" activities to do with their child, they were most likely to fall into what the researchers called a "Resilient profile" and they had limited decreases across all domains (22).

Vaccine hesitancy in CYSHCN

The COVID19 vaccine was approved for use in the US in late 2020. As of 8/31/2022, approximately 79.2% of the US population have had at least one dose of the COVID-19 vaccine while approximately 67.5% of the US population is fully vaccinated with the initial series according to the CDC (23). COVID-19 vaccine has a particular increase in hesitancy given the perception that it was developed more quickly than other vaccines. The overall populations vaccine hesitancy with the COVID-19 vaccine is high. According to a commentary by Overhage, et al. in July 2021, there were 33% of Americans who were not eager to get the vaccine. The groups of people most represented in this group included young adults, women, non-Hispanic black adults, adults living in non-metropolitan areas, and adults with lower educational attainment, with lower income and without insurance; all groups with higher risk for COVID-19 morbidity and mortality (24). This is like the rate of vaccine hesitancy in children according to a study by Alfieri et al. in Sept. 2021. This study looked at parents with children <18 years. old in Chicago and Cook County Illinois and found that approximately 33% of parents reported vaccine hesitancy with their child. Like in the Overhage commentary, the groups with the higher rate of vaccine hesitancy included non-Hispanic black parents, publicly insured parents, and parents with a lower income (25).

There is limited data on the rates of the COVID-19 vaccination in CYSHCN, however, there are studies that look at the overall vaccine hesitancy with CYSHCN. A study done by Bonsu et al. looked at vaccine hesitancy among parents whose children have autism spectrum disorder (ASD) compared to parents whose children did not have ASD. They found that 23.6% of parents in this study whose children had ASD were vaccine hesitant. This is compared to a referenced study where they looked general vaccine hesitancy among parents in the same medical institution and found that 8.2% were vaccine hesitant. Most of the vaccine hesitancy in the parents of children with ASD revolved around parents' belief about the causes of these children's developmental delays including "will of God" and "toxins present in the vaccines" (26). Therefore, there is hesitancy in this group regarding vaccines, which only prolongs the difficulty these families have faced during the pandemic.

Conclusion

Thus far, the COVID-19 pandemic had a devastating impact on CYSHCN and their families. Not only were CYSHCN more likely to get a severe case of COVID-19, but due to their complexity, they were not able to easily access medical care. Their developmental progress was either delayed due to physical, occupational, or speech therapists canceling services secondary to concerns of spread or placed as an increased burden on the caregivers to aid them during virtual sessions. Those who received only school based services may have had no services at all. A number of parents remained vaccine hesitant even for their vulnerable child. Finally, stay at home orders and the closing of schools and daycare centers placed an increased mental health burden on the children as their daily routines were disrupted. Not having access to their child's usual supports also resulted in their caregivers having increased child care and educational responsibilities with lack of parents' own supports. There was some light at the end of the tunnel however, particularly among parents who were able to cope well themselves and also assist their children in coping throughout the pandemic and the reopening of the services that these children need. In the United States, many health care centers were able to rapidly pivot to telehealth services and generate new types of home based care supports. These services are also under investigation for improvement in access, decreased burden of transportation, and health care disparities. Studies of the above mentioned data set with specific emphasis on CYSHCN are needed.

Author contributions

MM and ID participated equally in preparation of the manuscript with ID the senior author/attending MM as the resident author. 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.

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Global caregiver perspectives on COVID-19 immunization in childhood cancer: A qualitative study

Allison Silverstein [1,2], Julia M. Gumy[3], Jessica Bate[4] and Erica C. Kaye [1]* on behalf of the St. Jude Children's Research Hospital (SJCRH) and International Society of Paediatric Oncology (SIOP) Parent and Carer Advisory Group

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Introduction: SARS-CoV-2 has led to an unprecedented pandemic where vulnerable populations, such as those with childhood cancer, face increased risk of morbidity and mortality. COVID-19 vaccines are a critical intervention to control the pandemic and ensure patient safety. This study explores global caregiver's perspectives related to COVID-19 immunization in the context of pediatric cancer management.

Methods: A mixed methods survey was developed based on consensus questions with iterative feedback from global medical professional and caregiver groups and distributed globally to caregivers of childhood cancer via electronic and paper routes. We present qualitative findings through inductive content analysis of caregiver free-text responses.

Results: A total of 184 participants provided qualitative responses, 29.3% of total survey respondents, with a total of 271 codes applied. Codes focused on themes related to safety and effectiveness (n = 95, 35.1%), logistics (n = 69, 25.5%), statements supporting or opposing vaccination (n = 55, 20.3%), and statements discussing the limited availability of information (n = 31, 11.4%). Within the theme of safety and effectiveness, safety itself was the most commonly used code (n = 66, 24.4% of total segments and 69.5% of safety and effectiveness codes), followed by risks versus benefits (n = 18, 18.9% of safety and effectiveness codes) and efficacy (n = 11, 11.6%).

Discussion: This study provides insights to guide healthcare professionals and caregiver peers in supporting families during the complex decision-making process for COVID-19 vaccination. These findings highlight the multidimensionality of concerns and considerations of caregivers of children with cancer regarding COVID-19 vaccination and suggest that certain perspectives transcend borders and cultures.

KEYWORDS

pediatric oncology, SARS-CoV-2, immunization, global health, public health

Introduction

Vaccination decision-making has challenged healthcare professionals for decades, with vaccine hesitancy remaining a significant threat to global public health in the 21st century (1, 2). With the emergence of the SARS-CoV-2 pandemic and relatively recent approvals for vaccines for pediatric populations, global public concerns around vaccine safety and value for children have further intensified in recent months (3–6). These growing concerns not only threaten vaccine rates for community protection over time, but also more immediately place vulnerable individuals at increased risk.

The virulence of SARS-CoV-2, resulting in staggering morbidity and mortality worldwide from the disease known as COVID-19, has underscored the urgent need to explore and better understand roots and drivers behind vaccine decision-making, particularly within vulnerable pediatric subpopulations. While healthy children and adolescents infected by SARS-CoV-2 generally experience milder illness than adults (7), the Global Registry of COVID-19 in Childhood Cancer revealed that children and adolescents with cancer are more likely to develop severe or critical illness when exposed to SARS-CoV-2. Specifically, one in five patients developed severe or critical illness and ∼4% died, well above the projected statistics for healthy children (8). Additional reviews with global perspectives have emphasized this increased risk amongst patients with childhood cancer (9, 10).

While numerous studies have investigated attitudes and perceptions surrounding COVID-19 vaccination in adults (11–17), fewer studies have examined parental considerations for COVID-19 vaccination of children in the setting of recent authorization of a pediatric vaccine (3, 5, 6, 18–26). To our knowledge, one prior study has explored vaccine willingness and hesitancy in the context of pediatric cancer, targeting the views of U.S.-based caregivers of childhood cancer survivors; within this cohort, 29% of caregivers expressed vaccine hesitancy, and confidence in COVID-19 vaccination and its value for childhood cancer survivors emerged as a prominent theme (27).

The 2013 World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) Vaccine Hesitancy Working Group recognized vaccine decision-making as a complex and dynamic process where certain factors may be more important in specific contexts or during certain experiences (28). Currently, the perspectives, values, and concerns of caregivers about COVID-19 vaccination for children with cancer globally remain poorly understood. Understanding the views of pediatric cancer caregivers on COVID-19 immunization is important to enable healthcare professionals to better support families and provide anticipatory guidance on vaccine administration.

To address this gap in knowledge, a Vaccine Working Group collaboration between the International Society of Paediatric Oncology (SIOP) and St. Jude Children's Research Hospital (SJCRH) was formed with the goal of better understanding COVID-19 vaccine decision-making related to the care of children with cancer. In this paper, we present qualitative findings from a global assessment of caregiver perspectives related to COVID-19 vaccination in the context of pediatric cancer management.

Materials and methods

Survey tool development

A COVID-19 Vaccine Working Group on Pediatric Oncology was established in March 2021 to answer and investigate COVID-19 vaccine questions. Twelve members consisting of oncologists, infectious disease physicians, and nurses were selected to represent various regions around the world. Working group members nominated parent representatives to contribute to the project from their own country including the United Kingdom, the United States, Canada, Philippines, Indonesia, India, and Ghana. These parents established the Parent/Carer Advisory Group, comprising nine individuals representing patients with cancer and their families from various global regions (29).

A mixed methods survey was developed, guided by content from a professional statement by the COVID-19 and Childhood Cancer Vaccine Working Group collaboration between SIOP and SJCRH (30). The initial consensus questions were derived from global professional healthcare organizations and narrowed via a modified Delphi method amongst the Vaccine Working Group members, with a total of three voting sessions to reach consensus. The initial consensus questions were reviewed by the Parent/Carer Advisory Group, and members of the Advisory Group contributed or revised question items as needed to strengthen face and content validity; the survey underwent iterative stages of feedback with collaborative Advisory Group review to yield the final survey. The survey was piloted with a small group of parents with experience in childhood cancer to test face and content validity of the question items.

The final survey contained three background questions, 19 quantitative Likert scale questions, and a summative open-ended question asking participants to share their questions and perspectives about administration of the COVID-19 vaccine in children with cancer; the survey instrument is presented in Supplementary Table 1. The background or demographic questions focused on country of residence, type of childhood cancer, and timing of the child's cancer experience.

Eligibility criteria, recruitment, enrollment, and data collection

Any parents or primary caregivers of those with childhood cancer were eligible for participation. Each member of the Parent/Carer Advisory Group disseminated the survey to respondents in their own country primarily via social media, online forums, and email distribution. The Working Group members also disseminated the survey to caregivers in each of their countries. The survey was primarily distributed online via SurveyMonkey. A small proportion of respondents (i.e., those from South Africa and Ghana) were approached with paper forms due to limited WiFi in the clinic space where surveys were distributed; responses were then entered manually into the electronic database. The survey was translated into Spanish for dissemination in Spanish-speaking countries; otherwise, an English version was distributed. The survey was disseminated between April and May 2021, remaining open for 4 weeks. Sampling utilized convenience and snowball techniques, with an emphasis on targeting existing pediatric cancer caregiver forums including the international Momcology email distribution listserv and other country-specific online and social media pediatric cancer caregiver communities. Following collection of data via SurveyMonkey and paper surveys, a de-identified CSV file was produced, and a targeted file comprising demographic characteristics and open ended item responses was uploaded to MAXQDA, a qualitative and mixed methods data analysis software system.

The study was classified as informational by SJCRH and exempt from Institutional Review Board approval. The involvement of patients and public advisors was also not deemed subject to ethical approval by the U.K. National Research Ethics Services. Following a brief introduction to the aim, respondents provided informed consent prior to survey completion by answering "yes" to the first question explaining inclusion criteria and that no identifiable information would be collected.

Data analysis

This article presents findings from qualitative analysis of the summative open-ended question; analysis focused on responses to a single free text qualitative question, and all those who provided free text responses were included. Any free text response was considered to be a complete unit of response. We describe study methods and findings following the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist (Supplementary Table 2) (31). Inductive content analysis was conducted across free-text responses by researchers representing three distinct perspectives: (1) a pediatrician with global health training and expertise (A.S.), (2) a parent of a child with cancer with population health research expertise (J.G.), and (3) a pediatric oncologist with qualitative research expertise (E.K.) (Supplementary Table 3) (32).

Research analysists (A.S., J.G., E.K.) reviewed transcripts in depth and conducted memo-writing to begin identifying concepts and patterns. Through this process, an inductive codebook was developed and refined iteratively until no further concepts were identified and saturation was achieved. Code definitions and examples were pilot-tested (A.S., J.G.) across complex responses to identify areas of variance, with minor modifications to language and content made as needed to ensure consistency in code application across transcripts (A.S., J.G., E.K.). The final codebook comprised six broad categories which included a total of 17 codes and two embedded subcodes (Table 1).

The codebook was applied across all responses (A.S., J.G.) with data organized in MAXQDA. The research team met at regular intervals to review findings and reconcile variances, with third-party adjudication (E.K.) to achieve consensus. For responses that met criteria for multiple codes, responses were dual-coded to capture diversity and nuance within perspectives. Following finalization of coding, the team reviewed codes to identify patterns and generate themes (33). Once patterns were established, the team conducted quantitative analyses to describe frequencies of responses. Available demographics (e.g., respondent country's World Bank Income Group and WHO Region, type of childhood cancer, and timing of child's cancer experience) were evaluated for differences between those who responded to the qualitative question compared to those who did not and the entire cohort.

Results

Of the 627 total survey participants from 22 countries, a total of 184 persons (29.3%) provided free-text comments. Broad patient characteristics of those who responded to the open-ended question were similar to those who opted not to respond to the question (Table 2).

Across the transcript of free-text responses from 184 respondents, a total of 271 codes were applied. Approximately one-third of codes (n = 95, 35.1%) were related to safety and effectiveness, one-quarter (n = 69, 25.5%) related to logistics, and one-fifth (n = 55, 20.3%) related to statements in support of or against vaccination. Other emerging concepts included availability of information (n = 36, 13.3%) and overall frustrations (n = 2, 0.7%). The remaining codes referenced survey feedback or "other" comments not related to identified themes (n = 14, 5.2%). Supporting quotations for each of the themes are presented in Table 3. Frequencies of codes within each thematic domain are shown in Figure 1. Results from these analyses aligned with quantitative themes identified by Principal Component Analysis (34).

Safety and effectiveness

Statements related to safety and effectiveness were most commonly coded (n = 95, 35.1%). Within this category, statements asking questions or expressing concerns about safety were the single most used code (n = 66, 24.4% of total segments and 69.5% of safety and effectiveness codes). One caregiver asked, *"Vaccine safety and side effects (which may be different from children that haven't had cancer) are extremely important. My child is no longer on active treatment and hasn't been for years but she has a bunch of long term effects from surgery and treatment. Will this vaccine have any impact on them?"* Seven of these 66 coded safety segments were double coded as containing both acute and chronic or acute/chronic and non-specific safety comments. Of safety-specific segments, 20.5% (n = 15) specifically addressed acute safety concerns and 37.0% (n = 27) addressed chronic safety. Acute safety concerns included comments such as, *"Does the vaccine have the possibility of affecting how well my child's body will be able to fight off her cancer cells?"* while chronic safety included questions such as, *"How will it affect them long term. In general, what does the vaccine do for fertility...."* Some safety codes addressed broad safety concerns, relevant to the general pediatric population, while others were specific to oncologic concerns. The remaining safety and effectiveness codes addressed risks vs. benefits (n = 18, 18.9% of safety and effectiveness codes): *"What is the relative likelihood of a child with cancer having a severe reaction to vaccine vs. severe illness with COVID?"*; and efficacy (n = 11, 11.6%): *"I want to know... how effective it will be. Will it be less effective since his lymphocyte count is still low?"*

TABLE 1 Codebook.

Code	Definition
Logistics	
Who	**Who should get the vaccine?** Includes any questions or statements about who should receive the vaccine and/or in what order (prioritization/triaging). • *(1) For the cancer patient themselves (e.g., immunocompromised, stem cell recipient)* ○ *Questions specific to stratifying prioritization within this group* ○ *What age should start getting the vaccine?* • *(2) For household members/siblings* • *(3) For other close family and friends*
When	**When is best to vaccinate?** Includes any questions or statements about timing to receive the vaccine. • *Questions about recommendations for those with active cancer, those who finished treatment, or long-term survivors* • *Is it ideal to give before, during, or after finish chemo? Should we pause chemotherapy?* • *What about those who have had delayed/no immunizations due to cancer/treatment? (e.g., bone marrow transplant patients)*
How	**How is best to vaccinate?** Includes any questions or statements about the best administration regimen to promote efficacy or immunity. • *What is optimal timing between doses?* • *At what frequency should the vaccine be given?* • *Is there need to re-vaccinate or give a booster?* • *Can we do antibody testing/titers to avoid a false sense of security?*
Where	**Where is best to vaccinate?** Includes any questions or statements about the location that is best to vaccinate. • *Hospital, homecare, doctor's office*
Which	**Which is the best vaccine for this population?** Includes any questions or statements about which vaccine option is best for the population. Also includes questions about protectiveness against variants.
Contraindications	**Contraindications for vulnerable sub-populations.** Includes any questions or statements about which populations of patients may be at higher risk of side effects, decreased efficacy, or other undesirable issues. • *Trisomy 21; single kidney; T-ALL; radiation; allogeneic transplant; if genetic predisposition; if allergy (e.g., to peg-asparaginase)*
Safety and effectiveness	
Safety *subcodes:* Safety _Acute Safety _Chronic	**Safety related to oncology or general health.** Includes any questions or statements specific to potential side effects of the vaccine. Includes both short- and long-term potential effects of vaccine. **Acute** • *Potential to slow healing process after chemo or leads to challenges if during chemotherapy?* • *Any interactions with immunosuppressants/other cancer-directed therapies?* • *Potential to disrupt immune system's ability to fight off cancer post vaccine?* • *Potential for tumor growth or activation of graft vs. host disease (GVHD)?* • *Potential to interfere with scan results?* • *Any flu-like symptoms, fatigue, swelling at site, inflammatory response, respiratory issues, blood clots?* • *Okay in those breastfeeding?* • *Potential to shed from others vaccinated?* **Chronic** • *Potential to trigger relapse/growth?* • *Risk for developing secondary cancer?* • *In those off treatment but with long-term health conditions from treatment?* • *Potential for infertility?* • *Any potential to disrupt child development?*
Risk vs. benefits = RvB	**Risk vs. benefits of vaccine in comparison to risk of getting COVID-19.** Includes any questions or statements specific to risk vs. benefits of the vaccine specifically in comparison to risk of a child getting COVID-19. • *Feelings that vaccine potentially carries greater risk than virus (e.g., child already recovered from COVID without issues)* • *Question of short vs. long term effects in children with cancer, risk for severe reaction to vaccine vs. severe illness with COVID* • *Are children with history of cancer at higher risk of poor outcomes with COVID?* • *"Since kids rarely get serious COVID, why is this needed?"*
Efficacy	**Efficacy in sub-populations.** Includes any questions or statements about ability of specific populations of patients to mount protective response to vaccine. *If on chemotherapy? With low T cells? Low IgG? On neulasta? Low blood counts? Following CAR-T?*

(Continued)

TABLE 1 (Continued)

Code	Definition
Overall frustrations	
Frustration	**Frustration toward those not getting the vaccine.** • *Lack of herd immunity placing children with cancer at risk*
Access	**Worry or anger regarding difficulty with access or lack of access to vaccine.**
Availability of information	
Guidance	**Wanting guidance**. Includes any questions or statements seeking guidance or advice in making decision to vaccinate or not vaccinate child. • *Wanting provider advice regarding choosing between types of vaccines* • *Planning to ask doctor for input/recommendation*
Limited information = limited	**Uncertainty and lack of clarity amongst studies about effects of COVID and the vaccine and need for more research.** • *Wanting to know more information, wanting transparency* • *Worries about frequently changing information* • *Expressions that need to include children in research; children with cancer; minorities; double blind study; animal models; long-term studies*
Expressions pro/con	
Refusal	**Refusal.** Includes any statements or thoughts against the vaccine. Includes statements of intent not to get the vaccine. Nuanced differences from hesitancy. • *Children already suffering enough, don't need other chemicals/toxins/metal* • *Not enough known, no longevity studies* • *Feelings that masks are enough* • *Vaccine is experimental and only approved for emergency use* • *Not willing to do another "experimental" therapy, expressions of anger* • *Other vaccines not offered during treatment, COVID vaccine shouldn't be given either* • *Comments that child already got COVID and has natural antibodies* • *Do not support in children, with or without cancer; against vaccine in self* • *Fear that children with cancer not as strong secondary to chemotherapy* • *Vaccine is a scam; conspiracy; etc.*
Hesitancy	**Reluctance or skepticism/doubt about vaccine.** Includes any statements or questions that are not made in a clear pro or con mindset. • *Don't believe children are affected by COVID or only mildly if so* • *Concern about vaccine ingredients* • *Not wanting the vaccine to be mandated*
Favor	**In favor.** Includes any statements or thoughts in favor of the vaccine. Includes statements sharing having received the vaccine or intent to. • *Examples of self or child with cancer having received vaccine* • *Agree with prioritization as these children already have long-term treatment side effects to manage*
Other	
Feedback	• Feedback on overall study, design, content, importance, both for/against

Logistics

Out of the 69 coded segments related to logistics, 24 (34.8%) were specific to contraindications. One caregiver stated, *"Is it true that a patient who has had an allergic reaction to pegasparaganase [PEG-asparaginase] cannot have the vaccine?"* A similar number of segments (21, 30.4%) focused on who should get the vaccine (*"Should siblings and/or close family and friends also receive the vaccination?"*), while relatively fewer codes (13, 18.8%) centered on optimal timing for vaccination (*"What will be the recommended timeframe to receive the vaccine for children off treatment?"*). Other logistical concerns underscored best practices for children actively receiving cancer-directed therapy (7, 10.1%: *"How often should children undergoing treatment be given COVID vaccine boosters?"*); which vaccine is best (3, 4.3%: *"As the confusion around types of vaccines…I would be very interested to know which type of vaccine would be recommended for children with cancer—if there was a distinction."*); and where to receive the vaccine [1, 1.4%: *"What is the best way to vaccinate these children and their caregivers (In hospital clinic? Homecare visit? Family doctor's office?)?"*].

Statements against or in support of vacciation

Twenty (36.4%) of the 55 broad category statements were in favor of the vaccine, 19 (34.5%) refusing the vaccine, and 16 (29.1%) reflecting hesitation about the vaccine. Statements in favor included, *"Let's start vaccinating!"* Conversely, refusal statements expressed, *"I will never allow my child to get the COVID-19 vaccine."*

Availability of information

A total of 31 statements (11.4% of all coded segments) discussed the limited availability of information about the

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TABLE 2 Survey participant characteristics.

	Qualitative respondents ($n = 184$)	No qualitative response ($n = 443$)	Overall surveyed ($n = 627$)
World Bank income group			
Low middle income	8 (4.4)	18 (4.1%)	26 (4.2%)
Upper middle income	15 (8.2%)	26 (5.9%)	41 (6.5%)
High income	161 (87.5%)	398 (89.8%)	559 (89.2%)
Unknown	0 (0%)	1 (0.2%)	1 (0.2%)
WHO region			
African region	18 (9.8%)	28 (6.3%)	46 (7.3%)
European region	15 (8.2%)	47 (10.6%)	62 (9.9%)
Region of the Americas	145 (78.8%)	348 (78.6%)	493 (78.6%)
Southeast Asian region	4 (2.2%)	14 (3.2%)	18 (2.9%)
Western Pacific region	2 (1.1%)	5 (1.1%)	7 (1.1%)
Unknown	0 (0%)	1 (0.2%)	1 (0.2%)
Type of cancer			
Leukemia (e.g., ALL, AML)	91 (49.5%)	234 (52.8%)	325 (51.8%)
Lymphoma (e.g., B-NHL, Hodgkins disease)	17 (9.2%)	41 (9.3%)	58 (9.3%)
Brain or spinal tumor (e.g., ependymoma, medulloblastoma)	23 (12.5%)	58 (13.1%)	81 (12.9%)
Solid tumor outside the brain (e.g., Wilms, neuroblastoma, sarcoma)	49 (26.6%)	106 (23.9%)	155 (24.7%)
Other	1 (0.5%)	2 (0.5%)	3 (0.5%)
Unknown	0 (0%)	2 (0.5%)	2 (0.3%)
Timing of cancer experience			
Within last 12 months	19 (10.3%)	60 (13.5%)	79 (12.6%)
Between 1 and 3 years ago	60 (32.6%)	159 (35.9%)	219 (34.9%)
Between 3 and 5 years ago	52 (28.3%)	98 (22.1%)	150 (23.9%)
More than 5 years ago	53 (28.8%)	126 (28.4%)	179 (28.6%)

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; B-NHL, B-cell non-Hodgkin lymphoma.

vaccine, with one parent commenting, *"My daughter will not be receiving the vaccine until more studies have been done."* Other comments reflected wishes for guidance in their decision-making process given dearth of available information, such as, *"Should I confirm with my pediatric oncologist first before taking it."*

Overall frustrations

One caregiver discussed frustrations toward those not getting the vaccine: *"It is also difficult convincing grown humans who are healthy to get the vaccine to protect kids like my son. It is frustrating."* Another expressed frustrations around difficulty with access to the vaccine: *"I cannot believe how hard I had to fight to get the vaccine for my daughter...."*

Discussion

This study explores qualitative responses from a global assessment of caregiver perspectives on COVID-19 vaccination in childhood cancer, with the goal of gaining insights to guide healthcare professionals in supporting families during their complex decision-making process. As the first global study specific to childhood cancer to investigate COVID-19 vaccine views, we identified distinct themes with nearly three-quarters of caregiver comments focused on safety and effectiveness, logistics, and limited information to guide decision-making.

Although attitudes specific to COVID-19 vaccination are complex and multifactorial, thematic patterns appear to transcend borders and cultures. Studies from various countries consistently show that safety, effectiveness, and limited information are significant drivers of COVID-19 vaccination in Brazil (3), China (5, 25), Saudi Arabia (4), Turkey (22, 23), the United States (35, 36),

TABLE 3 Supporting quotations.

Code	Examples/supporting quotations
Logistics	
Who should get the vaccine?	• "My son is 5 and is undergoing treatment for ALL so I am not sure if/when he can get the vaccine during treatment." • "How do we prioritize immunocompromised cancer patients and stem cell transplant recipients to ensure that they get the vaccine ASAP when approved?" • "Should siblings and/or close family and friends also receive the vaccination?"
When is best to vaccinate?	• "What will be the recommended timeframe to receive the vaccine for children off treatment?" • "I think that a vaccine for children before chemotherapy is critical." • "I want the children to complete chemotherapy before the vaccine is administered." • "Should the COVID vaccine be given when children repeat their childhood immunisations post treatment or does there need to be a delay?"
How is best to vaccinate?	• "…An important question for lymphoma kids is what interval there needs to be between doses to achieve maximum immunity." • "How often should children undergoing treatment be given COVID vaccine boosters?" • "Will there be follow up to check for titers after the COVID vaccine? I don't want a false sense of security that my child is protected from COVID when indeed he may not be."
Where is best to vaccinate?	• "What is the best way to vaccinate these children and their caregivers (In hospital clinic? Homecare visit? Family doctor's office?)?"
Which is the best vaccine?	• "As the confusion around types of vaccines…I would be very interested to know which type of vaccine would be recommended for children with cancer—if there was a distinction." • "Also, which vaccine is recommended for immunocompromised." • "Is it safe for her to have one? What is riskier, that or? Blood clot from the other two?"
Contraindications	• "Is it true that a patient who has had an allergic reaction to pegasparaganase cannot have the vaccine?" • "If children who had a kidney removed due to wilms tumor can receive the vaccine? Is it safe for kids with single kidney?" • "If a child on Neulasta can they still get the vaccine?" • "Can it be given while blood counts are very low due to chemotherapy."
Safety and effectiveness	
Safety	• "Safety and protection are my biggest concerns" • "I would like to know if it is safe for them to take the vaccine…Will it have side effects." • "My son has completed his treatment but I am still concerned whether the vaccine for him as well as my other son for that matter is safe and the best option with no real evidence for the safety of children." • "Vaccine safety and side effects (which may be different from children that haven't had cancer) are extremely important. My child is no longer on active treatment and hasn't been for years but she has a bunch of long term effects from surgery and treatment. Will this vaccine have any impact on them?"
Acute safety	• "Will the vaccine interfere in results of scans?" • "Any risks to kids who are recently off treatment and are just rebuilding their immune systems?" • "Is it safe for a mom breastfeeding her cancer child who is off treatment to get the vaccine? Is it safe for a mom breastfeeding her cancer child who is receiving chemo to get the vaccine?" • "Many adults who have received the vaccine experience flu-like symptoms, to varying degrees of severity. Would children with cancer be more likely to experience worse flu-like symptoms as a natural reaction to the vaccine?"
Chronic safety	• "For kids who have had radiation-would the vaccine put them at any higher risk of developing another cancer later? These kids are already so much more at risk for secondary cancers as they age—how would this vaccine impact those risks?" • "What are the long term effects of the vaccine? With children that have been treated with radiation and chemotherapy there are often multiple long term effects. How will the long term effects of the vaccine affect those?" • "How will it affect them long term. In general, what does the vaccine do for fertility..." • "There are so many unknowns at this point about long term side effects."
Risk vs. benefits	• "I'd like to know the benefits outweigh the risks. My son has had COVID and it really didn't effect him so I'd be reluctant to give him a vaccine as the risks of the vaccine would be potentially more than getting the virus." • "Need for understanding of risk of COVID vs. risk of vaccine for cancer kids." • "What is the relative likelihood of a child with cancer having a severe reaction to vaccine vs. severe illness with COVID?" • "I don't care how many booster doses I would need, getting the vaccine certainly outweighs the "newness" and "inconvenience", plus the chance effects of COVID."
Efficacy	• "How much will chemotherapy intensity affect the vaccine efficacy and are there any objective tests that can prove vaccine efficacy" • "Will the vaccine work on a child whose IgG levels are impaired post-chemotherapy?" • "I want to know…how effective it will be. Will it be less effective since his lymphocyte count is still low."
Overall frustrations	
Frustration	• "It is also difficult convincing grown humans who are healthy to get the vaccine to protect kids like my son. It is frustrating."
Worry or anger regarding access	• "I cannot believe how hard I had to fight to get the vaccine for my daughter. JCVI you should be ashamed of yourselves!!!"

(Continued)

TABLE 3 (Continued)

Code	Examples/supporting quotations
Availability of information	
Wanting guidance	• "And for the children with cancer I will still ask the doctor whether to take vaccine or not" • "Should I confirm with my pediatric oncologist first before taking it." • "…his Dr. said that he can get it so we have him scheduled for an appointment"
Limited information	• "More studies have to be done on chemotherapy and the vaccine because of the so many long term side effects of chemotherapy" • "There are not nearly enough studies or research to determine what the side effects could be." • "My daughter will not be receiving the vaccine until more studies have been done." • "Are children with cancer in any of these studies for COVID vaccine? Our children are different and therefore react differently to this vaccine"
Statements frankly against or in support of vaccine	
Refusal	• "It should not be given. Not enough knowns and absolutely zero longevity studies. Our kids suffer enough without added man made chemicals and concoctions." • "We will not be getting the vaccine nor will any of our children." • "I will never allow my child to get the COVID-19 vaccine…if childhood cancer really wants to find a cure, they should stop injecting METAL into these poor children….Sincerely, an angry mother." • "I don't think any child should get this vaccine. Let alone a child with cancer. NO ONE SHOULD BE RECEIVING THIS VACCINE"
Hesitancy	• "Hope these questions/thoughts offer some helpful insights into the mind of a fully vaccinated parents of a child diagnosed with cancer). Definitely not against the vaccine, just have a lot of unanswered questions." • "We are questioning whether it is worth getting the vaccine given the increasing number of variants/it may not be effective and comes with a risk of side effects." • "Why is there cells/DNA from animals and aborted fetuses in the vaccine?"
In favor	• "Research and answers need to happen immediately—pediatric cancer patients have not had the chance to live full lives and if they beat cancer shouldn't then die from COVID? They should have been vaccinated with first group like essential workers instead of last?" • "My 21 year old with leukemia got the vaccine done and did very well with vaccine, he was diagnosed May 2018 and still has 6 months left in treatment" • "Let's start vaccinating!"
Other	
Feedback	• "All of the questions above are so important." • "There should be questions about immunotherapy not just chemotherapy. So many questions about whether vaccine is effective w Car T immunotherapy kids" • "For the responses I answered "not at all" it was because that information feels already available and accessible." • "It is hard to answer some of these questions based on how they are written" • "I did not answer questions that did not apply to our situations such as children that have already had COVID-19 or have had a bone marrow transplant."

and other countries. Our findings corroborate vaccine safety and effectiveness as a primary consideration across multiple countries, comprising over one-third of narrative content. More than one in ten caregivers commented on the availability of information, primarily related to how perceived deficits in knowledge adversely impacted their decision-making.

Among the 184 qualitative responses, a total of 271 codes were applied. This breadth of inductive coding underscores the multidimensionality of perspectives, where many caregivers considered multiple factors of vaccination and were not focused on one aspect of care. This highlights the complexity of caregivers' views and the need for healthcare providers to discuss a variety of considerations. Importantly, explored dimensions may be interrelated, and caregiver questions should be explored with awareness of how they may connect to other questions to encourage vaccine uptake.

With respect to safety, more caregivers reflected about chronic or long-term side effects compared to acute side effects. This may reflect uncertainty and fear related to limited knowledge about long-term side effects given the novelty of the COVID-19 vaccine. Caregivers already face uncertainty and fear about long-term impacts of cancer and cancer therapy on their child's future, which may exacerbate worries about any additional long-term vaccine effects. Additionally, we hypothesize that caregivers also may have concerns about long-term effects as a result of their prior or ongoing experiences with long-term effects from cancer treatment, sensitizing them toward these risks. Healthcare professionals should recognize these fears with compassion, acknowledge when data are limited, and anchor discussion and recommendations about vaccines in available information to address specific concerns. While the COVID-19 vaccine itself is relatively new, the science underpinning its development and the efficacy and safety of vaccination programs are supported by decades of extensive testing and expert guidance (37, 38). Public health strategies should focus on existing information to address myths or fears related to long-term effects.

Additionally, evidence suggests that perceived risk for COVID-19 disease in children informs parental decision-making (26, 27, 35, 39, 40). Our findings corroborate this phenomenon, with some caregivers questioning or asserting that children are

FIGURE 1
Frequencies of codes within each thematic domain.

unlikely to transmit or develop serious illness from COVID-19 while others believed that children with cancer face increased risk. We encourage healthcare professionals to explore upfront caregiver beliefs about COVID-19 risks to children prior to offering recommendations about vaccination. When caregivers think risk is negligible, early discussion around known risks of COVID-19 may lay a better foundation upon which to build future recommendations.

Caregivers also repeatedly expressed concerns about limited information and frustrations that data for children are often lagging. These data build upon existing research in which parents express a need for better evidence and transparency about vaccine development, efficacy, and safety (39). In pediatric cancer as a whole, consensus is lacking on general vaccination efficacy and timing to achieve immunogenicity, including holding and repeating vaccines (41–43). Cancer patients were excluded from initial trials for COVID-19 vaccinations, and data on the immunogenicity and safety of COVID-19 vaccines in cancer patients lags behind general pediatrics data. Subsequent studies have explored vaccine safety and efficacy in adult cancer patients at various disease stages of disease (active, remission, post-transplant) (44–51), yet data in pediatric cancer populations remains scarce. We encourage clinicians to acknowledge this lack of data and empathize with caregiver frustrations, affirming their feelings, prior to sharing available information.

Fortunately, healthcare providers can influence decision-making (18, 52). Specifically, caregivers of childhood cancer patients who received information from cancer care professionals were more likely to vaccinate both themselves and their children (27). Although each family is unique, there are common drivers for vaccine decision-making that can be addressed with intention and specificity (1). After asking questions, affirming emotions, and developing therapeutic alliance with caregivers, we advocate for healthcare providers to focus on explaining safety and effectiveness, providing information on logistics for administration, and filling in knowledge gaps in the setting of limited information.

While this analysis focused on the role of healthcare providers in supporting and encouraging families in their decision-making, we also emphasize the critical role that caregivers play in supporting decision-making for other families. In this study, no free-text responses focused on the role of peers or support groups in their own decision-making; however, prior studies have emphasized the value of peers as a form of emotional and informational support in the setting of shared personal experiences in oncology (53). Further research should explore the impact of peer support and guidance in vaccine decision-making.

Finally, caregiver perspectives in this study affirmed themes outlined by the WHO SAGE Vaccine Hesitancy Working Group in their characterization of vaccine hesitancy as "a behavior, influenced by a number of factors including issues of Confidence (do not trust a vaccine or a provider), Complacency (do not perceive a need for a vaccine or do not value the vaccine), and Convenience (access)," also known as the "three Cs" (28). While this study's intent was not to assess vaccine hesitancy, we nevertheless identified themes specific to vaccine decision-making that parallel those raised by individuals who historically expressed hesitancy. Issues related to confidence emerged as discussions of safety or efficacy and concerns regarding the speed in which the vaccine was created with limited information. Complacency materialized across caregiver beliefs that children will not get COVID-19 or will have less severe disease. Convenience manifested in comments specific to logistics, access, and barriers to vaccine availability and administration. Understanding how caregiver perceptions of the COVID-19 vaccine intersect the "three Cs" WHO model can help inform clinical strategies to navigate challenging conversations with families and guide public health messaging. Recent publications have emerged addressing the importance of dynamic public health communication strategies to aid vaccination uptake (54).

This study has several limitations. Certain demographics were not included in survey questions to ensure anonymity. As a result, details on participant gender, age, child age, and relationship to the patient with childhood cancer are unknown. These findings represent the perspectives of those who provided narrative responses, comprising 29% of survey respondents; sample bias may influence findings if participants who shared written responses represent outlier perspectives. However, content analysis of narrative responses indicated a bell curve of opinions, suggesting our findings represent a cross-section of caregivers. Notably, with respect to demographic information collected, qualitative respondents had similar demographics compared to those who opted not to provide free-text responses. The survey techniques relied heavily on internet and social media participation, which risks selection bias with respondents not necessarily representative of all caregivers in their respective countries. Further, survey data skewed toward responses from high income settings; this may reflect varying levels of literacy worldwide as well as unavailability of the survey in languages other than English or Spanish. Findings likely represent a subset of opinions, and further investigations in broader languages and low-income countries are needed. Regardless of commonalities across global responses, conversations must be individualized to the setting and situation. Despite known increased risk with SARS-CoV-2 amongst children with cancer (8), disparate global recommendations exist for childhood vaccinations. Each country has its own standards, with vaccine expansion to younger children or vulnerable populations occurring at different times since the advent of SARS-CoV-2 (55). Finally, we do not know the willingness of respondents to vaccinate themselves, which has been shown to influence perspectives on childhood vaccination (23), or their intent in vaccinating their children, all of which may influence their responses.

In summary, this global study examines the perspectives of caregivers of children with cancer on COVID-19 vaccines and provides insights to guide clinicians in counseling families and providing targeted information to support decision-making. It corroborates findings from the general pediatric population worldwide, with safety and effectiveness, logistics, and limitations in information driving questions and concerns around vaccine uptake and therefore important elements of vaccine counseling. These findings reveal the complexity and multidimensionality of perspectives on COVID-19 vaccination and highlight the interrelated nature of themes. This can help with further development of focused survey tools aimed at understanding attitudes to vaccines amongst the pediatric oncology community. We hope these data may contribute to clinical support tools and public health messaging to help healthcare professionals address vaccine hesitancy and refusal in the context of the COVID-19 vaccine and future novel immunizations for pediatric populations. Further research evaluating how caregiver perspectives influence actual vaccine uptake is needed to guide healthcare professionals in targeting efforts toward supporting medically vulnerable children and their families.

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.

Ethics statement

Ethical review and approval was not required for this study on human participants in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

St. Jude Children's Research Hospital (SJCRH) and International Society of Paediatric Oncology (SIOP) Parent and Carer Advisory Group

Members of the COVID-19 and Childhood Cancer Vaccine Global Parent and Carer Advisory Group as below contributed to the concept for this study and to the evaluation of its findings:

- Brian Regan, Dana Farber/Boston Children's Pediatric Patient/Family Advisory Committee, United States
- Meghan Shea, Dana Farber/Boston Children's Pediatric Patient/Family Advisory Committee, United States
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Author contributions

JB and JG worked to conceptualize and complete data collection for the study. EK led development of the research methodology. JG and AS led the formal analysis and investigation of data. AS wrote the original draft of the paper supervised by EK. All authors revised the paper critically and approved the final 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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1004263/full#supplementary-material

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The impacts of physical activity on psychological and behavioral problems, and changes in physical activity, sleep and quality of life during the COVID-19 pandemic in preschoolers, children, and adolescents: A systematic review and meta-analysis

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Background: The COVID-19 pandemic has greatly affected the level of physical activity (PA). However, little is known about its effect on health outcomes.
Methods: Articles without language restrictions published from the database inception through March 16, 2022, were retrieved using the CINAHL Complete, Cochrane Library, EMBASE, Medline, PubMed, and PsycINFO databases. High-quality articles assessing the effect of PA on psychological and behavioral problems. Additionally, PA, QoL, and/or sleep problems before and during the pandemic were included. Articles without data regarding PA or involving non-general populations were excluded. The PRISMA and MOOSE guidelines were followed. Data quality of the selected articles was assessed using the Newcastle-Ottawa Scale and GRADE approach. Data were pooled using a random-effects model and sensitivity analysis if heterogenicity was high ($I^2 \geq 50\%$). The relationship between PA and psychological and behavioral problems; and changes in PA, QoL, and sleeping patterns before and during the pandemic in preschoolers, children, and adolescents were investigated. A meta-analysis was conducted; odds ratios (ORs), mean differences (MD), and standardized MDs (SMDs) were calculated.
Results: Thirty-four articles involving 66,857 participants were included. The results showed an overall significant protective effect between PA and psychological and/or behavioral problems (OR = 0.677; 95% CI = 0.630, 0.728; p-value <0.001; $I^2 = 59.79\%$). This relationship was also significant in the subgroup analysis of children (OR = 0.690; 95% CI = 0.632, 0.752; p-value <0.001; $I^2 = 58.93\%$) and adolescents (OR = 0.650; 95% CI = 0.570, 0.741; p-value <0.001; $I^2 = 60.85\%$); however, no data on the relationship in preschoolers were collected. In addition, the overall time spent on PA significantly decreased by 23.2 min per day during the COVID-19 pandemic (95% CI = –13.5, –32.9; p-value <0.001; $I^2 = 99.82\%$). Moreover, the results showed an overall significant decrease in QoL (SMD = –0.894, 95% CI = –1.180, –0.609, p-value <0.001, $I^2 = 96.64\%$). However, there was no significant difference in sleep duration during the COVID-19 pandemic (MD = 0.01 h per day, 95% CI = –0.027, 0.225; p-value = 0.125; $I^2 = 98.48\%$).

Conclusion: During the pandemic, less PA was contributed to poor QoL and sleep quality. However, increases in PA are associated with reduced occurrences of psychological and behavioral problems. Implementing recovery plans to address the health effect of the pandemic is essential.

KEYWORDS

behavioral problems, COVID-19, physical activity, psychological problems, preschoolers, children and adolescents

1. Introduction

On March 11, 2020, coronavirus disease (COVID-19) was declared a global pandemic by the World Health Organization (1). The long incubation period, high transmission rate, and ongoing viral mutation and evolution have posed great challenges to pandemic control (2). As of March 21, 2022, this highly contagious disease had affected 227 countries, resulting in 471,079,831 confirmed cases and 6,101,020 deaths globally (3). In addition to the loss of human life, the estimated loss of global economic output reached 2.96 trillion USD in 2020 (4). To contain the spread of COVID-19 and minimize such losses, countries around the world adopted preventive measures with varying levels of stringency (5), including the prohibition of mass gatherings, closure of schools and public places, physical distancing, or even lockdowns. These restrictive measures had a negative impact on the overall Physical activity (PA) levels in MET-min/weeks, as well as increased in sedentary behavior in young population (6). The measures had also caused changes in PA among children, and adolescents. For instance, a meta-analysis reported decrease in PA levels across all age groups during the pandemic (7). Among the total of 57 included studies, 16 of them reported solely on children and adolescents, and half of those indicated reduction in PA parameters (7). In addition, moderate-to-vigorous activities and step counts were significantly reduced in children and adolescents (7). Moreover, PA restrictions have negatively affected the psychological health of children and adolescents (8), further exacerbating their anxiety and depression. It is estimated that the pooled prevalence of clinically elevated depression and anxiety in children and adolescents increased to 25.2% and 20.5% respectively, which is twice the pre-pandemic estimate (9). Another study involving more than 59,000 young participants reported increased depressive symptoms and deteriorated psychological health during the pandemic (10). In addition to affecting psychological health, disturbing daily routines may induce changes in behavioral problems (11, 12), sleep quality (13, 14), and resulting quality of life (QoL) (15) in children and adolescents. Yet, a systematic review revealed a positive correlation between PA and psychological health in children and adolescent during the pandemic, indicating PA improves psychological health among them (8). In addition, a study with adult participants reported PA was associated with anxiety, emotional, psychological and social well-being, and sleep quality during the pandemic (16). And participants who were more active reported lower levels of anxiety, higher levels of well-beings and better sleep quality than those who were less active (16). Whereas the pandemic restrictive measures appeared to decrease PA participation, active lifestyle should still be encouraged as PA is beneficial to psychological health, sleep quality, and emotion and social well-being.

When faced with high psychological distress during the pandemic, increasing the level of PA is a coping strategy to mitigate the associated negative effects. In a study involving more than 1.2 million adult participants (17), those who exercised regularly experienced fewer days of poor psychological health than those who did not. Although the effects of increasing PA of preschoolers, children, and adolescents on psychological health (18) had been reported in several studies, the quality of those remains unclear. One systematic review (19) investigating the association between PA and psychological health in children and adolescents during the first year of the COVID-19 pandemic reported that an increasing level of PA is associated with fewer depressive symptoms, lower anxiety and stress, and an improved well-being and QoL. However, this association was analyzed only qualitatively. Furthermore, the study time frame was limited to the first year of the COVID-19 pandemic, and only four studies included preschoolers, children, and adolescents. Another systematic review (8) reported an association between PA and psychological health in preschoolers, children, and adolescents. Yet, this study only used PubMed as a search engine to identify potential articles, and no meta-analysis was conducted. Moreover, the quality of the selected articles was not assessed. Therefore, the selected articles may have had a risk of bias, potentially compromising the overall results. In addition, the extent of psychological health changes has not been reported; thus, the effect of PA changes cannot be quantified. The effect of PA on psychological and/or behavioral problems or sleep quality remains unknown in these reviews. As preschoolers, children and adolescents are considered a vulnerable population who are susceptible to mental health issues (18); their difficulties may be underestimated, and more investigations are needed in this group. Therefore, a systematic analysis of the aforementioned aspects is required.

This meta-analysis aimed to quantitatively analyze the relationship between PA changes and psychological problems in particular depression, anxiety, stress and mood disturbance and/or behavioral problems including irritability, peer problems, conduct problem, hyperactivity or inattention, and prosocial behavior in preschoolers, children and adolescents. The study also explored the changes of PA levels with the differences in sleeping patterns and QoL before and during the pandemic among those population. We hypothesized that increasing PA levels are associated with decreasing the occurrence of psychological and/or behavioral problems in preschoolers, children and adolescents. Additionally, we hypothesized there will be significant differences in PA levels, sleeping patterns and QoL before and during the pandemic in preschooler, children and adolescents. The null hypothesis was that there would be no relationship between PA and psychological and/or behavioral problems and no differences in PA levels, sleeping patterns and QoL among those population. This study may provide valuable references for resource allocation and the formulation of effective management policies to address the needs of PA interventions for preschoolers, children, and adolescents.

2. Methods

2.1. Search strategy and selection criteria

This meta-analysis adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (20) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (21) guidelines. The protocol for this meta-analysis was published in the PROSPERO database (registration number: CRD42022309209). The current study was conducted in adherence with the published protocol. A comprehensive literature search of the CINAHL Complete, Cochrane Library, EMBASE, Medline, PubMed, and PsycINFO databases without language restrictions was conducted on March 16, 2022, for all relevant articles containing quantitative data. The reference lists of all relevant articles were also manually searched to minimize the possibility of missing data. For non-English articles, we initially used "Google Translate," followed by consultation of professional translations by native speakers. The search history is presented in **Supplementary Table S1**, while the search terms are listed in **Supplementary Table S2**. In order to identify the relationship between PA and psychological and/or behavioral problems as well as the pattern of changes of PA levels with sleeping patterns and QoL, articles that either provide correlational quantitative data assessing the effect of changes in PA on psychological and/or behavioral problems during the COVID-19 pandemic, or mean changes in various parameters regarding to PA levels, sleeping patterns and/or QoL before and during the COVID-19 pandemic in preschoolers (age 0–5 years), children (age 6–11 years), and adolescents (age 12–18 years) were included. Moreover, only articles with a low risk of bias were included in order to provide rigorous findings. We excluded articles that involved participants who were not representative of the general preschool, child, and adolescent populations (e.g., articles that exclusively involved participants with pre-existing physiological or psychological health problems and athletes). Abstracts, editorial comments, and unpublished studies were also excluded.

2.2. Risk of bias and certainty assessment

The quality and certainty of the included articles were assessed by two independent reviewers (JP and KR) using the Newcastle-Ottawa Scale (NOS) (22) for cohort studies and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence (23). The NOS has a maximum score of 9 points. The cut-off score for adequate quality in this meta-analysis was 7 points. Articles that scored 7–9, 4–6, and 0–3 points were considered to have a low, moderate, and high risk of bias, respectively (22). The GRADE includes four levels of certainty in evidence: very low, low, moderate, and high (23). The quality of evidence was applied to each outcome as this may vary across outcomes. A third reviewer resolved any disagreements regarding the scoring of the included articles.

2.3. Data extraction and statistical analysis

Based on the inclusion and exclusion criteria, the titles and abstracts of potential articles were screened by two independent reviewers, and the full texts of the remaining articles were evaluated. Disagreements were resolved by a third reviewer. Relevant data were extracted from the included articles by five reviewers using a standardized data extraction sheet. The variables are descripted as follow:

Relationship between PA and psychological and/or behavioral problems: quantitative data representing the relationship between PA and psychological and/or behavioral problems were retrieved. The impact of PA was measured by participants who were either being physically active, participated in moderate or high level of PA or indication of participation in PA during the pandemic on their occurrence of psychological problems, notably depression, anxiety, stress and mood disturbance and/or behavioral problems such as irritability, peer problems, peer problems, conduct problem, hyperactivity or inattention, and prosocial behavior. The participants' levels of PA and their occurrence of psychological and/or behavioral problems were quantified by their responses in the selected parameters in the included articles.

PA levels, sleeping patterns and QoL: the differences in participants' PA levels sleeping patterns including sleep duration and sleep quality, and QoL before and during the COVID-19 pandemic were extracted. Particularly, articles that reported the difference in time spent on PA and sleep duration were recorded to identify the mean time spent change in PA and sleep duration before and during the pandemic. For articles that did not provide changes in time spent in PA, and rather adopted other parameters, we provided standardized mean differences to identify the changes. Similarly, standardized mean differences were calculated for changes in sleep quality and QoL before and during the pandemic.

Additionally, confounding variables, including participants' age, were assessed in a subgroup analysis. The authors of the selected articles would be contacted and any missing data were reported. Comprehensive Meta-Analysis version 3.0 (Biostat, Englewood, New Jersey, United States) was used for the statistical analysis. The targeted outcomes were presented as the mean difference (MD) with 95% confidence intervals (CIs) for data reported in hours per day and standardized MD (SMD) with 95% CIs for data reported with other measures. To identify the relationship between PA and psychological and/or behavioral changes, we generated pooled effects estimated as odd ratios (ORs) with 95% CIs. All p-values in this meta-analysis were two-tailed, and statistical significance was set at ≤0.05. The risk of heterogenicity was assessed by the I^2 index, and a random-effects model was selected if the heterogeneity was ≥50%. The risk of publication bias was assessed by funnel plots and Egger's test (24). An asymmetric plot and $p \leq 0.05$ indicated the risk of publication bias. A sensitivity analysis was conducted to evaluate the robustness of the relationship (pooled ORs ratio) between PA and psychological and/or behavioral problems by removing each included study from the analysis one by one.

3. Results

3.1. Study characteristics

In total, 12,735 potential articles were retrieved from the literature search. After removing duplicates and screening titles and abstracts, 307 full-text articles were reviewed, of which 263 articles were further removed, leaving 44 articles (11, 14, 23, 25–66). The PRISMA flowchart of the study selection is shown in **Figure 1**, and the reasons for exclusion are detailed in **Supplementary Table S3**. The authors of the selected articles were not contacted to obtain additional data, as this was not required in this meta-analysis.

The NOS scores of all included articles are documented in **Supplementary Table S4**. After excluding studies with a high-to-moderate risk of bias, 34 articles (25, 27, 29–34, 36–50, 53, 55, 56, 58, 61, 62, 64–66), comprising 66,857 participants and 23 different countries, were included in the analysis. The included articles had NOS scores between 7 and 8 out of 9 points and were classified as having a low risk of bias and had a rating of 4 under the modified Oxford Centre for Evidence-based Medicine (67). The certainty of the included studies was assessed by GRADE (**Supplementary Table S5**). The characteristics of the included articles are summarized in **Table 1**.

3.2. Outcomes

3.2.1. Relationship between PA, and psychological and/or behavioral problems during the COVID-19 pandemic

Overall, 14 articles (29, 33, 39, 40, 43, 44, 48, 50, 55, 58, 61, 62, 64, 66) reported the relationship between PA and psychological and/or behavioral problems during the COVID-19 pandemic (**Table 2**). To measure the PA levels, ten studies (29, 33, 40, 43, 44, 50, 58, 62, 64, 66) used a self-designed questionnaire, three studies adopted a validated questionnaire including the International Physical Activity Questionnaire Short Form (IPAQ-SF) (48, 55) and Goldin-Shepard Leisure—The Physical Activity Questionnaire (61), and one study utilized an accelerometer (39). To identify the occurrence of psychological and/or behavioral problems, nine studies (29, 33, 40, 43, 44, 58, 62, 64, 66) used a self-designed questionnaire where 5 studies employed a validate questionnaire such as the simplified Chinese Profile of Mood Status (POMS) (48), Depression, Anxiety, Stress Scale-21 (DASS-21) (39), The Psychological Distress Index (50), 9-Items Patient Health Questionnaire (PHQ-9) (55) and Generalized Anxiety Disorder Scale (GAD-7) (55), and Brief Symptom Inventory (BSI) (61). Our results showed an overall significant protective effect between PA and psychological problems include depression, anxiety, stress and mood disturbance and/or behavioral problems such as irritability, peer problems, conduct problem, hyperactivity or inattention, and prosocial behavior (OR = 0.677; 95% CI = 0.630, 0.728; p-value <0.001; I^2 = 59.79%). This relationship was also significant in the subgroup analysis of children (OR = 0.690; 95% CI = 0.632, 0.752; p-value <0.001; I^2 = 58.93%) and adolescents (OR = 0.650; 95% CI = 0.570, 0.741; p-value <0.001; I^2 = 60.85%); however, no data on the relationship in preschoolers were collected. The funnel plot analysis is shown in **Supplementary Figure S1**.

3.2.2. Changes in PA before and during the COVID-19 pandemic

The mean time changes in PA before and during the COVID-19 pandemic were identified in nine articles (27, 31, 38, 41, 42, 45, 49, 53) (**Table 3A**). Overall, the time spent on PA significantly decreased by 23.2 min per day during the COVID-19 pandemic (95% CI = −13.5, 32.9; p-value <0.001; I^2 = 99.82%). In the subgroup analysis, the time spent on PA also significantly decreased for preschoolers by 29.6 min per day (95% CI = −14.1, −45.1; p-value <0.001; I^2 = 99.89%), for children by 18.8 min per day (95% CI = −2.0, −35.4; p-value = 0.028; I^2 = 97.34%), and for adolescents by 19.4 min per day (95% CI = −1.0, −37.9; p-value = 0.039; I^2 = 84.54%). In addition, six articles (25, 32, 34, 44, 47, 65) reported changes in PA using various measurements (**Table 3B**). There was no significant difference in the pooled SMD in PA during the COVID-19 pandemic (SMD = −0.506, 95% CI = −1.070, 0.059; p-value = 0.079; I^2 = 99.51%).

3.2.3. Sleeping patterns

The sleep duration before and during the COVID-19 pandemic was reported in 15 articles (25, 27, 34, 36–38, 41, 42, 45–47, 53, 56) (**Table 3C**). There was no significant difference in sleep duration during the COVID-19 pandemic (MD = 0.01 h per day, 95% CI = −0.027, 0.225; p-value = 0.125; I^2 = 98.48%). The subgroup analysis also showed no significant difference in sleep duration across age groups: preschoolers (MD = 0.01 h per day, 95% CI = −0.169, 0.190; p-value = 0.908; I^2 = 93.85%), children (MD = 0.17 h per day, 95% CI = −0.010, 0.357; p-value = 0.064; I^2 = 95.10%) and adolescents (MD = 0.36 h per day, 95% CI = −0.346, 1.074; p-value = 0.315; I^2 = 99.24%). However, five articles (25, 27, 44, 56) investigated changes in the sleep quality using different measurements (**Table 3B**). The pooled SMD indicated a significant decrease in sleep quality during the COVID-19 pandemic (SMD = −1.785, 95% CI = −3.392, −0.177; p-value = 0.030; I^2 = 99.80%).

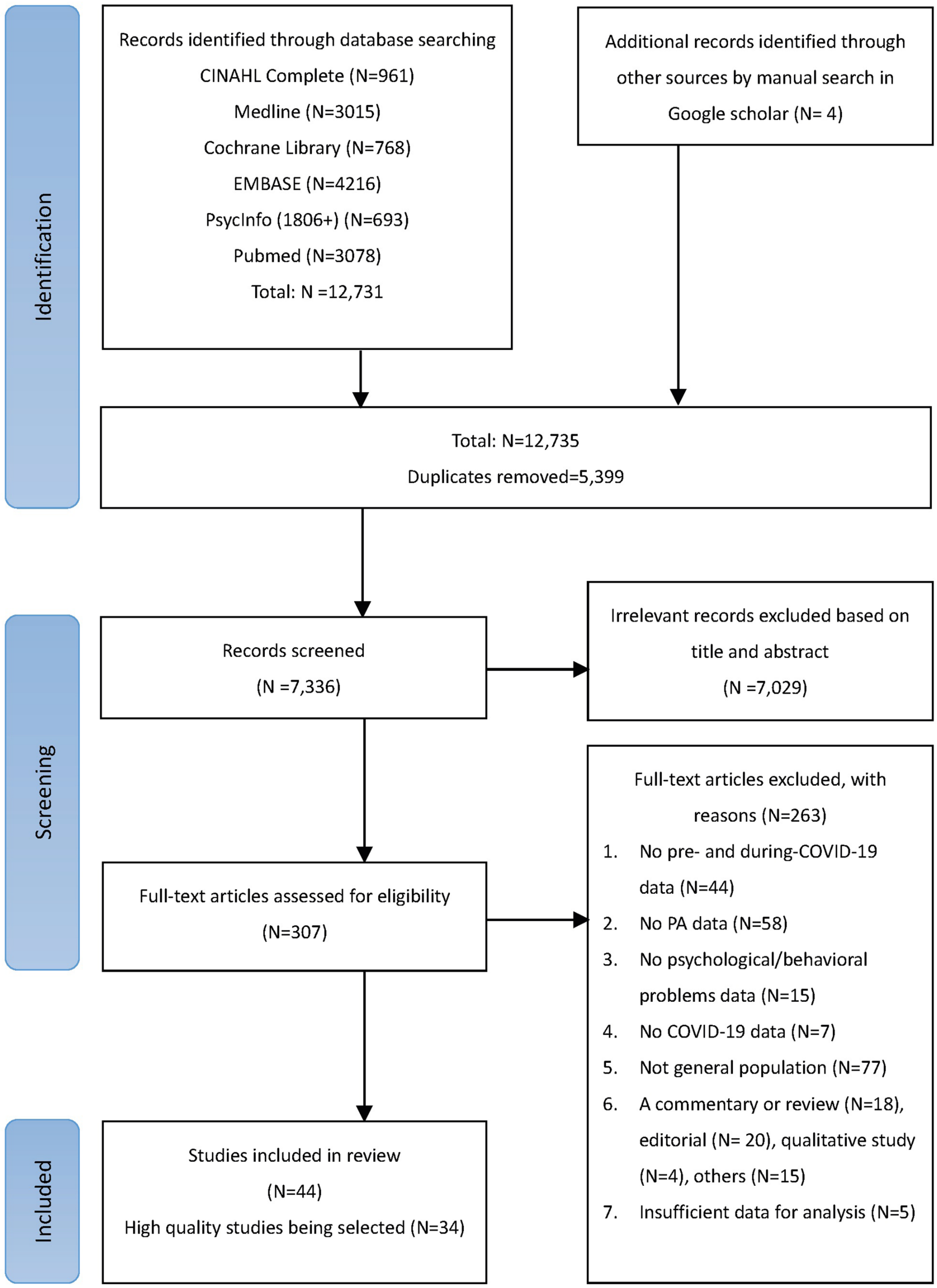


FIGURE 1
PRISMA flow chart of study selection in the systematic review.

3.2.4. QoL

Changes in QoL before and during the COVID-19 pandemic were revealed in two articles (30, 65) (**Table 3B**). The results showed an overall significant decrease in QoL (SMD = −0.894, 95% CI = −1.180, −0.609, *p*-value <0.001, $I^2 = 96.64\%$).

3.3. Publication bias

Funnel plot analysis and Egger's test (24) were performed to assess publication bias for the correlation between PA and psychological and behavioral problems. The shape of the funnel

TABLE 1 Characteristics of included articles.

Authors	Country	Age mean (SD)	Age range	Sample size	Sampling timepoint (Before COVID-19)	Sampling timepoint (During COVID-19)
Abid et al. (2021)	Tunisia	8.66 (3.30)	5–12	100	Not reported	(Apr to May 2020)
Aguilar-Farias et al. (2020)	Chile	3.10 (1.38)	1–5	3,157	Not reported	(Mar to Apr 2020)
Alonso-Martínez et al. (2021)	Spain	4.29 (0.76)	4–6	425	(Sep to Dec 2019)	(Mar to Apr 2020)
Breidokienè et al. (2021)	Lithuania	9.65 (1.94)	6–14	306	Not reported	2020
Bringolf-Isler et al. (2021)	Switzerland	Not reported	5–11	1,712	(2014 and 2015)	2022
Brzęk et al. (2021)	Poland	Not reported	3–5	1,316	Not reported	(Apr to Nov 2020)
Burdzovic Andreas and Brunborg (2021)	Norway	Grade 11 (est. 16)	Not reported	2,536	2017	(Oct to Dec 2020)
Chen et al. (2021)	China	Not reported	11–20	13,440	(Feb 2020)	(Apr 2020)
Chen et al. (2022)	Sweden	13.60 (0.4)	Not reported	1,901	(Sep 2017 and Jan 2020)	(Feb and Nov 2020)
Dragun et al. (2020)	Croatia	17.00 (1.00)	Not reported	1,093	(2018 and 2019)	(May 2020)
Francisco et al. (2020)	Italy, Spain, Portugal	9.15 (4.27)	3–18	1,480	Not reported	(Mar to Apr 2020)
Ghanamah and Eghbaria-Ghanamah (2020)	Israeli	Not reported	5–11	382	Not reported	(Dec 2020)
Ghorbani et al. (2021)	Iran	16.28 (0.97)	15–17	136	Not reported	(Oct 2020 to Feb 2021)
Gibert et al. (2021)	USA	8.01 (1.75)	Not reported	144	Not reported	(May to Jul 2020)
Hossain et al. (2021)	Bangladesh	4.50 (0.15)	Not reported	65	(Mar to Jun 2019)	(May 2020)
Hyunshik et al. (2021)	Japan	3.60 (0.3)	3–5	591	(Oct 2019)	(Oct 2020)
Ishimoto et al. (2022)	Japan	Not reported	8–12	293	(Dec 2019)	(March 2020)
Jackson et al. (2021)	USA	13.84 (2.74)	10–18	624	Not reported	(Apr to Jun 2020)
Jauregui et al. (2021)	Mexico	3.30 (0.20)	1–5	631	Not reported	(Apr to Jul 2020)
Jester and Kang. (2021)	UK	16.64 (1.29)	15–18	55	Not reported	(Apr to Jun 2020)
Jovanović et al. (2021)	Croatia	12.72 (1.17)	10–15	1,370	Not reported	(May 2021)
Kang et al. (2021)	China	16.30 (1.30)	Not reported	4,898	Not reported	(Mar 2020)
Kuhn et al. (2022)	USA	Not reported	3–15	75	(Oct 2017 to Mar 2020)	(May to Jul 2020)
Laurier et al. (2021)	Canada	15.26 (1.46)	11–17	133	Not reported	(Jun to Aug 2020)
Lim et al. (2021)	Singapore	*Median (IQR) 8 (6–11)	3–16	593	Not reported	(Apr to Jun 2020)
Lu et al. (2021)	China	15.26 (0.46)	Not reported	965	Not reported	(May 2020)
Łuszczki et al. (2021)	Poland	10.51 (2.13)	6–15	1,016	(Feb to Mar 2020)	(Feb to Mar 2021)
McArthur et al. (2021)	Canada	Not reported	9–11	846	(2017–2019)	(May to Aug 2020)
Medrano et al. (2021)	Spain	12.10 (2.40)	8–16	404	(Sep to Dec 2019)	(Mar to Apr 2020)
Mzadi et. al. (2022)	Morocco	16.55 (0.96)	15–18	807	(2014–2015)	(Sep 2020 to Feb 2021)
Ren et al. (2021)	China	13.14	10–17	1,487	Not reported	(Apr 2020)
Wang et al. (2021)	China	9.10 (1.33), 13.90 (1,40)	6–11, 12–16	12,186	Not reported	(May to Jul 2020)
Wunsch et al. (2021)	Germany	10.36 (4.04)	4–17	1,711	Not reported	(Apr 2020)
Zhang et al. (2020)	China	11.63 (1.23)	9–14	9,979	Not reported	(Mar 2020)

*Only age median.

plots appeared fairly symmetrical, which suggested that the risk of publication bias was low. The findings from Egger's test for odds ratios further confirmed that there was no publication bias ($t = 0.48$, $p = 0.6312$) (**Supplementary Figure S1**). Additionally, Egger's test for the changes of PA, sleep duration, sleep quality and QoL before and after pandemic also confirmed that were no publication bias ($t = 0.06$, $p = 0.118$; $t = 0.09$, $p = 0.464$; $t = 1.00$, $p = 0.195$; $t = 0.55$, $p = 0.680$).

3.4. Quality of evidence

In our meta-analysis, only the cohort studies with the data comparing pre and during COVID-19 were included for the analysis of the changes in PA, sleep pattern and QoL. Additionally, those cohort studies reported the correlation of PA and psychological and behavior problems were selected. Overall quality of evidence for different outcomes and assessing the relationship between the changes in PA and psychological and behavioral changes was high to moderate. The heterogeneity of outcomes and small sample size downgraded the quality of evidence (**Supplementary Table S5**).

3.5. Sensitivity analysis

The pooled ORs of the relationship between PA and psychological and/or behavioral problems during the COVID-19 pandemic were not modified when removing each included study one by one. Further details are displayed in (**Supplementary Table S6**).

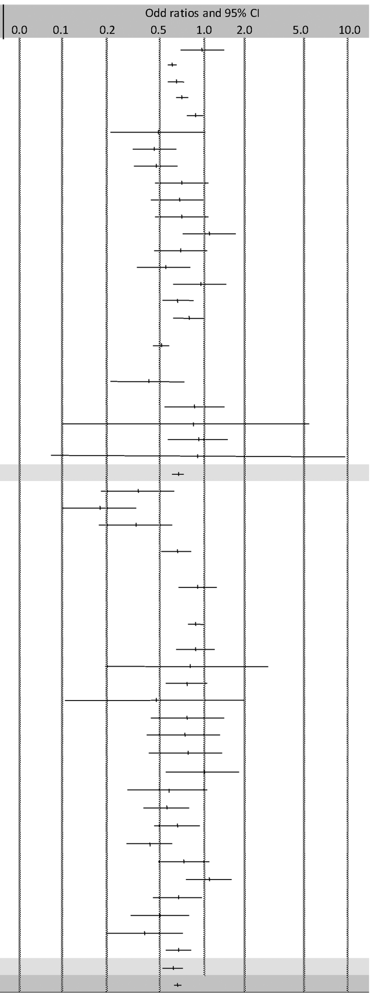
4. Discussion

This meta-analysis included more than 66,000 participants (preschoolers, children, and adolescents) from 23 countries. The findings support that increased PA (protective exposure) is associated with a reduced occurrence of psychological and behavioral problems during the COVID-19 pandemic for children (OR = 0.690, $p < 0.001$) and adolescents (OR = 0.650 $p < 0.001$). There was a significant decrease in the overall PA, sleep quality and QoL during the COVID-19 lockdown or constraints. However, the sleep duration was not significant change during the pandemic. Similar finding was reported by (68) that the duration of sleep time was not significant change ($p = 0.11$)

TABLE 2 The relationship between PA and psychological and/or behavior problems.

Authors	Contrasts: PA	Contrasts: Psychological/behavioural problems	Age group	Odds Ratio	Lower limit	Upper limit	P-value
Breidokienė *et al.* (2021)	Being physical active	Emotional well-being/ behaviour	Children	0.970	0.620	1.519	0.894
Chen *et al.* (2021)_1	30-60 min PA/day	Depression	Children	0.640	0.601	0.681	0.000
Chen *et al.* (2021)_2	>60 min PA/day	Depression	Children	0.670	0.586	0.765	0.000
Chen *et al.* (2021)_3	30-60 min PA/day	Anxiety	Children	0.730	0.668	0.798	0.000
Chen *et al.* (2021)_4	>60 min PA/day	Anxiety	Children	0.840	0.725	0.973	0.020
Gibert *et al.* (2021)	Decrease in PA	Perceived change in MWB	Children	0.470	0.222	0.997	0.049
Ishimoto *et al.* (2022)_1	Being physical active	TDS	Children	0.477	0.311	0.731	0.001
Ishimoto *et al.* (2022)_2	Being physical active	ES	Children	0.477	0.311	0.731	0.001
Ishimoto *et al.* (2022)_3	Being physical active	CP	Children	0.694	0.456	1.057	0.089
Ishimoto *et al.* (2022)_4	Being physical active	HI	Children	0.645	0.423	0.983	0.041
Ishimoto *et al.* (2022)_5	Being physical active	PP	Children	0.694	0.456	1.057	0.089
Ishimoto *et al.* (2022)_6	Being physical active	PB	Children	1.115	0.734	1.694	0.610
Ishimoto *et al.* (2022)_7	Being physical active	AI	Children	0.720	0.473	1.096	0.126
Ishimoto *et al.* (2022)_8	Being physical active	AR	Children	0.535	0.350	0.818	0.004
Ishimoto *et al.* (2022)_9	Being physical active	AA	Children	0.964	0.635	1.465	0.865
McArthur *et al.* (2021)_1	Being physical active	Depression	Children	0.669	0.523	0.856	0.001
McArthur *et al.* (2021)_2	Being physical active	Anixiety	Children	0.804	0.629	1.028	0.081
Wang *et al.* (2021)_1	Being physical active	Psychological and behavioural problems in Wuhan	Children	0.510	0.440	0.591	0.000
Wang *et al.* (2021)_2	Being physical active	Psychological and behavioural problems outside Wuhan	Children	0.416	0.218	0.793	0.008
Zhang *et al.* (2020)_1	Moderate PA level	Depression	Children	0.859	0.541	1.363	0.518
Zhang *et al.* (2020)_2	Moderate PA level	Total mood disturbance	Children	0.833	0.102	6.782	0.864
Zhang *et al.* (2020)_3	High PA level	Depression	Children	0.968	0.578	1.621	0.901
Zhang *et al.* (2020)_4	High PA level	Total mood disturbance	Children	0.922	0.089	9.594	0.946
			Children	0.690	0.632	0.752	0.000
Ghorbani *et al.* (2021)_1	MVPA	Depression	Adolescents	0.333	0.175	0.634	0.001
Ghorbani *et al.* (2021)_2	MVPA	Anxiety	Adolescents	0.201	0.103	0.395	0.000
Ghorbani *et al.* (2021)_3	MVPA	Stress	Adolescents	0.322	0.169	0.615	0.001
Jackson *et al.* (2021)_1	Play-based activity participation during COVID-19	Change in SWB score	Adolescents	0.661	0.516	0.848	0.001
Jackson *et al.* (2021)_2	Nature-based activity participation during COVID-19	Change in SWB score	Adolescents	0.894	0.649	1.231	0.491
Jackson *et al.* (2021)_3	Outdoor family activity participation during COVID-19	Change in SWB score	Adolescents	0.881	0.764	1.015	0.080
Kang *et al.* (2021)_1	Moderate PA level	Depression	Adolescents	0.870	0.654	1.156	0.336
Kang *et al.* (2021)_2	Moderate PA level	Total meed disturbance	Adolescents	0.809	0.217	3.014	0.752
Kang *et al.* (2021)_3	High PA level	Depression	Adolescents	0.752	0.546	1.036	0.081
Kang *et al.* (2021)_4	High PA level	Total meed disturbance	Adolescents	0.496	0.120	2.055	0.333
Laurier *et al.* (2021)_1	Sport prior to confinement = yes	IDP total	Adolescents	0.775	0.415	1.449	0.425
Laurier *et al.* (2021)_2	Sport prior to confinement = yes	IDP depression	Adolescents	0.720	0.385	1.348	0.305
Laurier *et al.* (2021)_3	Sport prior to confinement = yes	IDP anxiety	Adolescents	0.747	0.400	1.397	0.362
Laurier *et al.* (2021)_4	Sport prior to confinement = yes	IDP irritability	Adolescents	1.000	0.536	1.866	1.000
Laurier *et al.* (2021)_5	Sport prior to confinement = yes	IDP cognitive problems	Adolescents	0.555	0.295	1.045	0.068
Lu *et al.* (2021)_1	Low PAT and low ST	Depressive symptoms	Adolescents	0.550	0.379	0.798	0.002
Lu *et al.* (2021)_2	High PAT and high ST	Depressive symptoms	Adolescents	0.650	0.452	0.934	0.020
Lu *et al.* (2021)_3	High PAT and low ST	Depressive symptoms	Adolescents	0.430	0.297	0.623	0.000
Lu *et al.* (2021)_4	Low PAT and low ST	Anxiety symptoms	Adolescents	0.730	0.492	1.083	0.118
Lu *et al.* (2021)_5	High PAT and high ST	Anxiety symptoms	Adolescents	1.050	0.723	1.526	0.798
Lu *et al.* (2021)_6	High PAT and low ST	Anxiety symptoms	Adolescents	0.650	0.433	0.976	0.038
Mzadi et. *al.* (2022)_1	Frequency of PA = sometimes	Depressive symptoms	Adolescents	0.500	0.311	0.803	0.004
Mzadi et. *al.* (2022)_2	Frequency of PA = often	Depressive symptoms	Adolescents	0.400	0.217	0.739	0.003
Ren *et al.* (2021)	Being physical active	Depressive symptoms	Adolescents	0.694	0.577	0.836	0.000
			Adolescents	0.650	0.570	0.741	0.000
			Overall	0.677	0.630	0.728	0.000

Odd ratios and 95% CI



Key: The number after all the authors indicated different sets of data extracted for analysis in the outcomes accordingly. PA, physical activity; MWB, mental well-being; TDS, total difficulties score; ES, emotional symptoms; CP, conduct problems; HI, hyperactivity/inattention; PP, peer problems; PB, prosocial behavior; AI, anxiety related to infection; AR, anxiety related to returning to school; AA, anxiety related to academic delay; SWB, subjective well-being; IDP, psychological distress index; PAT, physical activity time; ST, sitting time.

though the sleep quality showed significant change that affect children's psychological difficulties ($b = 0.14$, $t = 6.87$, $p < 0.01$). Besides, previous systematic review reported the magnitude of change in PA before and during the pandemic was difficult to be evaluated due to the limitation of lacking baseline data and heterogenicity of measurements (69). To our knowledge, this meta-analysis is the largest and most comprehensive evaluation of this relationship, with substantial evidence (overall OR = 0.677, $p < 0.001$), and quantified the changes of PA, sleep duration, sleep quality and QoL. Although the outcomes showed high heterogenicity due to the limitation of using varies measurements in the included studies, we have used random model to minimize the influence and we monitored the risk of publication bias. The current meta-analysis was based on the relative symmetrical shape of the funnel plot and the results from Egger's test, and the quality of evidence was high to moderate by using a GRADE approach.

In addition, the association between the reduction in PA and psychological and behavioral problems during the COVID-19 pandemic remained when we performed subgroup analyses by age. Among the three groups, preschoolers were the most vulnerable, with significant reductions in PA (MD = −0.50, $p < 0.001$), followed by adolescents (MD = −0.32, $p = 0.039$) and children (MD = −0.31, $p = 0.028$). Policymakers and health-care professionals should provide more resources to cope with potential problems in these two groups. However, the change in sleep duration only increased by 0.001 h ($p = 0.908$). A significant overall decrease in PA may indicate that lifestyles become more sedentary (29, 66). In addition, the overall QoL decreased (SMD = −0.894, $p < 0.001$), and the sleep quality decreased (SMD = −1.785, $p = 0.030$), which may also be associated with adapted PA and a more sedentary lifestyle (29, 70). The potential adverse effects on the health of preschoolers, children, and adolescents are of great concern.

The relationship between interventions and the overall psychological well-being has not been established through meta-analyses. PA has inconsistent effects on mental health problems among younger and older children (9, 71); in addition, studies

TABLE 3A Outcomes: the mean time change in PA before and during COVID-19.

Authors	Subgroup	Age group	Mean diff (mins/day)	Lower limit	Upper limit	*p*-value
Aguilar-Farias et al. (2020)	Not reported	Preschoolers	−47.4	−41.28	−53.52	<0.001
Alonso-Martínez et al. (2021)_1	MVPA	Preschoolers	−43.2	−2.88	−83.52	0.036
Alonso-Martínez et al. (2021)_2	Total PA	Preschoolers	−16.8	−0.84	−32.76	0.039
Brzęk et al. (2021)	Not reported	Preschoolers	−7.38	−5.58	−9.18	<0.001
Hossain et al. (2021)_1	MVPA	Preschoolers	−58.8	−48.60	−69	<0.001
Hossain et al. (2021)_2	Total PA	Preschoolers	−193.8	−174.66	−212.94	<0.001
Hyunshik et al. (2021)_1	Weekdays	Preschoolers	−4.8	−0.42	−9.18	0.031
Hyunshik et al. (2021)_2	Weekend	Preschoolers	−20.4	−15.18	−25.62	<0.001
Jáuregui et al. (2021)_1	MVPA	Preschoolers	−60.6	−59.22	−61.98	<0.001
Jáuregui et al. (2021)_2	Total PA	Preschoolers	−34.8	−33.90	−35.7	<0.001
Kuhn et al. (2022)_1	MVPA, weekday	Preschoolers	8.52	14.28	2.76	0.004
Kuhn et al. (2022)_2	MVPA, weekend	Preschoolers	30.36	53.82	6.9	0.011
Kuhn et al. (2022)_3	LPA, weekday	Preschoolers	0.48	0.84	0.12	0.014
Kuhn et al. (2022)_4	LPA, weekend	Preschoolers	28.8	49.74	7.86	0.007
		Preschoolers	−29.64	−14.10	−45.12	<0.001
Ghanamah and Eghbaria-Ghanamah (2020)	Not reported	Children	−51.6	−42.72	−60.48	<0.001
Kuhn et al. (2022)_5	MVPA, weekday	Children	0.96	1.62	0.3	0.004
Kuhn et al. (2022)_6	MVPA, weekend	Children	17.88	31.68	4.08	0.011
Kuhn et al. (2022)_7	LPA, weekday	Children	−32.1	−6.60	−57.6	0.014
Kuhn et al. (2022)_8	LPA, weekend	Children	−58.98	−16.26	−101.7	0.007
Lim et al. (2021)	Not reported	Children	−13.2	−8.64	−17.76	<0.001
		Children	−18.78	−2.04	−35.46	0.028
Kuhn et al. (2022)_9	MVPA, weekday	Adolescents	−15.3	−4.74	−25.86	0.004
Kuhn et al. (2022)_10	MVPA, weekend	Adolescents	−1.08	−0.24	−1.92	0.012
Kuhn et al. (2022)_11	LPA, weekday	Adolescents	−73.38	−14.22	−132.54	0.015
Kuhn et al. (2022)_12	LPA, weekend	Adolescents	−51.9	−13.62	−90.18	0.008
		Adolescents	−19.44	−1.02	−37.92	0.039
		Overall	−23.16	−13.50	−32.88	<0.001

TABLE 3B Outcomes: the standardized mean difference in quality of life, PA and sleep quality.

Outcomes	Authors	Age	Measurements	Std diff in mean	Upper limit	Lower limit	*p*-value
Quality of life	Bringolf-Isler et al. (2021)	5–11	KINDL-R questionnaire	−1.106	1.207	1.004	<0.001
	Wunsch et al. (2021)_1	4–10	KIDSCREEN-10 index	−0.964	1.067	0.861	<0.001
	Wunsch et al. (2021)_2	11–17	KIDSCREEN-10 index	−0.612	0.717	0.507	<0.001
Overall				−0.894	1.180	0.609	<0.001
Physical activity	Abid et al. (2021)_1	8.66 (3.30)	Total PA score from PA Questionnaire	−0.695	0.980	0.409	<0.001
	Abid et al. (2021)_2	8.66 (3.30)	Leisure PA score from PA Questionnaire	−0.673	0.958	0.388	<0.001
	Abid et al. (2021)_3	8.66 (3.30)	Daily PA score from PA Questionnaire	−0.974	1.267	0.681	<0.001
	Burdzovic Andreas and Brunborg (2021)	Grade 11 (est. 16)	% of adolescent participated in organized sports	−0.205	0.331	0.078	0.002
	Chen et al. (2022)	13.50 (0.40)	PA 60 min/day (days/week)	0.000	0.097	0.097	1.000
	Jackson et al. (2021)	13.84 (2.74)	Outdoor Activity Score (Times per week from 5-point scale questionnaire)	−0.600	0.713	0.486	<0.001
	Jovanović et al. (2021)	12.72 (1.17)	MET-min/week	−2.164	2.259	2.070	<0.001
	Łuszczki et al. (2021)	10.51 (2.13)	PA 60 min/day (days/week)	−0.294	0.422	0.166	<0.001
	Wunsch et al. (2021)_1	11–17	Mo Mo Physical activity Questionnaire	0.169	0.067	0.270	0.001
	Wunsch et al. (2021)_2	4–10	Mo Mo Physical activity Questionnaire	0.361	0.271	0.451	<0.001
Overall				−0.506	1.070	0.059	0.079
Sleep quality	Abid et al. (2021)	8.66 (3.33)	Global PSQI score	−1.810	2.139	1.481	<0.001
	Aguilar-Farias et al. (2020)	3.10 (1.38)	Likert Scale score	−0.452	0.502	0.402	<0.001
	Alonso-Martínez et al. (2021)	4.28 (0.80)	Device-measured sleep efficiency (%)	−0.443	1.055	0.169	0.156
	Jaureguić et al. (2021)	3.30 (0.20)	Likert Scale score	−6.325	6.054	6.054	<0.001
	Łuszczki et al. (2021)	10.51 (2.13)	Four-point scale questionnaire	0.121	0.006	0.248	0.063
Overall				−1.785	3.392	0.177	0.030

TABLE 3C Outcomes: the mean time change in sleep duration before and during COVID-19.

Authors	Subgroup	Age group	Mean diff (h/day)	Upper limit	Lower limit	*p*-value
Aguilar-Farias et al. (2020)	Not reported	Preschoolers	0.090	0.000	0.180	0.050
Alonso-Martínez et al. (2021)	Not reported	Preschoolers	0.110	−0.520	0.740	0.730
Hossain et al. (2021)	Not reported	Preschoolers	−0.210	−0.400	−0.020	0.030
Hyunshik et al. (2021)	Not reported	Preschoolers	0.070	−0.030	0.170	0.190
Jaureguić et al. (2021)	Not reported	Preschoolers	−0.200	−0.210	−0.190	<0.001
Lim et al. (2021)	Preschoolers	Preschoolers	0.340	0.083	0.597	0.010
		Preschoolers	0.011	−0.169	0.190	0.908
Abid et al. (2021)	Not reported	Children	0.010	−0.230	0.250	0.930
Francisco et al. (2020)_1	Total	Children	0.400	0.290	0.510	<0.001
Francisco et al. (2020)_2	Italy	Children	0.360	0.190	0.530	<0.001
Francisco et al. (2020)_3	Spain	Children	0.220	0.050	0.390	0.010
Francisco et al. (2020)_4	Portugal	Children	0.680	0.470	0.890	<0.001
Ghanamah and Eghbaria-Ghanamah (2021)	Not reported	Children	0.610	0.500	0.720	<0.001
Jovanović et al. (2021)	Not reported	Children	0.290	0.230	0.350	<0.001
Medrano et al. (2021)_1	Weekday	Children	0.000	−0.210	0.210	1.000
Medrano et al. (2021)_1	Weekend	Children	−0.200	−0.460	0.060	0.130
Lim et al. (2021)	Primary schoolers	Children	0.500	0.371	0.629	<0.001
Łuszczki et al. (2021)_1	Weekday	Children	−0.280	−0.454	−0.106	0.002
Łuszczki et al. (2021)_2	Weekend	Children	−0.590	−0.768	−0.412	<0.001
		Children	0.174	−0.010	0.357	0.064
Chen et al. (2022)_1	Non-school day	Adolescents	−0.260	−0.380	−0.140	<0.001
Chen et al. (2022)_2	School day	Adolescents	−0.610	−0.700	−0.520	<0.001
Dragun et al. (2020)_1	Non-working day	Adolescents	−0.500	−0.650	−0.350	<0.001
Dragun et al. (2020)_2	Working day	Adolescents	1.500	1.350	1.650	<0.001
Jester and Kang (2021)	Not reported	Adolescents	2.000	1.448	2.552	<0.001
Lim et al. (2021)	Secondary schoolers	Adolescents	0.200	−0.064	0.464	0.137
		Adolescents	0.364	−0.346	1.074	0.315
		Overall	0.099	−0.027	0.225	0.125

Key: The number after all the authors indicated different sets of data extracted for analysis in the outcomes accordingly. PA, physical activity; MVPA, moderate to vigorous physical activity; LPA, light physical activity; PSQI, Pittsburg Sleep Quality Index.

had highlighted the importance of prevention in mental health and behavioral problems in children and adolescents by limiting risk exposure and identifying high risk individuals early (72–75). Decrease in PA has shown to have detrimental effects in children and adolescents' psychological and behavioral problem (76–78). Hence, a strategy for the early identification and prevention of decreased PA is essential.

Although the underlying mechanisms responsible for the effects of decreased PA on the psychological and behavioral status of preschoolers, children, and adolescents remain unclear, several hypotheses have been proposed. First the decreased participation in PA may elicit feelings of loneliness that negatively affect mental health (25). Second, restrictive measures during the pandemic may lead to social isolation and, hence, to psychological and behavioral problems (80). Those measures may also lead to less time participating in PA (81). Third, replacing healthy with unhealthy behaviors may have negative consequences for preschoolers, children, and adolescents. Given the limited evidence, more studies focusing on potential mechanisms between decreased PA and the psychological and behavioral status are needed to confirm these hypotheses. As the exact mechanisms are unknown, we investigated the relationship through a meta-analysis of valid studies focusing on preschoolers, children, and adolescents worldwide.

The strength of our meta-analysis lies in three key aspects. First, we included all available high-quality prospective studies based on the NOS. The quality of evidence was further analyzed by GRADE and the publication bias was evaluated by sensitivity analysis. Second, we quantified the amount of PA and assessed its association with psychological and behavioral problems in children and adolescents, thereby obtaining more meaningful information. Third, we did not exclude any non-English publications. As the pandemic is a worldwide health concern, it is necessary to include and analyze all scientific studies of different cultures in different countries.

4.1. Clinical implications

Previous studies reported that in reaction to the drastic decrease in PA among children and adolescents due to the policy restrictions in different countries, the change in healthy lifestyle triggered the changes in sleep quality and QoL (66, 82). In addition, prolonged stays at home increase the risk of inactivity that may contribute different psychological and behavior problems. However, there is no conclusion of the extent of the changes during the pandemic. Our study provides scientistic evidence to quantify the extent of changes in the PA, sleep pattern and QoL in the preschoolers, children and adolescents before and during the pandemic. Previous studies reported PA or physical exercise had little effect on psychological status (83–85). However, the current situation is changed during the pandemic. This meta-analysis was one of the first to reveal the association between PA and psychological and behavioural problems of preschoolers, children and adolescents of different countries in the context of the pandemic. Our findings provide robust evidence and theoretical guidance for related health promotion and psychological rehabilitation of preschoolers, children and adolescents in the epidemic or post-epidemic era. Our meta-analysis can also provide effective reference for relevant health promotion and policy implementation to help young people to recover from the adverse effects of the social isolation period in the epidemic.

4.2. Limitations

First, a limited amount of empirical data retrieved during the pandemic met the inclusion criteria. The aims were to identify the relationship of PA and psychological and/or behavioral problems and compare different aspects before and during the pandemic. Thus, only articles involving before and during pandemic comparisons or those reporting the relationship between PA and psychological and/or behavioral problems were included. Some articles that reported either only PA or only psychological or behavioral problems were excluded. Consequently, some data from cross-sectional investigations on PA and psychological or behavioral problems in some worldwide populations were excluded. The association between changes in PA and psychological and behavioral problems in preschoolers remains unknown as no empirical study has yet been conducted. This limitation may be caused by difficulties in assessing the psychological and behavioral changes of subjects who are too young to express themselves through questionnaires or formal interviews. Data from caregiver and parental observations may have risks of bias and inaccuracy. Further development of the direct silent observation of preschoolers is needed to solve this gap for future studies (86). Third, although we searched six scientific databases and expected the findings to cover nearly all relevant published articles without any language limitations, we cannot exclude the possibility that additional relevant articles may have been missed. However, in addition to manually searching other databases, the reference lists of all relevant articles were searched; thus, the number of missed articles was likely small and would have little effect on the analysis. Fourth, most studies included in the analysis collected information *via* self-report questionnaires and from different outcome measures, which could have led to errors in the measurement of PA. Consequently, the heterogeneity of the outcomes was high, which may indicate the high diversity of the effects with different level of PA. The variability derives mainly from the clinical heterogeneity that is difficult to minimize, because the selection of outcome measures is always diverse in empirical studies (87). The risk of methodological heterogeneity among the included studies was examined and minimized. Our findings support that the included studies share a similar cohort study design. The quality of these studies was assessed, and the risk of publication bias was evaluated. In addition, the statistical heterogeneity among the included study was controlled by using a random effect model as the heterogeneity I^2 was ≥50% (88). Fifth, we could not entirely rule out the possibility that the caregivers or the children and/or adolescents themselves may have missed preclinical or undiagnosed psychological and behavioral problems. Based on our meta-analysis, further prospective studies are necessary to confirm the effect of decreased PA on psychological and behavioral problems in preschoolers, children, and adolescents. The potential reverse causality between decreased PA and psychological and behavioral problems should be identified early. Consequently, policymakers, health-care providers, and caregivers can minimize the risks of the adverse effects of decreased PA on society.

4.3. Conclusion

During the COVID-19 pandemic, less PA and longer screen times may induce a sedentary lifestyle. This may increase the risk of poor QoL and poor sleep quality. Increased PA is associated with fewer psychological and behavioral problems. Our results showed an overall significant protective effect between PA and psychological and/or behavioral problems. This relationship was also significant in terms of the subgroup analysis of children and adolescents. These findings may guide caregivers, health-care providers, and health-care policy makers in making recommendations and developing guidelines with respect to the degree of PA to help reduce the risk of psychological and behavioral problems at both the individual and population levels. More epidemiological studies with larger sample sizes and detailed quantifications of PA and psychological and behavioral problems will establish more precise information regarding this association. The influence of decreased PA on preschoolers' psychological and behavioral problems remains uncertain due to the paucity of studies. The scientific gap can be resolved using sophisticated technology to provide accurate observations and assessments of preschoolers in the future.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

Author contributions

JP initiated this study. All authors contributed to the design of the review structure and performed the literature search. JP and KR performed selection and interpretation of data, and drafted the manuscript including tables and figures. All authors contributed in critical revision of the manuscript and approval for the final version. 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1015943/full#supplementary-material.

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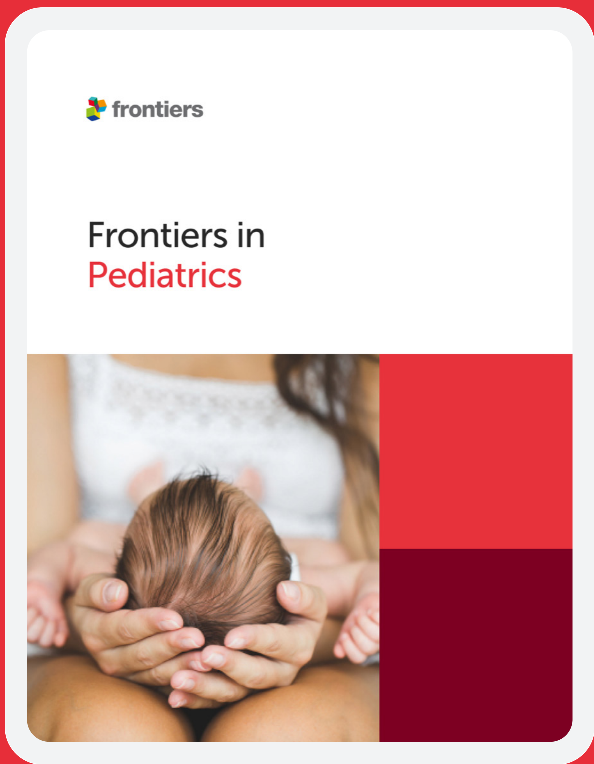

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