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How Is Mass Spectrometry Tackling the COVID-19 Pandemic?

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Most of us have never faced a pandemic before. The World Health Organization declared the 2019 novel coronavirus infectious disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus), a pandemic by March 11th, 2020. Today, this illness has reported more than 5′331,019 fatalities worldwide (December 17th, 2021). The COVID-19 pandemic has posed an unprecedented global challenge and put the academic community on "the spot." The following mini-review reports how the MS community improved the understanding of the SARS-CoV-2 virus pathophysiology while developing diagnostic procedures to complement the PCR-based approaches. For example, MS researchers identified the interaction sites between the SARS-CoV-2 virus and their hosts; this new knowledge is critical for developing antiviral drugs. MS researchers also realized that COVID-19 should be considered a systemic disease and not just a respiratory illness since its metabolic, lipidomic, and proteomic profile reflects four different clinical disorders: 1) acute inflammatory response, 2) a cardiovascular disease, 3) a prediabetic/diabetes and 4) liver dysfunction. Furthermore, MS researchers put forth the knowledge that the metabolic and lipidomic profile of several patients remained altered after being discharged, thus hinting at the scientific basis for the long COVID syndrome.

Keywords: COVID-19, SARS-CoV-2, mass spectrometry, Covid19-MSC, omics analyses

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of the *Coronaviridae* family (Feng et al., 2020; Keni et al., 2020; Machhi et al., 2020; Tse et al., 2020; Wiersinga et al., 2020). Other coronaviruses are the severe acute respiratory syndrome coronavirus (SARS-CoV) and the middle-east respiratory syndrome-related coronavirus (MERS-CoV). Unfortunately, compared with SARS-CoV and MERS-CoV, the SARS-CoV-2 virus is highly contagious (Keni et al., 2020; Machhi et al., 2020; Tse et al., 2020; Hu et al., 2021). The SARS-CoV-2 virus is the cause of the coronavirus 2019 (COVID-19) disease (Feng et al., 2020; Keni et al., 2020; Machhi et al., 2020; Tse et al., 2020; Wiersinga et al., 2020; Hu et al., 2021), which was first reported in Wuhan (Hubei Province, China) in December 2019 (Feng et al., 2020; Keni et al., 2020; Machhi et al., 2020; Tse et al., 2020; Wiersinga et al., 2020; Hu et al., 2021).

The COVID-19 human challenge study revealed that only 89% of infected participants showed symptoms (Killingley et al., 2022). Interestingly, researchers have also discussed the SARS-CoV-2 virus origin and propagation (Medema et al., 2020; Morens et al., 2020; Platto et al., 2020; Tiwari et al., 2020; La Rosa et al., 2021); some discovered that the SARS-CoV-2 virus had circulated in several countries before their first local case was reported (Medema et al., 2020; La Rosa et al., 2021). Thus, making it clear that the SARS-CoV-2 virus is difficult to contain. On March 11th, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic due to its rapid spread

worldwide (Machhi et al., 2020). According to the WHO, more than 271′963,258 million cases have been reported worldwide, having thus far resulted in 5′331,019 deaths (World Health Organization, 2021).

In 2020, the mass spectrometry (MS) community formed the COVID-19 MS coalition (Covid19-MSC) (Struwe et al., 2020). MS-based technologies are especially suited for uncovering information for precision medicine, *i.e.*, discovering biomarkers in a non-targeted and unbiased manner for disease diagnostic and prognosis. Thus, there has been a surge in the development of MS-based strategies for diagnosing COVID-19 disease from an exhaled breath, a nasopharyngeal swab, or a gargle solution (Cardozo et al., 2020; Ihling et al., 2020; Nachtigall et al., 2020; Ruszkiewicz et al., 2020; Bankar et al., 2021; Chen et al., 2021; Maus et al., 2021; Renuse et al., 2021; Tran et al., 2021). Furthermore, an exciting research line has focused on identifying biomarkers that reflect the severe COVID-19 phenotype (Chen et al., 2020a; Gordon et al., 2020; Kimhofer et al., 2020; Messner et al., 2020; Shen et al., 2020; Wu et al., 2020; Chevrier et al., 2021; Holmes et al., 2021; Lee et al., 2021; Messner et al., 2021; Wierbowski et al., 2021; Zhang et al., 2021).

Still and despite this progress, the full potential of MS applications against the COVID-19 pandemic remains to be seen. While previous MS-based reviews have zoomed in primarily on how MS approaches complement other types of diagnostics (Mahmud and Garrett, 2020; SoRelle et al., 2020; Appiasie et al., 2021; Yuan and Hu, 2021; Zhong et al., 2021; Amiri-Dashatan et al., 2022; Lima et al., 2022; Spick et al., 2022), in the following paragraphs, we will also showcase examples of MS-based strategies focused on improving our understanding of the SARS-CoV-2 virus' pathophysiology.

MS for COVID-19 Detection

Once the SARS-CoV-2 virus was sequenced and made available, real-time quantitative reverse transcription-polymerase chain reaction (RT-qPCR) and digital droplet polymerase chain reaction (dd-PCR) became the gold-standard methods of diagnosing COVID-19 (Feng et al., 2020; Walsh et al., 2020; Wiersinga et al., 2020; Hammerling et al., 2021). Unfortunately, during the beginning of the pandemic, the supply chain for these assays was inconsistent (SoRelle et al., 2020; Hammerling et al., 2021). Thus many researchers had to develop alternative strategies for SARS-CoV-2 virus detection (Cardozo et al., 2020; Grant et al., 2020; Ihling et al., 2020; Nachtigall et al., 2020; Ruszkiewicz et al., 2020; Bankar et al., 2021; Chen et al., 2021; Maus et al., 2021; Renuse et al., 2021; Tran et al., 2021; Lin et al., 2022; Mou et al., 2022).

One of Covid19-MSC's goals is to develop diagnostic procedures to complement the PCR-based approaches (Struwe et al., 2020). These MS-based strategies will possess poorer detection limits—samples must have a higher viral load (10^5–10^6 genome copies per mL)—than PCR-based assays (10 to 10^2 genome copies per mL) (SoRelle et al., 2020). The reason is that MS-based approaches lack the amplification step used in PCR-based assays (*i.e.,* polymerase chain reaction). Nevertheless, the developed MS-based methods can still appeal to some laboratories (Cardozo et al., 2020; Ihling et al., 2020; Nachtigall et al., 2020; Ruszkiewicz et al., 2020; Bankar et al., 2021; Chen et al., 2021; Maus et al., 2021; Renuse et al., 2021; Tran et al., 2021). Examples of such approaches are:

(a) Measurement of volatile organic compounds from breath samples (Ruszkiewicz et al., 2020; Chen et al., 2021). In this approach, exhaled breath samples are collected in tubes or bags. The samples are later injected into a gas chromatographer coupled with an ion mobility spectrometer (GC-IMS). The MS data is subsequently processed using machine-learning algorithms and other statistical tools; and
(b) Identification of a protein/peptide pattern. There are two variations to this approach:
(i) Nasal secretion samples are analyzed with a matrix-assisted laser/desorption ionization mass spectrometer (MALDI-MS) (Nachtigall et al., 2020; Tran et al., 2021). In this case, the sample is extracted using a nasopharyngeal swab. Subsequently, the swab is placed in a sterile tube with a viral transport medium. This solution is then spotted on a MALDI steel plate mixed with α-CHCA matrix solution and analyzed. The MS data is later processed using machine-learning algorithms; and
(ii) Nasal secretion or gargle samples are analyzed using a liquid chromatographer coupled mass spectrometer (LC-MS) (Cardozo et al., 2020; Ihling et al., 2020; Bankar et al., 2021; Maus et al., 2021; Renuse et al., 2021). The protein sample is collected using a nasopharyngeal swab or taken from a (gargle) solution. The proteins are then precipitated, digested, desalted, and measured using an LC-MS instrument, following a data-dependent acquisition (DDA) or a targeted multiple reaction monitoring (MRM) strategy.

While the metabolomics-based (*i.e.*, GC-IMS) strategy detects the host's response to the viral infection, the proteomics-based approach can directly detect the SARS-CoV-2 viral infection in the host (*i.e.*, viral proteins). Independently of the approach, the reported sensitivity may not be sufficient to diagnose patients at an early infection stage (SoRelle et al., 2020; Walsh et al., 2020) (**Figure 1**). Nevertheless, MS remains a promising tool to diagnose the COVID-19 severity by monitoring the host's proteome, metabolome, and/or lipidome after infection.

MS for Understanding the COVID-19 Disease

Successful pathogen adaptation to the host's metabolic landscape is a prerequisite for a strong viral replication (Sauer and Zamboni, 2008; Ayres, 2020; Harrison et al., 2020; Aggarwal et al., 2021; Filbin et al., 2021). Understanding the host's metabolic network changes induced by the SARS-CoV-2 viral infection is valuable for the subsequent prognosis and treatment of COVID-19 (Ayres, 2020; Tse et al., 2020; Wiersinga et al., 2020; Aggarwal et al., 2021; Filbin et al., 2021).

Our state-of-the-art knowledge about the SARS-CoV-2's disease is that the SARS-CoV-2 virus is more stable than the SARS-CoV virus (Van Doremalen et al., 2020) and has a more

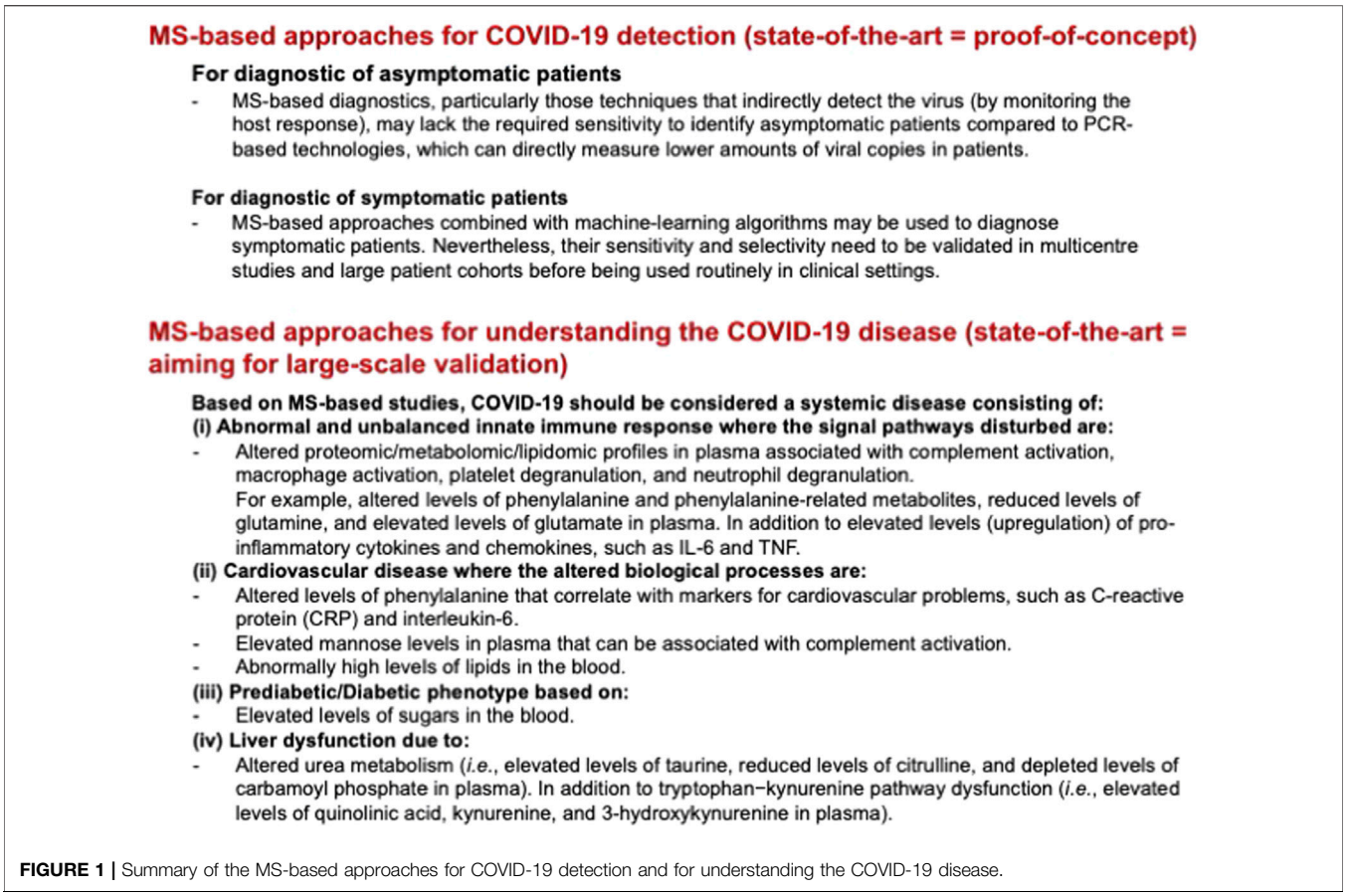

FIGURE 1 | Summary of the MS-based approaches for COVID-19 detection and for understanding the COVID-19 disease.

flexible spike-protein that facilitates human cells infection (Turoňová et al., 2020; Ahn et al., 2021). Bioinformatic calculations (Cava et al., 2020; Wierbowski et al., 2021) and affinity purification mass spectrometry (Gordon et al., 2020; Wierbowski et al., 2021) were two key technologies that helped scientists identify SARS-CoV-2 proteins (and their active sites) that interact with their host during its life cycle and identify therapeutic targets for developing antiviral drugs to treat COVID-19 patients (Gordon et al., 2020). For example, antiviral compounds against COVID-19 target the active sites of enzymes involved in the virus's replication cycle (Mehta et al., 2020; Riva et al., 2020; Shannon et al., 2020; Shi and Puyo, 2020; Wang et al., 2020; Bakowski et al., 2021).

We also know that the clinical outcome of the SARS-CoV-2 viral infection can be highly diverse (Feng et al., 2020; Wiersinga et al., 2020; Hu et al., 2021). The result can range from the host being an asymptomatic or not-severe patient (*i.e.*, concludes with a fast and full recovery) to a severe patient (*i.e.*, suffers from various complications) (Docherty et al., 2020; Guan et al., 2020; Munayco et al., 2020). These complications can lead to organ dysfunction and death due to an abnormal and unbalanced immune response, known as sepsis. Thus, an additional goal of Covid19-MSC was to complement the PCR-based diagnostics, which cannot predict the severity of the strains, by defining clinical phenotypes of interest and monitoring patient treatment/recovery (Struwe et al., 2020).

Before reviewing the excellent work done by researchers to understand the COVID-19 pathogenesis, it is crucial to mention common limitations that all these scientists expressed in their publication:

1) One limitation was the size of the patient cohorts in some studies (*i.e.*, less than 100 patients). Hence, the authors validated their hypothesis with available published studies by other research groups.
2) Another challenge was correlating a particular MS signal profile with a specific clinical phenotype, such as COVID-19 severity. Especially when circulating proteins, metabolites, and lipids from blood or plasma samples may have multiple sources (*e.g.*, comorbidities). Thus, authors use alternative methods to validate their results (*i.e.*, multi-omics data analysis).
3) When trying to find markers for COVID-19 disease severity, the authors considered that severe COVID-19 patients were usually older or had additional clinical risk factors than mild COVID-19 patients. Furthermore, they also thought of the skewing of the data in favor of sicker patients at later time-points since mild COVID-19 patients are less likely to stay hospitalized for several days than severe COVID-19 patients.

Messner *et al.* identified a plasma proteome signature (24 proteins) differently expressed depending on COVID-19 severity

in two independent studies with different population sizes using an ultra-high-performance liquid chromatography/tandem mass spectrometry (UHPLC-MS/MS) (Messner et al., 2020; Messner et al., 2021). These proteins were associated with the complement system and the inflammatory response (*i.e.,* several inflammation modulators). The protein signature allowed them to reclassify a suspected COVID-19 patient suffering from an influenza type B infection, showing the potential of the UHPLC-MS/MS method to support clinical decision-making (Messner et al., 2020).

Using a stable isotope-labeled nano-liquid chromatography coupled to mass spectrometry (nLC-MS) proteomic strategy, Shen *et al.* identified 93 blood sera proteins correlated with severe COVID-19 patients (Shen et al., 2020). From these 93 proteins, 50 proteins belong to three major pathways: 1) complement system, 2) macrophage activation, and 3) platelet degranulation. They verified their results in an additional cohort of patients and performed a non-targeted metabolomic study. The metabolomic study showed 80 metabolites that significantly changed with COVID-19 severity and were involved in the three biological processes revealed in the proteomic analysis. Thus, the authors proposed a classifier for COVID-19 severity based on monitoring 22 serum proteins and 7 metabolites in patient serum. Although the overall classifier achieved an accuracy of 93.5% in the training set, it misclassified a few patients, reflecting the complexity of the clinical cohort. Nevertheless, it was able to classify five severe patients 1–4 days before they were clinically diagnosed as severe patients.

Interestingly, the correlation between COVID-19 severity and the macrophage activation and complement activation was confirmed by a single-cell mass cytometry clinical study and MRM-based assay. Chevrier *et al.* (Chevrier et al., 2021) showed using single-cell mass cytometry that mild and severe disease patients showed a similar composition of myeloid cells during the early symptom stage. Nevertheless, a stronger inflammatory phenotype is observed in patients experiencing severe symptoms during the later stages of the disease, *i.e.,* $CD169^{-}$ monocytes and higher pro-inflammatory cytokines. The work of Bankar *et al.* showed using an MRM strategy an increase in peripheral neutrophil degranulation and the increase of pro-inflammatory cytokines (Bankar et al., 2021). Neutrophil degranulation may induce complement activation (Camous et al., 2011; Bankar et al., 2021) to eliminate the SARS-CoV-2 virus. Nevertheless, an unbalanced release of granule-derived mediators may lead to septic shock (Lacy, 2006). Thus, Bankar *et al.* pointed out that it is unclear whether SARS-CoV-2 directly targets the neutrophil degranulation pathway or is just a consequence of the SARS-CoV-2 complications (Bankar et al., 2021).

The increment of pro-inflammatory cytokines can dysregulate lipid metabolism and vascular permeability (Calder, 2002; Aslani et al., 2021). Zhang *et al.* explored this concept by monitoring the levels of serum proteins during the progression of the COVID-19 disease using a SWATH-MS (*i.e.,* UHPLC-MS/MS) workflow combined with machine learning (Zhang et al., 2021). Their study found that low-density lipoproteins (LDLs) and other apolipoproteins significantly decrease in COVID-19 patients, possibly due to pro-inflammatory cytokines. Hence, they propose that serum protein levels of proteins involved in lipid metabolism can be used as a potential predictor of the prognosis in COVID-19 patients.

Additionally to the proteome, the metabolome and lipidome in COVID-19 patients vary with infection and could be correlated to the severity of the SARS-CoV-2 viral infection. Wu *et al.* observed altered metabolic and lipidomic profiles using an LC-MS system (Wu et al., 2020). These profiles proved that SARS-CoV-2 hijacks the host cell's nucleic acids biosynthetic metabolic pathways (*i.e.*, biosynthesis of purine and pyrimidine nucleotides) and its ability to balance its energy metabolism (*i.e.*, TCA cycle) (Wu et al., 2020).

Wu *et al.* also observed that guanosine monophosphate (GMP) and carbamoyl phosphate were depleted in COVID-19 positive patients. Since GMP production depends on enzymes that have a role in the immune system (Wu et al., 2020), and carbamoyl phosphate is synthesized by enzymes in the urea metabolism (Strick-Marchand et al., 2004; Wu et al., 2020), the authors proposed that COVID-19 patients might suffer from immune and liver dysfunction (Wu et al., 2020), respectively; in addition to the possibility of cardiovascular complications due to the abnormally high levels of lipids in their blood (Kris-Etherton, 1999; Wu et al., 2020).

Lee *et al.* used a combination of gas chromatography-mass spectrometry (GC-MS) and UHPLC-MS/MS to analyze plasma samples (Lee et al., 2021). They also used a cell sorter for better classifying disease severity and predicting clinical outcomes by performing their metabolomic analysis on a homogenous cellular population. The authors observed two independent modes of metabolic reprogramming due to the SARS-CoV-2 viral infection. The first corresponds to changes in the quantity of the metabolically active immune cell subpopulations, while the second involves shifts in the metabolism within individual cells within a subpopulation. By doing so, the authors observed that metabolites (*e.g.*, phenylalanine) that are correlated with pro-inflammatory cytokines are also positively correlated with COVID-19 severity. In contrast, other metabolites and lipids (particularly those associated with cytokine synthesis) were negatively correlated with the disease severity (Lee et al., 2021). The observed profiles by Lee *et al.* are similar to those identified by Meoni *et al.* (Meoni et al., 2021) using an NMR-based approach. Lee *et al.* (Lee et al., 2021) and Meoni *et al.* (Meoni et al., 2021) correlate these changes to an inflammation and immune activation response against COVID-19.

Lee *et al.* also detected high plasma levels of mannose and glucose that correlated with the severity of the COVID-19 disease. They suggested two hypotheses 1) that mannose levels in plasma can be derived from residues of SARS-CoV-2 spike protein, potentially reflecting high viral loads; and 2) that the high mannose levels in plasma may indicate the complement pathway activation. Although the latter explanation has been proposed by other authors (Camous et al., 2011; Zhang et al., 2021), Lee *et al.* expressed that this profile is also consistent with patients suffering from coronary heart disease (Jones et al., 1999; Murr et al., 2014; Chen et al., 2020b; Lee et al., 2021).

Chen *et al.* demonstrated that significant changes in the levels of lipoprotein subclasses and their compositional components are

correlated with COVID-19 severity using a combination of nLC-MS and nuclear magnetic resonance (NMR) techniques (Chen et al., 2020a). For example, levels of triglycerides (TG) in low-density lipoprotein subclass 1 (LDL 1) and free cholesterol (FC) in all very-low-density lipoprotein subclass 5 were significantly elevated in both mild and severe patients when compared with healthy controls. Moreover, key proteins involved in lipoprotein and related metabolic pathways were elevated considerably or reduced beyond typical healthy values (as shown by Zhang *et al.* (Zhang et al., 2021) and Wei *et al.* (Wei et al., 2020)). Fortunately, most enzymes and lipoprotein levels recovered when the patients were discharged, thus showing a transient behavior. Therefore, Chen et al. propose that during SARS-CoV-2 infection, there is a significant dysregulation in lipoprotein metabolism (*e.g.*, hypolipidemia), glycolysis, and TCA cycle (Chen et al., 2020a).

Kimhofer *et al.* also performed a deep UHPLC-MS/MS and NMR-based metabolomic and lipidomic study on plasma samples (Kimhofer et al., 2020). They observed metabolomic and lipidomic profiles that other authors correlated with four different clinical disorders: 1) acute inflammatory response (Kimhofer et al., 2020; Meoni et al., 2021), 2) a cardiovascular risk signature (Kris-Etherton, 1999; Kimhofer et al., 2020), 3) a prediabetic/diabetes-like signature (Krauss, 2004; Kimhofer et al., 2020), and 4) liver dysfunction (Kopple, 2007; Kimhofer et al., 2020). The authors described that these metabolic disturbances appeared independently of the severity of the respiratory symptoms or the exact sampling time-point with respect to the onset of the COVID-19 symptoms (Kimhofer et al., 2020).

Interestingly, Kimhofer *et al.* (Kimhofer et al., 2020) reminded us that patients who had recovered from SARS-CoV-1 infection had further complications such as hyperlipidemia, cardiovascular abnormalities, and glucose metabolism disorders. Concerning this point, Wu *et al.* (Wu et al., 2020) and Kimhofer *et al.* (Kimhofer et al., 2020) argue that COVID-19 should be considered a systemic disease and not just a respiratory illness. This sentiment is echoed by other COVID-19 independent studies (Gupta et al., 2020; Nalbandian et al., 2020; Wang et al., 2021a; Duan et al., 2021; Frontera et al., 2021; Lopez-Leon et al., 2021; Sanchez-Vazquez et al., 2021). Furthermore, many authors (Kimhofer et al., 2020; Zhu et al., 2020; Logette et al., 2021) make a case that comorbidities will complicate the patients' treatment and should be addressed and managed as early as possible to avoid long-term complications that have recently been described as "long COVID syndrome." Therefore, MS techniques may be required to monitor post-covid patients, since although mild and severe patients diagnosed with COVID-19 had met the official hospital discharge criteria (*i.e.,* COVID-19 nucleic acid tests were negative, and many clinical signs had disappeared), many levels of proteins, metabolites, and lipids had not returned to normal by the time they were discharged (Balachandar et al., 2020; Wu et al., 2020; Holmes et al., 2021).

Holmes *et al.* used an NMR and UHPLC-MS/MS-based approach to monitor the blood plasma samples to understand the long COVID syndrome (Holmes et al., 2021). For this study, the authors defined three different cohorts: 1) a healthy control group, 2) a hospitalized patient group sampled during the acute infection phase), and 3) a recovery cohort consisting of a non-hospitalized group. The latter group was sampled 3 months post the acute phase (hospitalization stage) and 6 months post their tentative date of COVID-19 infection. Thus, the authors assessed the phenoconversion, i.e., the change from a standard (i.e., healthy) phenotype to an altered (*i.e.,* sick) phenotype. Furthermore, they were able to identify the metabolic profiles of patients suffering from long COVID-19, *i.e.*, with incomplete functional recovery. Interestingly, 57% of the participants recorded one or more persistent symptoms within the recovery cohort. The majority had more than one symptom not associated with the respiratory system.

As in the works of Wu *et al.* (Wu et al., 2020) and Kimhofer *et al.* (Kimhofer et al., 2020), Holmes *et al.* identified that while metabolic and lipoprotein parameters which were altered during SARS-CoV-2 infection returned to a healthy range, other parameters such as the glutamine/glutamate ratio, which is essential for immune cell homeostasis, remained altered (Holmes et al., 2021). Unfortunately, they could not provide a mechanistic significance to the glutamine/glutamate ratio during the acute and post-acute infection stages with SARS-CoV-2. Nevertheless, they propose that this low glutamine/glutamate ratio implies a continuing post-COVID immune dysregulation.

Other altered metabolic patterns observed by the authors were: 1) elevated taurine and low citrulline (associated with liver dysfunction) (Yu et al., 2017; Holmes et al., 2021), 2) high quinolinic acid, kynurenine, 3-hydroxykynurenine (associated with inflammation and liver dysfunction) (Heyes et al., 1997; Holmes et al., 2021), and 3) increased levels of 3-indole-acetic acid, which may imply a microbiome functionality shift in recovered COVID-19 patients (Blasco et al., 2020; Holmes et al., 2021). Nevertheless, due to the high degree of interindividual variability (age and comorbidities) in the follow-up patients, the authors expressed that the long-term clinical significance of these observations will require further investigation (Holmes et al., 2021).

Although the exact patterns of altered biomarkers (proteins, lipids and metabolites) were not identical in all reviewed publications, the data shows that COVID-19 disease is a mixture of four different clinical disorders (**Figure 1**): 1) inflammation and cell death triggered by the innate immune response (Chen et al., 2020a; Kimhofer et al., 2020; Messner et al., 2020; Shen et al., 2020; Wu et al., 2020; Bankar et al., 2021; Chevrier et al., 2021; Holmes et al., 2021; Lee et al., 2021; Messner et al., 2021; Zhang et al., 2021); 2) a cardiovascular disease (Kimhofer et al., 2020; Wu et al., 2020; Lee et al., 2021), 3) a prediabetic/diabetes-like disease (Kimhofer et al., 2020; Wu et al., 2020), and 4) liver dysfunction (Kimhofer et al., 2020; Wu et al., 2020; Holmes et al., 2021; Lee et al., 2021). Furthermore, severe COVID-19 cases show a temporally delayed activation of monocyte pathways and an increased expression over time of pro-inflammatory cytokines, which may lead to a septic shock (Bankar et al., 2021; Chevrier et al., 2021). These profiles can be the basis for developing clinical testing for COVID-19 severity prognosis, which relies on targeted strategies using reliable and low-cost effective (accessible) instrumentation. Examples of such diagnostic methods that can be used to determine the severity of

COVID-19 patients are image-based diagnostics looking for lung inflammation (Docherty et al., 2020; Guan et al., 2020; Liu et al., 2020; Okolo et al., 2021) and blood/urine-based approaches looking for inflammation, cardiovascular, diabetes-type, and liver dysfunction biomarkers (Gross et al., 2020; Gross et al., 2021; Siemens Healthineers. Lev, 2021).

The reviewed data also shows that discharged patients still present an incomplete functional recovery, *i.e.*, long COVID (Kimhofer et al., 2020; Liu et al., 2020; Nalbandian et al., 2020; Wu et al., 2020; Holmes et al., 2021; Lopez-Leon et al., 2021; Taquet et al., 2021; Xie et al., 2022). Mobile apps could help monitor better long COVID symptoms (Menni et al., 2020; Wise, 2020; Chang et al., 2021; Louca et al., 2021). For example, a Peruvian mobile app (ARIM) is used by medical personnel to register clinical data from patients (Characterizing COVID-19, 2020; ARIM 2.0, 2021). If used uniformly at a regional/national level, ARIM and similar apps can provide anonymized data for early warnings of an epidemic infection outbreak (wave) and improve our understanding of the long COVID disease symptomology (SoRelle et al., 2020).

CONCLUSION

It is uncertain how the COVID-19 pandemic will develop (Clark et al., 2020; Gandhi et al., 2020; Korber et al., 2020; Long et al., 2020; Almufarrij and Munro, 2021; Wang et al., 2021b; Gao et al., 2021; Hodcroft et al., 2021; Karim and Karim, 2021; McCallum et al., 2021; Peacock et al., 2021; Subramanya et al., 2021; Thomson et al., 2021; Ward et al., 2021; Garcia-Beltran et al., 2022; Katzourakis, 2022; Konrath et al., 2022). In retrospect, the scientific community managed to rise to the challenge (Rijs and Fenter, 2020). Compared to PCR-based COVID-19, MS-based strategies are less sensitive. Nevertheless, mass spectrometry can identify the metabolomic, lipidomic, and proteomic profiles associated with COVID-19 disease severity. These profiles provide valuable information on the underlying biological processes responsible for the severe disease phenotype and can be the basis for designing cost-effective diagnostics of COVID-19 severity. Interestingly, image-based and blood/urine-based approaches have already been validated in multicenter studies. We hope that the Covid19-MSC initiative will catalyze in the near future multicenter initiatives to validate targeted MS-based quantification of biomarkers to determine COVID-19 disease severity.

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Author Contributions Conceptualization: AI Data curation: AI Writing — original draft, review and editing: AI.

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