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REVIEW

Long COVID, a comprehensive systematic scoping review

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Abstract

Purpose To find out what is known from literature about Long COVID until January 30, 2021.

Methods We undertook a four-step search with no language restriction. A preliminary search was made to identify the keywords. A search strategy of all electronic databases resulted in 66 eligible studies. A forward and backward search of the references and citations resulted in additional 54 publications. Non-English language articles were translated using Google Translate. We conducted our scoping review based on the PRISMA-ScR Checklist.

Results Of 120 papers, we found only one randomized clinical trial. Of the 67 original studies, 22 were cohort, and 28 were cross-sectional studies. Of the total 120 publications, 49.1% focused on signs and symptoms, 23.3% on management, and 10.8% on pathophysiology. Ten publications focused on imaging studies. The results are also presented extensively in a narrative synthesis in separated sections (nomenclature, diagnosis, pathophysiology, risk factors, signs/symptoms, management).

Conclusions The controversies in its definition have impaired proper recognition and management. The predominant symptoms were: fatigue, breathlessness, arthralgia, sleep difficulties, and chest pain. Recent reports also point to the risk of long-term sequela with cutaneous, respiratory, cardiovascular, musculoskeletal, mental health, neurologic, and renal involvement in those who survive the acute phase of the illness.

Keywords COVID-19 · Long COVID-19 · Long haulers COVID · Post COVID-19 Syndrome · Post-acute COVID-19 · Corona virus · SARS-Cov-2 · Novel Corona Virus 2019 · Post-acute SARS-CoV-2 · PASC post-acute sequela SARS-COV-2

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Introduction

Descriptions of long-lasting symptoms after influenza-like illnesses can be traced back to 1892 when Josephine Butler, a women's right campaigner, wrote to her son complaining of unresolved fatigue after being infected with the Russian Influenza. In 1895, politicians in the United Kingdom, including the prime minister, who were infected with the Russian Influenza reflected in their periodicals and diaries about the long-lasting fatigue and insomnia [1]. More recent viral infections such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) have also been associated with unabating post-acute phase lingering symptoms. In a systematic review of prolonged symptoms of SARS-CoV-1 and MERS-CoV by Ahmed et al., approximately one-third of the patients suffered from prolonged anxiety, depression, and post-traumatic stress disorder (PTSD) up to 6 months after complete recovery from the acute illness [2]. Moreover, they found that 11–45% of the patients had diminished DLCO (diffusing capacity of the lungs for carbon monoxide) at one-year follow-up [2].

SARS-CoV-1 survivors have been reported to suffer from long-term pulmonary complications, such as impaired exercise capacity, reduced DLCO, and interstitial lung abnormalities [3]. Additionally, in long-term follow-up of 121 SARS-CoV-1 survivors, cardiovascular complications were quite common: hypotension (50.4%), tachycardia (71.9%), bradycardia (14.9%), and cardiomegaly (10.7%) [4]. Other long-term abnormalities associated with SARS-CoV-1 were persistent hyperlipidemia and derangements in glucose hemostasis [5]. While acute renal impairment [6], acute gastrointestinal effects [7], acute viral hepatitis [8], and acute diabetes mellitus from the binding of the virus to its receptors on pancreatic islets cells [9] were reported, the long term consequences were not mentioned. Moreover, hematologic abnormalities, such as lymphopenia, leukopenia, thrombocytopenia, prolonged activated partial thromboplastin time (aPTT), coagulopathy (elevated D-dimer) and disseminated intravascular coagulation (DIC), and a pro-thrombotic state at micro- and macro- vasculature involving both veins and arteries with thromboembolic complications have been observed in the acute phase of these viral infections with potential long term consequences [10, 11]. In regard to psychosocial manifestations, a considerable number of SARS-CoV-1 patients suffered from chronic widespread musculoskeletal pain, fatigue, psychological stress, and disturbed sleep, hindering their return to productive work for up to 2 years after acute illness [12, 13]. In their 1-year follow-up of the survivors, Tansey et al., reported that more than half of the patients still experienced fatigue and sleep disturbance [14]. The subject of post-acute COVID-19 was recently reviewed by Amenta et al. [15].

Similarly, in a study of recovered patients from MERS-CoV, abnormal chest radiographs with ground-glass opacities and pleural thickening, indicative of pulmonary fibrosis, were still present at a median of 43 days after discharge from the hospital [16]. Although both SARS-CoV-1 and MERS-CoV have been associated with neurologic sequela, the latter is believed to be more neuro-invasive, causing complications such as paralysis, ischemic stroke, Guillain–Barre syndrome, and neuropathy [10, 17].

Despite considerable concerns about the long-lasting symptoms of COVID-19, our collective understanding and approach to its management are still in their infancy. This scoping review elaborates upon the up-to-date knowledge regarding this so-called "Long COVID" and attempts to shed light on future needs in this area. Due to the diversity and yet relative paucity of evidence, conducting a conventional systematic review would be less beneficial; thus, we conducted a systematic scoping study on this topic to highlight the currently available literature and to identify gaps in our knowledge. We hope our effort would reveal areas that need immediate attention and guide future research efforts.

Our focus here is to synthesize what is known from literature about the persistent COVID-19, its signs and symptoms, its pathophysiology, and the current management recommendations. We also wish to highlight the gaps in our knowledge regarding 'long COVID' syndrome.

Method

Since the review question is comprehensive, we found the systematic scoping review as the most suitable methodology to answer the question. To achieve clarity and transparency and to avoid poor reporting, we used Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [18].

Review question

What is known from literature about the long COVID-19, its nomenclature, diagnosis, risk factors, signs/symptoms, pathophysiology, and the currently recommended management, and what are the gaps in this issue?

Inclusion criteria

- Those related to long COVID, post-acute COVID, and long haulers of COVID-19
- Those related to nomenclature, diagnosis criteria, pathophysiology, signs and symptoms, and managements

- All types of reports were included: original studies (cohort, RCT, case–control, case-report, case series, and qualitative), reviews and editorials, viewpoints, guidelines, letter to editors and commentaries.
- The articles should have been published in a peer-reviewed journal or be an organizational report
- No language restriction was considered.

Exclusion criteria

- Those irrelevant to COVID-19
- Those related to acute COVID-19
- Preprints
- Unavailable full texts

Search strategy

We followed a four-step search strategy. First, on January 20, 2021 a limited preliminary search was done in multiple databases such as Google Scholar and PubMed for identifying the appropriate keywords. Next, on January 30, 2021 we adopted a search strategy including electronic databases of the following sources: Cochrane Library, PsycINFO, PubMed, Embase, Scopus, and the Web of Sciences. The results were reviewed using Endnote 20. After duplicate publications were removed, two authors separately checked the titles and abstracts and removed irrelevant studies according to the inclusion and exclusion criteria. Discrepancies about the inclusion/exclusion of any paper were resolved through discussion. Third, the two authors separately checked the included papers' reference lists for identifying more relevant studies. In the fourth step, we glimpsed at google scholar for articles' citing and current publications, maximizing our efforts to collect all relevant studies. Again, discrepancies were discussed for final approval in the third and fourth steps. We used the following keywords for our literature search: "long COVID" or "long haulers," or "post-acute COVID" or "chronic COVID syndrome" or "late sequela COVID" or "persistent COVID". Table 1 shows our search strategy on all databases. As we had chosen no language restriction, we used Google to translate non-English papers and checked their eligibility.

Data extraction and synthesis

The following items were extracted from included papers: first author, country of the first author (also region and income level of the country), date of publication, date of submission, type of study (also the methodology in case of an original study), study category (diagnosis, nomenclature, pathophysiology, risk factors, signs/symptoms, or management), main topics in the categories (rehabilitation, pharmacologic options, thromboembolism, etc.), and the number of patients studied in the original investigations, their countries' population and income level.

Moreover, for the original investigations, we extracted the following data from the articles: methodological approach, number of patients, the country and the geographic region where patients were investigated, based on World Bank report (2020–2021 fiscal year) [19]. A data extraction form was designed in Excel, and 3 independent authors extracted the data. Discrepancies were resolved through discussion. In the discussion section, we have synthesized the core themes of the study. The discussion section is divided into 6 categories where we present perspectives around nomenclature, diagnosis, pathophysiology, signs and symptoms, risk factors, and management of long COVID. Finally, we address the gaps and propose suggestions in the conclusion section.

Results

We retrieved 290 publications from our search (Fig. 1). After removing duplicates, publications were screened for the relevance of the title and abstract, resulting in the exclusion of 33 more publications. Then, 86 publications were evaluated for full-text eligibility. Of those, 20 articles were excluded (14 articles were not related to the Long COVID subject, and 6 were not available in full text). We were left with 66 articles for data synthesis. We then performed forward and backward screening of these papers' references and citations to identify as many relevant studies as possible. We found 54 additional relevant publications, that made a total of 120 publications as the basis for our analysis (see Online appendix 1).

Table 1 Keywords and search strategy

Database	Search strategy and keywords	
Pubmed	Title and abstract	"Long COVID" or "long haulers" or "post-acute COVID" or "late sequela COVID" or "persistent COVID" or "chronic COVID syndrome"
Embase Web of sciences Scopus Psycinfo Cochrane Library	Title, abstract, and keywords	"Long COVID" or "long haulers" or "post-acute COVID" or "late sequela COVID" or "persistent COVID" or "chronic COVID syndrome"

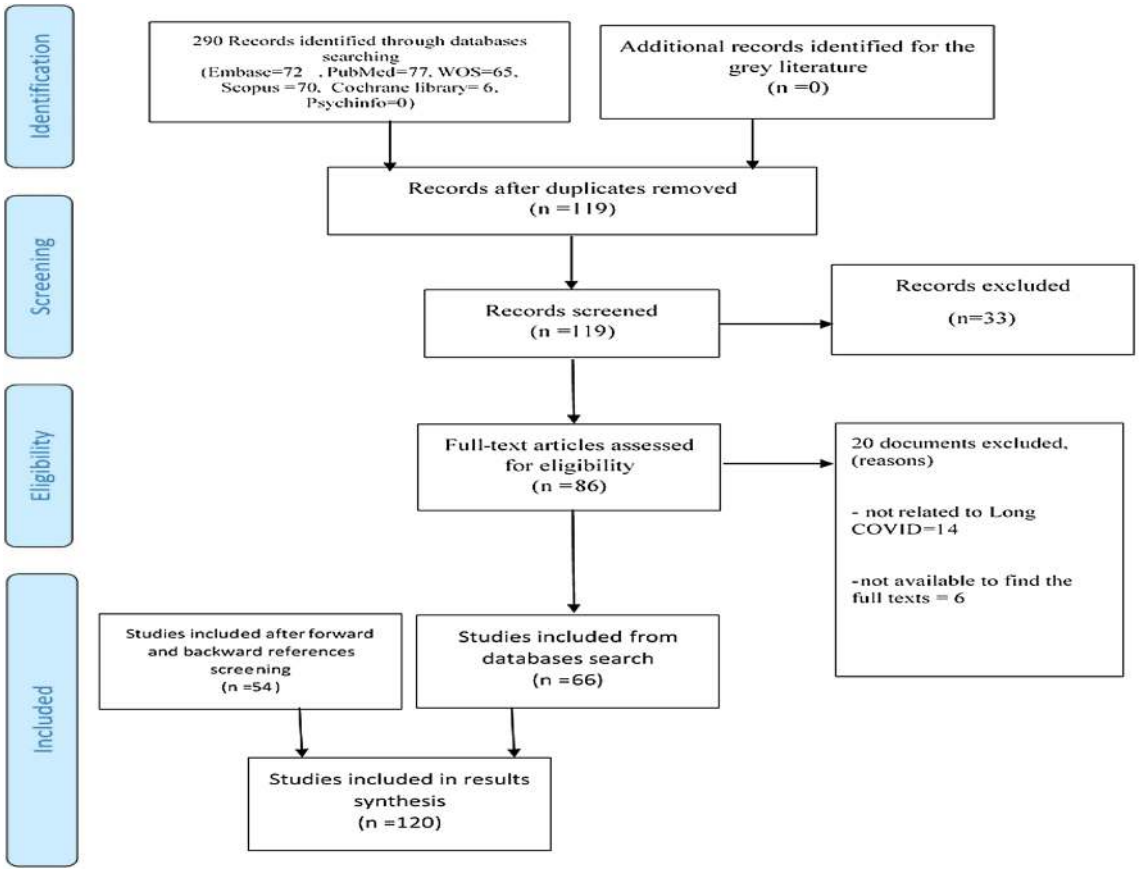

Fig. 1 PRISMA flow chart, the process of study selection. *WOS* Web of Science

Types of included papers

The first published papers date back to March 2020. The number of publications significantly increased over time. The distribution of the publications, based on the type of publication, is shown in Fig. 2. Of the 120 publications (Table 2), 67 (55.9%) presented original data as follows: 43 (35.9%) were original articles/papers [20–62]. Fifteen (12.5%) publications were short articles with original data, as follows: 7 brief communications/reports [63–69] (5 cohort and 1 cross-sectional studies, and 1 case series), 1 commentary [70] (cross-sectional study), 6 letters to editors [71–76] (4 cross-sectional and 1 cohort studies, and 1 case series), and 1 short communication [77]. Fifty-four (45%) articles did not present original data. Among them were 33 (27.5%) short articles (shown in Fig. 2 as "non-original short communications") as follows: 5 commentaries [78–82], 3 letters to the editors [83–85], 1 short communication [86], 1 "piece of mind" [87], 4 "news" [88–91], 1 perspective [1], 15 editorials [92–106], 1 special article [107], and 2 viewpoints [108, 109]. The other articles in this category were: 9 case reports/case series [110–118], 10 narrative reviews [10, 15, 119–126], 1 systematic review on the respiratory system [127], 4 guideline papers, 3 clinical updates, 1 "report", and 1 consensus statement [128]. There was only 1 systematic review that elaborated on the pulmonary aftermaths of Long COVID [127]. There were 3 qualitative studies [26, 47, 57], only in 2 of them [26, 57], the study populations were well described. That was of significant concern since in qualitative studies the populations' cultural and contextual aspects should be vividly mentioned.

We found only one randomized clinical trial in our search [60]. Of all documents, 67 (55.9%) were studies with original data. Of those with original data, cross-sectional and cohort studies were the most common methodologies comprising 28 and 22 manuscripts, respectively. We found 3 qualitative studies; 2 from the UK and another 1 that did not explicitly mention the population region. More details are shown in Fig. 3. In our classification, we distinguished papers with original information from those that did not present empiric information. For instance, we divided the letter to the editors into two separate groups, those that contained original data and mentioned specific methodology, and those that did not do so.

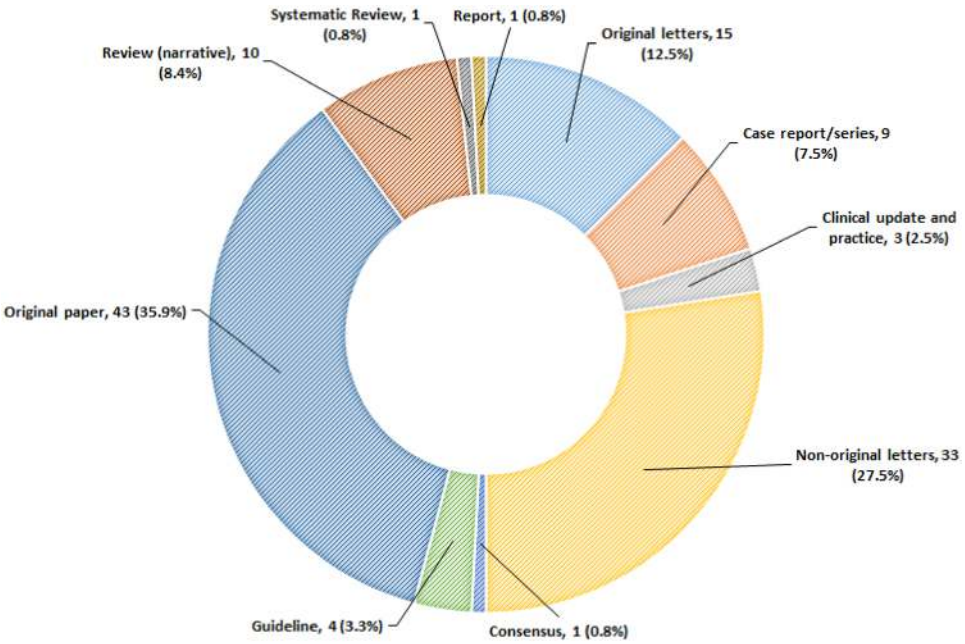

Fig. 2 Distribution of included papers based on types of publication

Table 2 The distribution of papers, based on types of publication

Type of article	Total number
Original articles [20–62]	43
Brief communications/reports [63–69, 77, 86]	9
Letter to editor [71–76, 83–85]	9
Commentary [70, 78–82]	6
Editorial [92–106]	15
Case series [110, 111, 113]	3
Case reports [112, 114–118]	6
Guideline [129, 132, 133, 135]	4
Narrative Review [10, 15, 119–126]	10
Systematic review [127]	1
News [88–91]	4
Viewpoint [108, 109]	2
Perspective [1]	1
Piece of mind [87]	1
Clinical update [136]	1
Consensus statement [128]	1
Reports [130]	1
Special article [107]	1
Practice [131, 134]	2

Categories of included papers

As shown in Fig. 4, 13 (10.8%) articles, mainly editorials and commentaries, discussed a mixture of the following categories: nomenclature, signs/symptoms, pathophysiology, management, diagnosis, and risk factors. Fifty-nine (49.2%) articles presented signs and symptoms of Long COVID. Twenty-three (19.2%) articles reported on the generalized signs/symptoms (21 adults, 2 pediatrics), and the remaining 36 (30%) articles focused on specific organs/systems (9 focused on thromboembolism [29, 30, 36, 50, 66, 69, 114, 117, 118], 8 respiratory [23, 27, 37, 41, 44, 67, 75, 127], 4 neurology [46, 61, 102, 116], 2 musculoskeletal [53, 72], 5 cardiovascular [39, 49, 54, 112, 120], 3 mental health [21, 58, 108], 2 Multisystem Inflammatory Syndrome [MIS] [43, 113] (one about pediatrics MIS [43] and one on adults MIS [113]), 1 skin manifestations [70], 2 were exclusively about post-acute infectious fatigue [33, 122].

Thirteen (10.8%) articles evaluated the pathophysiology of Long COVID, including 8 neurologic [20, 32, 40, 73, 93, 104, 109, 126], 2 cardiovascular [77, 92], 1 fatigue [124], and 1 MIS in pediatric [121]. One paper was concerning the pathophysiology of multiple systems called in Fig. 4 by "multi-system" [31].

Twenty-eight (23.3%) articles were regarding management options: 13 rehabilitation care [22, 28, 45, 59, 60, 71, 94, 115, 119, 123, 129–131], 5 general care [26, 47, 57, 105, 132], 1 designed and validated a psychometric tool for assessing mental health consequences of Long COVID [42], and 1 was about "how to return back to the pre-morbidity activity level" [63], and 8 articles were on more comprehensive "multidisciplinary-care" of long COVID patients [84, 90, 98, 107, 128, 133–135].

Among the articles that are included in our report is an editorial from The Lancet that discusses historically the persistent symptoms after Russian influenza up to the current COVID-19 [1]. We also included a letter that proposed criteria for the definition of Long COVID [82].

There were several articles concerning the imaging features of Long COVID; but only 10 had focused explicitly

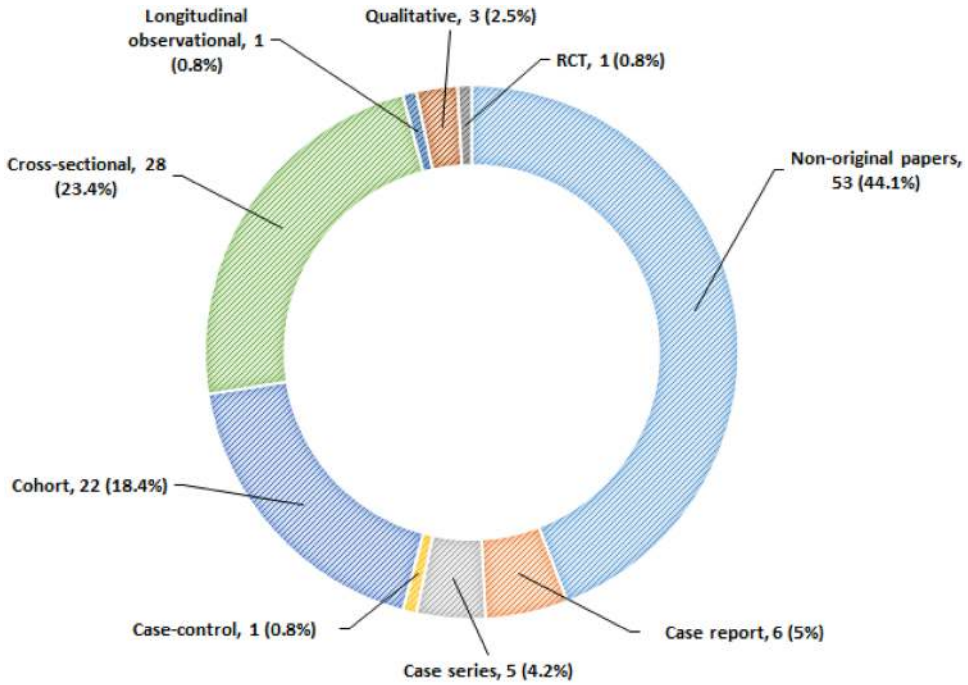

Fig. 3 Distribution of included papers based on their methodology. *RCT* Randomized Clinical Trial

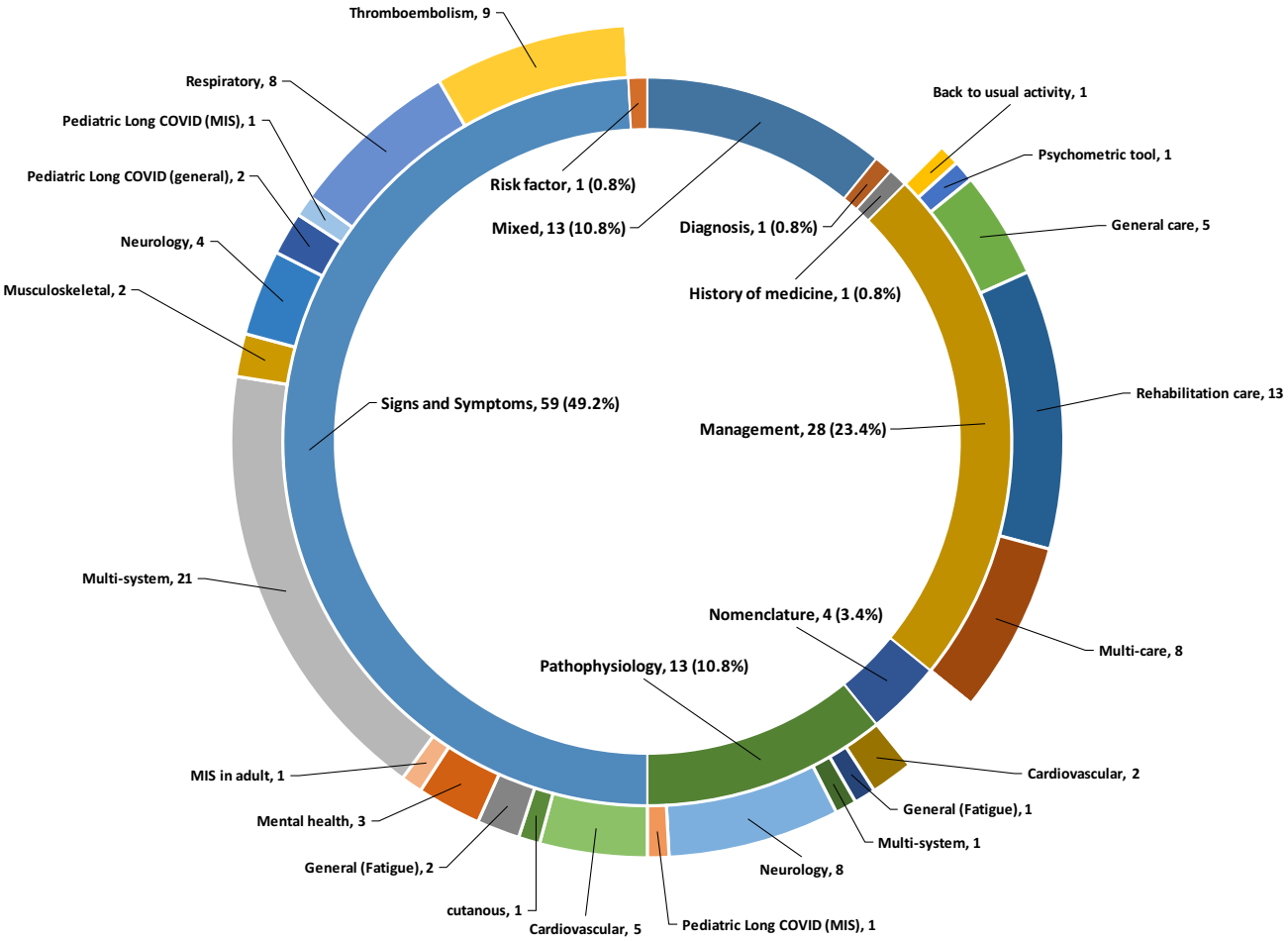

Fig. 4 Categories and main topics of included papers; Inner doughnut illustrates the categorization of documents, and the outer doughnut illustrates the main topics of each category. *MIS* Multisystem Inflammatory Response

and precisely on the radiologic features (3 MRI of the brain and olfactory nerves [20, 32, 40], 5 cardiovascular system including MRI, PET/CT and Echocardiography [39, 49, 54, 63, 77], 2 lung CT scan [44, 75]).

There were several articles that discussed the risk factors and predictors of developing Long COVID. However, only 1 article focused on the risk factors for developing mental health problems post-COVID [125]. Also, 1 article was about developing a psychometric tool to assess the mental health consequences of long COVID [42].

Date of submission and publication

There has been an increasing interest in literature on Long COVID. Our search was limited to the end of Jan 2021 (search in databases) and early February 2021 (backward and forward search). In our forward and backward search, we found three articles with a "first-online" in February 2021. Our analysis tried to evaluate the submission date, but we could not find the submission date for 53 articles. We report both dates of submission and publication to be more informative (Fig. 5).

Countries and regions

To overview the global spread of the works done on long COVID, we chose the first authors' countries for the authors' representativeness. For each country, geographical region and level of income were included in our analysis as well.

In regard to the countries and geographic regions of the first authors, 74 (62%) authors were from 4 countries: 31 from UK, 19 from USA, 14 from Italy, and 10 from China. In regard to geographic regions, 61 (58%) authors were from Europe and Central Asia, 21 (17.6%) from North America, 12 from East Asia and Pacific, 6 from South Asia, 5 from the Middle East and North Africa, 2 from Sub-Saharan Africa, and 1 from Latin America and the Caribbean. According to the World Bank categorization of countries in 2020–2021 fiscal year, we categorized these regions to High, Upper-middle, lower-middle, and low-income countries [19]. Ninety-three (78.2%) first authors were from high-income countries, and only one author was from a low-income country.

There were 7 original studies on rehabilitation as the cornerstone management of Long COVID: 3 from Italy [28, 45, 71], 2 from China [59, 60], 1 from Austria [22], and 1 from Malawi [115].

Number of patients

As shown in Table 3, we report the number of patients based on the methodology of studies, level of income, and the regions of the investigated populations.

Language of the papers

Also, as the study was done without any language restriction, we screened title/abstract as well as the main text of

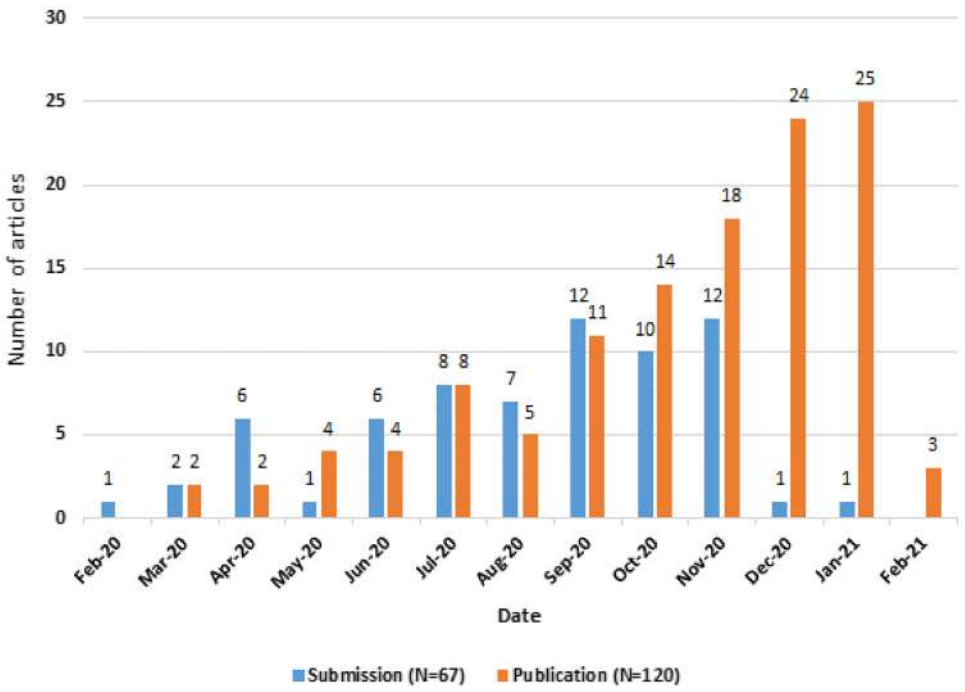

Fig. 5 Number of articles according to dates of submission and publication

Table 3 Number of articles and number of patients studied, based on study methodology, country income, and geographic region

	Number of studies	Number of patients
Methodology		
Case report	6	1 for each
Case series	5	5, 5, 7, 16, 145
Case–control	1	157
Cohort	22	10–1877*
Cross-sectional	27	8–6049*
Longitudinal observational	1	51
Qualitative	3	24, 43, 114
RCT	1	72
Level of income		
High	46	1–2286*
Upper middle	14	1–6049*
Lower middle	1	1
Low	2	1 for each
Region		
Europe and Central Asia	40	1–2286*
North America	9	1–570*
East Asia and Pacific	9	26–6049*
The Middle East and North Africa	2	52, 1529
South Asia	1	1
Sub-Saharan Africa	2	1 for each
Multinational	3	16, 234, 2113

*Range

non-English papers. Finally, we included one non-English paper in the Spanish language [137].

Discussion

Our study retrieved 120 papers based on inclusion and exclusion criteria. Hereby, we present them in five separate sections: “debates on nomenclature”, “pathophysiology”, “sign and symptoms”, “management”, and “concluding comments and suggestions”.

Debates on nomenclature

A standardized nomenclature is a gateway to adequate service provision and proper management of an illness. Thus, the lack of a standardized universally accepted definition and nomenclature for this disorder makes its appropriate diagnosis and management quite challenging. Many healthcare professionals and researchers are worried about attributing all symptoms to a single diagnosis. This could lead to a binary or even a quadripartite view that the symptoms such patients experience could be the result of up to four different syndromes (Permanent damage to vital organs; Post-intensive-care syndrome; Post-viral fatigue syndrome; and continued COVID-19 syndrome) [89]. This confusion has led to many patients with ongoing symptoms being ignored or not taken seriously. The hashtag "#Long COVID" has been frequently used in social media [86]. However, we found in our search that it lacks a universal definition. For example, National Institute for Health and Care Excellence (NICE) defined the "Long COVID" as "signs and symptoms that develop during/after the COVID-19 infection persisting for more than 4 weeks and could not be explained by any other diagnosis". In this categorization, the Long COVID consists of two categories, "Ongoing symptomatic COVID-19″, which indicates the symptoms lasting for 4–12 weeks; and "Post-COVID-19 syndrome", which means symptom persistence beyond 12 weeks [134].

Sivan et al., concur with our viewpoint that the definition presented by NICE is based on an obscure "by exclusion" diagnostic criteria. And that this categorization is not inclusive enough for all the post-acute complications of SARS-COV-2 under a single unified definition. It is suggested that the definition be changed to "continuing signs/symptoms beyond 4 weeks that can be attributed to COVID-19 infection" [103].

Baig has suggested using the term "Chronic COVID syndrome (CCS)" as opposed to “Long-COVID” or “Long-Haulers”. He also presented an organ-based staging of the illness to prioritize immediate care needs [78]. However, in a publication in the journal Nature, Marshall proposed the term "Coronavirus Long-Haulers" for those suffering from this condition [88]. Moreover, Greenhalgh et al., has proposed the term "post-infectious COVID-19" for those who continued with symptoms beyond 3 weeks after the onset of the disease. In this definition, the pre-requisition of a definite positive test for diagnosis was not considered since many patients are not tested, and false negatives are common [134]. In agreement with prior classification, Amenta et al., suggested that for COVID-19 patients hospitalized for 3 weeks, the onset of the post-infectious state could be delayed to the time of discharge from inpatient acute care services [15]. More recently, Anthony Fauci, MD director of the National Institute of Allergy and Infectious Diseases (NIAID), suggested the name “post-acute sequelae of SARS-CoV-2 infection” (PASC) [138].

Reaching an agreement on a definite terminology is vital. Using terms such as "post", "chronic", or "syndrome" carries assumptions about the underlying pathophysiology, which is unclear yet [97]. In our third and fourth phase of the search (looking at references and citations) we found almost a similar number of publications as our initial search (66 vs. 54 publications) of the databases. The authors believe that the lack of a standardized nomenclature resulted in poor homogeneity of the titles. This suggests that the WHO and other

related organizations should make relevant unified terms to homogenize the literature. Besides, we suggest that other investigators use similar multi-step search strategies not to miss any relevant studies.

Diagnosis

In addition to debates on the nomenclature, there is also uncertainty on diagnostic criteria. There is the scarcity of discussion and proposals for such diagnostic criteria. We found only 1 article focused on the diagnostic criteria. Raveendran's proposed criteria for Long COVID-19 consisted of 3 sectors: essential criteria, clinical criteria, and duration criteria [82]. Symptomatic and asymptomatic cases (during the acute phase) were separated, and each group based on RT-PCR, serologic testing, characteristic radiologic findings, and being in a high- or low- prevalence community was categorized into four subgroups: confirmed, probable, possible, or doubtful. In regard to duration criteria for such diagnosis the author proposed: beyond 2 weeks for mild disease, beyond 4 weeks for moderate to severe illness, and beyond 6 weeks for the critically ill in the acute phase. For those with asymptomatic acute phase: appearance of symptoms 1 week after antibody positivity or 2 weeks after having a positive RT-PCR or positive radiologic finding or contact with a suspected or positive COVID-19 case. Doubtful cases in the acute phase would fulfill the duration criteria of long COVID once they develop symptoms [26].

A few other reports have merely suggested a duration-criteria for long COVID, as persistence of symptoms beyond 3 weeks of the disease onset. The above-mentioned article is the only one that proposed a full-spectrum diagnostic-criteria. This lack of well-defined criteria to define Long COVID-19 emphasizes the need for international-health-organizations, such as, WHO to address this issue.

Pathophysiology

SARS-COV-2 virus invades many tissues and has a multiorgan and multisystem impact [130]. It is not unexpected, given that the Angiotensin-Converting Enzyme 2 (ACE2) receptor is expressed in many tissues [95]. Regarding the pathophysiology and underlying mechanism(s) involved in Long COVID, Baig suggested that oxidative stress and inflammation leads to weak immunologic response and incomplete virus eradication [109]. In addition, virus residuals and antigen remnants cause the ongoing inflammatory response and a vicious cycle leading to a chronic phase known as long COVID [109]. Meanwhile, the persistence of viremia and insufficient antibody generation [139], as well as, psychological factors like post-traumatic stress disorder (PTSD) may contribute to the development of the long COVID [42, 58]. The reason that some individuals are more prone to develop long COVID possibly lies in their genetic profile primarily related to the immune system, such as human leukocyte antigen (HLA). Future whole genomic studies may shed more light on this [109].

It has been shown that RNA of SARS-COV-2 may remain in the central nervous system after the acute phase and may result in the neuronal loss [140]. The considerable systemic inflammation in COVID-19, causes generalized endothelitis and disruption of the blood–brain barrier (BBB) [141, 142]. Moreover, it is known that systemic hyper-inflammation is a leading cause of neurodegeneration and cognitive decline [143, 144]. The latter requires longitudinal follow-up and studies on the pathogenesis and preventive measures, considering the already significant burden of neurodegenerative ailments such as Alzheimer's and Parkinson's disease, to prevent a delayed pandemic of new neurodegenerative conditions [10, 137].

It is thought that the direct invasion of the virus is responsible for persistent neuropsychiatric features of SARS-COV-2 [145]. Another suggested mechanism for the persistent syndrome is dysregulated immunologic response and virus-induced cytokine storm. Moreover, the production of pro-inflammatory cytokines such as IL-7 and IFNγ (interferon-gamma) can result in post-stroke depression, which is highly similar to pathobiology of SARS-COV-2 [93]. The COVID-19 patients have a higher level of NLRP3 inflammasome activation that in combination with interleukin-18 and interleukin-1β have been shown to adversely impact cerebral function [22]. Also, NLRP3 inflammasome-mediated systemic inflammation can lead to pathological accumulation of the peptides/proteins such as fibrillar amyloid-β resulting in the induction and aggravation of neurodegenerative illnesses such as Alzheimer's disease [146, 147]. It has been suggested that SARS-COV-2 infection may impair cognitive function that would lead to brain fog via selective targeting of the mitochondria of the neurons [104].

Dani et al., described long COVID symptoms, such as tachycardia, palpitation, orthostatic intolerance, breathlessness, and chest pain as the consequences of autonomic nervous system instability caused by deconditioning, hypovolemia or immune- or virus-mediated autonomic nervous system destruction [110]. In a case report of a COVID-19 patient with anti-microbial resistant Pseudomonas Aeruginosa infection, it was documented that 6 weeks after clearing of the viral infection, a significant number of activated T-cells and T-cells-specific for unrelated antigens were present, suggesting "a significant amount of by stander activation" which might contribute to recurring anti-bacterial-resistant infections [148]. A study measuring 96 immune response-associated proteins showed that even 40 days post-COVID-19 viral infection high levels of biomarkers related to innate anti-inflammatory and stress response were present [31].

The risk factors for developing long COVID

Currently, the healthcare systems of all countries are overwhelmed with providing care for acutely ill COVID-19 patients. Soon, the health care systems will also be overwhelmed with providing long-term care for the survivors of the acute phase of the illness who are suffering from post-acute-phase signs and symptoms, i.e., long COVID. That made it of paramount importance for the authors to search for the existing literature on the risk factors for developing long COVID after surviving the acute phase. Having reliable criteria to identify such vulnerable individuals would help the healthcare authorities to prepare for early screening and diagnosis, and providing proper facilities to care for their special needs.

In a prospective cohort study of confirmed COVID-19 infected adults, anosmia-dysgeusia was associated with younger age (< 65 years old), and in cases with severe pneumonia only opacities of lung surface on X-rays > 50% and higher heart rate at admission were independent predictors of Long COVID symptoms [50]. Estimated glomerular filtrate (eGFR) ≤ 60 mL/min/m^2 and male sex were predictors of lingering abnormalities on spirometry. Moreover, a higher imaging score during the acute phase of illness was associated with the persistence of radiologic lung involvement, as expected [34]. Another prospective cohort study showed that the duration of oxygen supplementation in the acute phase of the disease was strongly associated with predicted DLCO % and total CT scores 12 weeks after symptom onset. Also, a significant association was found between dyspnea severity score on 12-week follow-up and predicted DLCO% [67]. Moreover, in a report of 52 cases of COVID pneumonia with at least 2 chest CT scans of around 3 months apart, a higher initial CT severity score, ICU admission, longer hospitalization, underlying medical conditions, higher initial WBC count, and development of leukocytosis during hospitalization were predictors of persistent pulmonary abnormalities on the second CT scan [23].

Long COVID patients are claimed to be susceptible to post-viral conditions similar to chronic fatigue syndrome and myalgic encephalomyelitis [83]. It was also reported that those with more than 5 symptoms in the first week of the acute illness were 4 times more susceptible to develop Long COVID; fatigue, headache, shortness of breath, hoarse voice, and myalgia were the most predictive symptoms; and the illness was more prevalent among women, older people, and those with obesity [136]. In another study, nearly two-thirds of adults with non-critical COVID-19 had complaints, including anosmia, dyspnea, and asthenia, up to 2 months following symptom onset. These prolonged symptoms were associated with age 40–60 years, hospital admission at symptom initiation, severe COVID-19, and dyspnea or abnormal chest auscultation [48].

The long-term effects of SARS-CoV-2-associated myocarditis are not known, however, based on the experience with other viral myocarditis, it is anticipated that those with a moderate to severe decrease in left ventricular ejection fraction, almost half would recover in the next 6–12 months, 25% would develop chronic systolic dysfunction, and 25% would require advanced therapies such as heart transplantation [92]. In addition, as post-viral myocarditis and other post-viral cardiac complications can result in a variety of cardiac sequela ranging from atrial and ventricular arrhythmias to sudden cardiac death, cardiac monitoring is recommended in such COVID-19 patients for 2–6 months post-recovery [120].

When it comes to long-term mental health problems, there are multifold risk factors. In regard to PTSD and chronic psychological distress after the acute phase of COVID-19, the greater exposure to the illness was associated with a higher incidence of subsequent PTSD. Loss of a loved one, hospitalization, containment measures such as isolation and quarantine, being in low-income regions, financial stressors, having disabilities, female gender, and older age were the most common mental health risk factors reported by preliminary studies [125]. Another study revealed that previous psychiatric diagnoses and higher systemic immune-inflammatory index are associated with higher post-COVID psychiatric problems. Systemic immune-inflammatory index (SII) is an objective marker of the balance between host systemic inflammation and immune response status considering together peripheral neutrophil, platelet, and lymphocyte counts. In this study, the authors explained that hospitalization duration was inversely correlated with mental health consequences because less in center healthcare support would increase self-isolation and loneliness [21]. It has also been reported that young people, women, and those with responsibilities and concern for others are more prone to develop post-traumatic symptomatology (PTS) following COVID-19 exposure, and hence, they deserve more attention [58].

Defining the factors that predict the development of Long COVID require more cohort and longitudinal studies. Since it is anticipated that there will be an enormous number of long COVID patients in the near future, identifying such predictors could help the Long COVID-specified clinics to prioritize the most vulnerable people and provide care to those in need.

Signs and symptoms

Multisystem studies and those related to general signs and symptoms

The persistent symptoms have been frequently reported. Huang et al., studied 1733 patients (nearly half men, median age of 57) in a clinical cohort follow-up in Wuhan, China. With a median follow-up of 186 days, 76% of the patients reported at least one persistent symptom, especially in women. The most reported symptoms were muscle weakness and fatigue (63%), followed by sleep difficulty (26%), and anxiety/depression (23%). More than half of them still had abnormalities in their chest computed tomography (CT) scan, that was independently associated with their pulmonary involvement during their acute illness. Also, of 86 patients who had experienced critical acute respiratory symptoms requiring oxygen mask/cannula and/or invasive/non-invasive mechanical ventilation during their hospital stay, 48 (56%) had impaired pulmonary diffusion tests in follow up (odds ratio of 4.6, range of 1.85–11.48). Besides, 13% of those with intact kidney function at the time of admission showed abnormal estimated glomerular filtration rate (eGFR) of < 90 mL/min/1.73 m^2 in follow-up. Moreover, among 94 patients with antibody testing, the seropositivity of neutralizing antibodies was significantly lower in follow-up (58.5% with a median titer of 10) comparing to the acute phase (96.2% with the median titer of 19) [149].

In a prospective cohort study of 183 patients (mean age 57 years, 61.5% male), the persistence of symptoms at 35 days after hospitalization were: fatigue in 55%, dyspnea in 45%, and muscle pain in 51%, associated with a lower rating of physical health, mental health, quality of life, and active social role [55].

In a longitudinal study of 180 non-hospitalized RT-PCR proven COVID-19 patients, 53% of patients reported persistence of at least 1 symptom, and 33% reported 1 or 2 symptoms after a mean of 125 days from the onset of disease. The most prevalent persistent symptoms were fatigue, loss of smell and taste, and joint pain [51].

An app-based study about COVID-19 reported that while most of the patients fully recovered within 2 weeks, 1 in 10 patients still reported symptoms for 3 or more weeks. Their research showed that some people experienced fatigue, headache, cough, anosmia, sore throat, delirium, and chest pain as long-lasting symptoms [89]. The Public Health England Guidance implied that 1 in 10 mild cases who have not been admitted to the hospital had symptoms lasting for 4 weeks [133]. A cross-sectional study by Mandal et al., reported that the prevalence of persisting symptoms after a median follow-up of 54 days following hospitalization were: breathlessness (53%), cough (34%), fatigue (69%), and depressive symptoms (14.6%) [64].

Van den Borst et al., studied 124 patients (mean age 59 ± 14 years, 60% male) 3 months after recovery from acute COVID-19; 27 patients with mild, 51 with moderate, 26 with severe, and 20 with the critical disease. They found that a substantial number of patients reported problems across some domains of Nijmegen Clinical Screening Instrument (NCSI), including impairment in general quality of life (72%), fatigue (69%), and functional impairments in daily life (64%) [25].

Arnold et al., conducted a prospective cohort study with 110 COVID-19 survivors (median age of 60 years) who were followed with a median of 83 days after hospital admission and 90 days following the onset of COVID-19 symptoms. They divided the patients into mild ($n = 27$), moderate ($n = 65$), and severe ($n = 18$) groups. At follow-up, although most symptoms had been improved, however, 74% of the patients were still suffering from at least 1 ongoing symptom such as: breathlessness 39%, fatigue 39%, and insomnia 24%. In the mild group, 59% of patients reported ongoing symptoms, whereas the rates of ongoing symptoms for the moderate and severe groups were 75% and 89%, respectively [65].

Townsmen et al., studied 128 post-acute COVID-19 patients (mean age ± SD, 49.5 ± 15 years) at a median follow-up of 72 days after initial COVID-19 symptoms. More than half of the participants (52.3%) reported persistent fatigue regardless of the severity of their acute phase. They also found no association between post-acute COVID-19 fatigue and routine laboratory markers of inflammation and cell turnover (leukocyte, neutrophil or lymphocyte counts, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, C-reactive protein) or pro-inflammatory molecules (IL-6 or sCD25) [33].

In a longitudinal study of 538 COVID-19 survivors (54.5% female; median age, 52.0 years), Xiong et al., found that after a median follow up of 97 days following discharge from the hospital, almost half of the patients (49.6%) had one or more of these symptoms: fatigue (28.3%), excessive sweating (23.6%), arthralgia-most commonly in the knee joint (7.6%), myalgia (4.5%), chills (4.6%), limb edema (2.6%), and dizziness (2.6%) [24].

Liang et al., studied 76 COVID-19 survivors (72% female; median age, 41.3 years) for 3 months after discharge from the hospital. During the 3-month follow-up, 62% of patients complained of chest tightness and palpitation with physical activity. Other symptoms were fatigue (60%), cough (60%), increased sputum production (43%), diarrhea (26%), and fever (20%). Interestingly, some of the laboratory values during the acute phase of illness correlated with post-COVID-19 symptoms. Serum troponin-I

level during the acute illness had a strong correlation with fatigue at follow-up (correlation coefficient 0.78, *P*-value 0.008). Also, lymphocyte count during acute illness had a negative correlation with chest tightness and palpitations with activity at 3 months follow up (correlation coefficient − 0.29, *P*-value 0.03) and (correlation coefficient − 0.36, *P*-value 0.004), respectively. AST and ALT levels in the acute phase were positively correlated with fever at follow-up (correlation coefficient 0.29, *P*-value 0.02) and (correlation coefficient 0.26, *P*-value 0.04), respectively. Moreover, AST level and CD4 cell count in acute illness positively correlated with diarrhea in the follow-up period (correlation coefficient 0.26, *P*-value 0.047) and (correlation coefficient 0.29, *P*-value 0.04), respectively [62].

A study of 143 patients (37% females, mean age ± SD of 56.5 ± 14.6 years) with a mean follow up of 60.3 ± 13.6 days after onset of the first symptoms demonstrated that a high proportion of individuals still complained of fatigue (53.1%), dyspnea (43.4%), joint pain (27.3%), and chest pain (21.7%). At follow-up, only 12.6% of the patients were completely symptom free, while 32% had 1 or 2, and 55% had 3 or more symptoms, and 44.1% experienced worsened quality of life [74].

Halpin et al., surveyed 100 COVID-19 survivors (32 ICU patients, 68 ward patients) with a mean follow-up duration of 48 ± 10.3 days. They found that dysphagia, laryngeal sensitivity, and voice change were more prominent in ICU patients (12.5%, 25%, and 25%, respectively) than ward patients (5.9%, 11.8%, and 17.6%, respectively) [35].

Goërtz et al., studied 2113 COVID-19 survivors in a web-based search in the Netherlands and Belgium [56]. The median ± SD of the persistent symptoms was 79 ± 17 days after the beginning of the signs/symptoms. Of the patients surveyed 112 had been hospitalized, and 2001 had been outpatients. Fatigue and dyspnea were the most common complaints of the patients at the onset of illness and at follow-up. Fatigue that had been present in 95% of the patients at disease presentation, was still present in 87% at follow-up. Similarly, breathlessness that had been present in 90% of the patients at the onset of the disease was still present in 71% at follow-up.

Carvalho-Schneider et al., studied 150 patients in Tours University hospital with a follow-up of 30 and 60 days [48]. Two-thirds of the patients had symptoms in their one and two-month follow-ups (68% vs. 66%, respectively). The most-reported signs/symptoms in the day 30 and 60 were anosmia/ageusia (28% vs. 23%), dyspnea (36.7% vs. 30%), and asthenia (49.5% vs. 40%), respectively. Their study concluded that persistent symptoms at 2 months of disease onset are associated with age (40–60 years-old), abnormal pulmonary sound at the initial examination, and admission to hospital [80].

Respiratory

Multiple studies have looked at long-term effects of COVID-19 on the respiratory system. In a retrospective study of 57 adult patients (17 severe and 40 non-severe cases during their admission), serial lung function tests, imaging studies and exercise capacity were examined 1 month following the discharge [150]. In this follow-up on their convalescent phase, 31 (54%) showed the abnormality in their chest CT scans. They evaluated the following values: diffusing capacity for carbon monoxide (DLCO), maximal inspiratory pressure (PI max), maximal expiratory pressure (PE max), total lung capacity (TLC), forced expiration volume during the first second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio. With regards to pulmonary function tests, 30 (53%), 25 (44%), 7 (12%), 6 (10.5%), and 5 (9%) patients had lower values than 80% of predicted in DLCO, TLC, FVC, and FEV1, respectively. More than half of the participants had PI max and PE max less than 80% of predicted values, suggesting decreased respiratory muscles strength. Severe cases had more impaired tests in their follow-up tests. For instance, they showed significant impairment of the DLCO (76% vs. 42.5%, *P*-value 0.019) and a considerably lower TLC [150].

Zhao et al., followed 55 COVID-19 survivors 3 months after their discharge using HRCT of the thorax, pulmonary test, and IgG antibody for SARS-COV-2. Thirty-five participants (63%) still complained of the persisted symptoms [75]. CT abnormalities were still detectable in 39 of 55 (71%) participants. These included almost resolved ground grass opacities, interstitial thickening and crazy paving pattern with few showing evidence of fibrosis. A quarter of them had impaired respiratory function tests. Besides, 47 of 55 (85%) patients had positive IgG for SARS-COV-2, in which females showed a more robust generation of the antibody as compared to males in the rehabilitation phase. Moreover, they suggested that on-admission D-dimer levels may help predict impaired respiratory test in the follow-up (OR 1.066, 95% CI 1.006–1.129, *P*-value 0.03). In addition, they highlighted the correlation between blood urea nitrogen level with the presence of lung abnormalities (OR 7.15, CI 1.038–49.126, *P*-value 0.46) [27]. In another prospective cohort study, 277 patients were followed 77 days after the disease onset. Among them, 141 (51%) were detected to have at least one clinical symptom. Spirometry abnormalities were detectable in 9.3%, and chest radiology findings were noted in 19%; however, the signs/symptoms and changes were reported mostly as "mild". In this study, no independent risk factor and baseline clinical feature was notable as a predictor for long COVID [34].

In another retrospective cohort study, Tabatabaei et al., investigated chest CT findings of 52 COVID-19 survivors with a 3-month interval between the initial and follow-up

CTs. Thirty (57.7%) patients had complete resolution of pulmonary findings, whereas 22 (42.3%) had the residual disease, including ground-glass opacities (54.5%), mixed ground-glass and subpleural parenchymal bands (31.8%), and pure parenchymal bands (13.7%) on follow-up CT. Patients with the residual disease had higher CT severity score on the initial exam (*P*-value 0.036), longer duration of hospitalization, higher rates of ICU admission, more underlying medical conditions, higher initial WBC count, and higher rates of leukocytosis occurrence during hospitalization (all *P*-values < 0.05) [23].

Guler et al., evaluated pulmonary function and radiological features of COVID-19 survivors 4 months after mild/moderate or severe/critical as defined by the WHO severity classification [37]. After adjustment for potential confounding factors, they found that people with severe/critical COVID-19 had a 20.9% lower predicted DLCO than mild/moderate COVID-19 patients (*P*-value 0.01). They demonstrated predicted DLCO as the most potent independent factor associated with previous severe/critical COVID-19 after including age, sex, BMI, 6-MWT, and minimal SpO_2 at exercise in the multivariable model (adjusted OR per 10%-predicted 0.59, 95% CI 0.37–0.87, *P*-value 0.01). In terms of radiological evaluation, they found mosaic hypoattenuation on follow-up chest CT to be significantly associated with previous severe/critical COVID-19 after adjustment for age and gender (adjusted OR 11.7, 95% CI 1.7–239, *P*-value 0.03) [37].

In a retrospective study of 51 patients with "common COVID-19", defined by them as fever with some respiratory-infection symptoms and pneumonia on radiographic images [41], patients had been followed at 2 weeks and 4 weeks after discharge. In the second follow-up, as compared with the first, the cases with focal ground-glass opacity, multiple ground-glass opacities, consolidation, interlobar septal thickening, subpleural lines, and irregular lines were reduced from 17.7 to 9.8%, 80.4 to 23.5%, 49.0 to 2.0%, 80.4 to 35.3%, 29.4 to 7.8%, and 41.2 to 15.7%, respectively. Moreover, lung lesions were fully resolved in 25.5% of patients on the first follow-up, and in 64.7% of patients by the 4-week-follow-up [41].

In a meta-analysis of the respiratory function of 380 patients in 6 studies assessed at least 1 month after the onset of symptoms, altered diffusion capacity, restrictive pattern, and obstructive pattern were observed in 39%, 15%, and 7% of the patients, respectively [127].

Truffaut et al., evaluated 22 COVID-19 associated ARDS survivors 3 months after ICU discharge. In their study, PFT remained abnormal in 55% of patients with a restrictive pattern ± altered DLCO. Fibrosis was the most abundant finding of 3-month follow-up chest CT. Low TLC was associated with the need for mechanical ventilation (*P*-value 0.044). The initial number of the affected segments on chest CT correlated with DLCO impairment, low FEV1, and the number of affected segments on 3-month follow-up CT (*P*-value < 0.0001, < 0.0001, and 0.01, respectively). Glucocorticoid administration was associated with better outcomes in the aforementioned parameters (*P*-value 0.02, 0.008, and 0.04, respectively). The presence of obstructive sleep apnea was the only predictor of fibrosis on the three-month chest CT scan among demographic and medical data [75].

Shah et al., conducted a prospective cohort study in which they investigated PFT, 6MWT, and HRCT of the chest of 60 previously hospitalized patients with a mean age of 67 years (IQR 54–74 years), and a mean interval of 11.7 weeks after the onset of symptoms. Regarding pulmonary function, 58% of patients had at least one abnormal variable in PFT. Abnormal DLCO was seen in 52% of patients, with 45% of them also having an abnormal total lung capacity indicating a concurrent restrictive ventilatory deficit. Airflow obstruction, which was defined as $FEV_1/FVC < 0.70$, was observed in 11% of patients. By the end of a 6MWT, 4 (7%) patients had $SpO_2 < 88\%$. In terms of radiologic findings, 83% of patients had ground-glass abnormality, whereas 65% had reticulation, and 12% had neither imaging abnormality. More than half (55%) of patients had > 10% of lung volume affected by either ground glass or reticular appearance. The aforesaid patients accounted for most patients who warranted mechanical ventilation (67%) and oxygen supplement (65%). They also observed that the number of days on oxygen supplementation during the disease's acute phase correlated with both DLCO%-predicted and total CT score. Similarly, there was a strong association between dyspnea severity and predicted DLCO [67].

Xiong et al., studied symptoms in 538 COVID-19 survivors (54.5% female) with a median age of 52.0 years (IQR 41.0–62.0 after a median time of 97.0 (95.0–102.0) days from discharge to first follow-up. They found that 39% of patients had one or more respiratory symptoms, including post-activity polypnea (21.4%), which was caused by just mild activity, chest distress (14.1%), chest pain (12.3%), cough (7.1%), nonmotor polypnea (4.7%), throat pain (3.2%), and excessive sputum (3%). Except for excessive sputum, the prevalence of all symptoms was significantly higher in the survival group as compared with the comparison group (all *P*-values < 0.05) [24].

Bellan et al., evaluated PFT in 224 hospitalized COVID-19 patients (59.7% male) with a median age of 61 years (IQR 50–71 years) 3–4 months after discharge. Median FEV1 was 101% (IQR 91.5–112%) of expected, and median FVC was 98.5% (IQR 90–109%) of expected. Five patients were unable to complete the assessment of DLCO; therefore, it was measured in 219 patients. Median DLCO was 79% (IQR 69–89) of expected. 51.6% of patients had DLCO less than 80% of expected, for which the risk factors were female sex (OR 4.33, 95% CI 2.25–8.33; *P*-value < 0.001),

CKD (OR 10.12, 95% CI 2.00–51.05; *P*-value 0.005), and the modality of oxygen delivery during hospital stay (OR 1.68, 95% CI 1.08–2.61; *P*-value 0.02). DLCO < 60% of expected was observed in 15.5% of patients and the risk factors were female sex (OR 2.70, 95% CI 1.11–6.55; *P*-value 0.03), COPD (OR 5.52, 95% CI 1.32–23.08; *P*-value 0.02), and ICU admission during hospital stay (OR 5.76, 95% CI 1.37–24.25; *P*-value 0.02) [68].

In a study of 124 patients (27 patients with mild, 51 with moderate, 26 with severe, and 20 with the critical disease) with a mean age of 59 ± 14 years (60% male) 3 months after recovery from acute COVID-19, Borst et al., reported that patients referred from general practitioners with the mild persistent disease had a higher score on modified Medical Research Council (mMRC) dyspnea scale in comparison to moderate to critical patients. Mean resting oxygen saturation was 96 ± 1%, and mean spirometric indices were normal among all study groups. Moderate to critical patients had significantly lower mean DLCO as compared with mild patients who had normal mean DLCO. Also, critical patients had the lowest mean TLC and residual volume (RV). In regards to radiologic findings, 93% of mild referred patients had normal chest X-rays while only 7% had signs of mild bronchial disease. Ground glass opacities were decreased on follow-up chest CT in 99% of discharged patients and was unchanged in 1%. Nine percent of patients had no abnormalities on chest CT scan. In contrast, residual ground-glass opacity, bronchi(ol)ectasis, lines or bands, and radiological signs of fibrosis were still present in 86%, 60%, 64%, and 26% of patients, respectively. The presence and number of residual CT scan abnormalities were associated with lower DLCO. Moreover, the presence of signs of fibrosis was in association with older age ($P = 0.004$), lower TLC ($P = 0.03$), and more frequent desaturation during the 6MWT ($P = 0.03$) [25].

After studying 76 COVID-19 survivors (72% female) with a median age of 41.3 years (IQR 24–76 years) 3 months after discharge from the hospital, Liang et al., found that lung HRCT had returned to normal in 82% of patients; while 42% of the survivors still had mild pulmonary function abnormalities 3 months following the discharge [62].

Cardiovascular

The long-lasting effects of COVID-19 frequently involve the cardiovascular system. In one longitudinal study, 60% of patients still had myocardial inflammation 71 days after their initial diagnosis, a finding that was possibly contributing to concomitant chest pain, dyspnea, and fatigue. Moreover, an astounding 78% of study subjects had abnormal cardiac MRI findings [54]. Sollini and colleagues used positron emission tomography/computed tomography (PET/CT) to demonstrate that SARS-COV-2 infection could also induce vasculitis, which again was correlated with patients' prolonged symptoms [77]. In a study of 538 COVID-19 survivors (median age of 52.0 years, 54.5% female) followed for a median time of 97 days (range 95–102 days) from discharge to first follow-up, Xiong et al., found that 13% of patients complained of persistent cardiovascular symptoms [24]. Of these patients, 75% experienced increased resting heart rate which had lingered since index hospitalization and 4.8% suffered from palpitations. High resting heart rate was significantly more prevalent in the survival group than the comparison group (*P*-value < 0.05) [24]. More unusual heart rate syndromes have also been reported. In a case report of a 26-year-old female who recovered from the acute phase of COVID-19, postural tachycardia syndrome (POTS) was reported early in her disease process which persisted for the entire 5.5 months of follow-up [112].

Depending on the age-group involved, there is evidence that COVID-19 infection can predominantly promote features of subclinical myocarditis. This is best illustrated in a cardiovascular magnetic resonance (MRI) study of 26 competitive college athletes [151]. None of the 26 participants required hospitalization, and most (73%) were asymptomatic. Twelve athletes (27%; including 7 female athletes) experienced mild symptoms such as sore throat, myalgia, dyspnea, and fever 12–53 days following their quarantine period. Subsequent cardiac MRI revealed ongoing myocarditis or prior evidence of myocardial injury in 12 subjects (46%) despite largely normal ejection fraction [151]. In a similar study, Malek et al. evaluated the cardiac MRI of 26 consecutive elite athletes with a median age of 24 years [39]. Participants were mainly asymptomatic or experiencing a mild course of the disease (77%). Although there was no evidence of pathologic electrocardiogram abnormalities or elevated troponin levels, cardiac MRI was abnormal in 5 of 26 (19%) athletes, including 4 with features of isolated myocardial edema and 1 manifesting non-ischemic late gadolinium enhancement with pleural and pericardial effusion [39].

With more ongoing longitudinal studies of the cardiovascular effects of COVID-19 reporting evidence for myocardial damage, there is increased concern for late-onset myocardial dysfunction and heart failure in the general population. As seen with other organ systems, this will manifest more overtly in the elderly population with co-morbidities [152]. However, evidence for subclinical myocarditis in young athletes raises concerns for undetected arrhythmic episodes and the potential for sudden cardiac death in subjects with overtly preserved ventricular function [153].

Musculoskeletal

A cross-sectional study demonstrated a high prevalence of skeletal muscle weakness and poor physical performance in post-acute COVID-19 patients who had no prior

musculoskeletal problems. For instance, weakness of quadriceps and biceps muscles was found in 86% and 73% of the post-acute COVID-19 patients, respectively [53]. Other studies have shown that most of the post-acute COVID-19 survivors suffered from impairment of functional and muscular performance and dyspnea resulting in severe disability and poor perceived health [45, 72].

Cutaneous

There are a number of reports on the cutaneous manifestations of COVID-19 [154–156]. The International League of Dermatological Societies and the American Academy of Dermatology recently released the first report of their international registry of skin manifestation of COVID-19 in Lancet Infectious Disease [90]. The healthcare providers of 41 countries had shared their observation of cutaneous manifestations of suspected and confirmed COVID-19 cases in that registry. In their report, among the laboratory-confirmed patients, urticarial eruptions lasted for a median of 4 days (maximum of 28 days), papulosquamous eruptions lasted for a median of 20 days (maximum of 70 days), pernio (COVID toe) lasted for a median of 12 days (maximum of 133 days). Of 103 patients with pernio, 7 (6.8%) patients experienced pernio for longer than 2 months [70]. Interestingly, pernio is attributed to inflammation in acral small vessels, highlighting the pathogenic role of chronic inflammation and vasculitis [157]. In another study of 538 COVID-19 survivors (54.5% female, median age of 52.0 years) at a median follow-up time of 97 days after hospital discharge alopecia was reported in 28.6% of the patients [24]. Interestingly, alopecia occurred significantly more in females than males (P-value < 0.01). Moreover, among 154 COVID survivors with alopecia, in only 42 (27%) patients it had started during hospitalization, and in the remaining 112 (73%) patients it had started after discharge from the hospital [24].

Neurologic

Headache, vertigo, “Brain fog”, loss of smell and taste sensations (anosmia and ageusia), collectively referred to as "Neuro-COVID" or “Post-COVID-19 Neurological Syndrome” are among the most reported complications of long COVID in the central nervous system (CNS) [109, 158]. As an example, loss of smell (anosmia) may last beyond 2 months in 10% of the inflicted population [46]. It is suggested that viremia and invasion of the brain and olfactory bulb leads to anosmia [152]. Imaging studies of the olfactory bulb have revealed that olfactory cleft and olfactory bulb abnormalities are present in patients with persistent COVID-19 anosmia, and that a majority of such patients have olfactory bulb atrophy and degeneration [32, 73]. One-third of the COVID-19 survivors had cognitive and/or motor impairment at their discharge from the hospital [159]. A case report also raised the possibility of Guillain-Barré syndrome being a rare late neurological complication of long COVID-19 syndrome [116]. In an imaging analysis using positron emission tomography (PET Scan) several regions of the brain showed hypometabolism, such as orbital gyrus, olfactory gyrus, temporal lobe, amygdala, hippocampus, thalamus, pons/medulla brain stem and cerebellum with 100% accuracy in distinguishing symptomatic long COVID-19 patients from matched normal controls. Such brain involvements could explain the neurologic symptoms, such as hyposmia/anosmia, memory/cognitive impairment, pain and insomnia. The hypometabolism seemed to be associated with the consumption of ACEI medications, reflective of the possible role of ACE receptors; meanwhile, this study suggested that using nasal decongestant sprays might be protective in this context [20].

Mental health

One of the great concerns of long COVID is its mental health consequences, such as major mood swings, depression, the feeling of loneliness and isolation, high levels of stress and anxiety, and sleep–wake disorders [160]. The survivors are also at risk of the community-wide psychological toll of the pandemic with a higher chance of chronic fatigue syndrome, depression, post-traumatic stress disorder (PTSD), substance/drug abuse and anxiety [152]. Decreased health-related quality of life was implicitly reported in a case–control study as a significant consequence of long COVID [38].

In a qualitative study of the persistent symptoms after COVID, multiple diverse and often relapsing–remitting symptoms were reported. The patients felt a heavy sense of stigma, not being taken seriously and achieving a diagnosis, inability to access specialists’ services, inconsistent criteria for investigating or referring the patients. Moreover, the researchers found a considerable degree of emotional feelings, such as anger, frustration, fear, and hopelessness among these patients [57]. Another qualitative study implied the following themes: the hard and heavy work of enduring and managing symptoms and accessing appropriate care, living with uncertainty, helplessness and fear, particularly over whether or not recovery is possible. The authors also mentioned the importance of finding the ’right’ general physician/family practitioner to present an adequate level of understanding, empathy, and support [47]. Moreover, another study estimated that long COVID might cause unexpected cognitive dysfunction, equivalent to a 10-year decrease in global cognitive performance between the ages of 20 and 70 years [136].

Furthermore, Mazza, et al., studied a cohort of 402 adult survivors of COVID-19 who were screened for psychiatric symptoms of post-traumatic stress disorder (PTSD),

depression, obsessive–compulsive disorder (OCD), anxiety and insomnia at 1 month follow up after hospital treatment. They found that 56% of the post-COVID patients had ongoing symptoms of at least one, 37% had two, 21% had three, and 10% had four of the aforementioned psychopathological conditions. The authors also found that females, patients with a preexisting psychiatric diagnosis, and those who were managed at home had an increased score on most measures. Outpatients suffered from increased anxiety and sleep disturbances, whereas the duration of hospitalization had a negative correlation with PTSD disorder, depression, anxiety, and OCD symptoms. Moreover, higher levels of depression and sleep disturbances were observed among the younger patients [21]. Their results were in agreement with another cohort of 238 COVID-19 survivors studied 4 months after hospital discharge in whom PTSD symptoms were reported in 43% (26% had mild, 11% had moderate, and 6% had severe PTSD symptoms). Moreover, in contrast to the previous study, male sex was independently associated with moderate to severe PTSD symptoms [68].

Xiong et al., reported on 538 COVID-19 survivors (54.5% female, median age of 52.0 years) after a median follow-up of 97 days from hospital discharge. They found that psychological symptoms were present in 22.7% of patients as follows: somnipathy in 17.7% (mainly described as difficulty falling asleep or short and interrupted sleep), and depression and lack of interest in things in 4.3% [24].

Pediatric long COVID

Long COVID in the pediatric field is a real challenge, which is poorly defined. Only one published case series considered the long COVID in 5 inflicted children. The most common signs/symptoms reported were fatigue, dyspnea, palpitations, and chest pain. However, the symptoms ranged from headache to skin rashes. This study also mentioned that the duration of illness was longer in children than in adults [111].

Predominantly in children and recently found few cases in adults, the SARS-COV-2 has resulted in a hyperinflammatory state called multisystem inflammatory syndrome (MIS), which was later divided into MIS in Children (MIS-C) and MIS in adults (MIS-A). The disease resembled acute rheumatic fever, toxic shock syndrome and Kawasaki disease that was misdiagnosed in the beginning [161–163]; however, later, it was found to be a post-infectious state of the SARS-COV-2 primarily following 4–6 weeks after infection. In general, the syndrome may present with a combination of fever, abdominal pain, dermatologic manifestations, diarrhea, nausea, and organ failure [162]. Among the presentation sign/symptoms, the cardiovascular symptoms are more prominent: up to 80% of the patients may have symptomatic myocarditis, 9–24% may present with coronary artery abnormalities and valvular regurgitation, pericarditis, and pericardial effusion [162]. The prognosis and long-term complications of the MIS are currently unclear. However, the hyperinflammatory nature of the syndrome may predispose the victims to complications such as, coagulopathy, aneurysm, and thrombosis [9], which necessitate further investigations. In the most extensive study of MIS-C cases across the united states, 570 children were assessed. Three-fourth of the cases had serological evidence of SARS-COV-2 infection, and less than half of them had negative PCR test for SARS-COV-2 [43]. Moreover, CDC has described MIS in 16 adults (MIS-A); in 11 of them anti-SARS-COV-2 antibody was checked, all had positive serology. Six of the 16 adult patients had negative SARS-COV-2 PCR tests [113]. These findings highly suggest that MIS-C and MIS-A are post-acute and postinfectious phenomenon. It has been suggested that endothelial injury and activation of Interlukin-1 pathway has an important role in the pathogenesis of MIS-C and may serve as a common determinant among MIS-C, acute rheumatic fever, and Kawasaki disease [121].

Thromboembolism

As far as coagulation dilemmas are concerned, there have been case reports of thrombosis occurring after discharge from the hospital [114, 117, 118]. In a study of 163 COVID-19 patients who had not receive any anticoagulation prophylaxis during their illness, it was shown that 30 days after discharge from hospital the cumulative incidence of both arterial and venous thrombosis was 2.5%; the cumulative incidence of venous thromboembolism alone was 0.6%. The 30-day cumulative incidence of major hemorrhage was 0.7%, and clinically relevant non-major bleeds were 2.9% [66]. Consistent with these results, another study reported 2.6% incidence of venous thromboembolism within 42 days of discharge from the hospital [30]. This should raise our awareness toward continuing and/or starting thromboprophylaxis after discharge. However, another study of 102 patients with 44 days of follow-up, revealed less than 1% incidence of venous thromboembolism, thus no need for a routine prophylaxis regimen [50]. Moreover, a large study comparing hospital-acquired venous thromboembolism associated with COVID-19 and all other medical illnesses in 2019, showed that the incidence was 4.8 and 3.1 per 1000 discharged individuals, which was not significantly different. In this study, hospital-acquired venous thromboembolism was defined as occurring in the hospital at least 48 h after admission, or postoperatively, or occurring up to 90 days post-discharge [36]. Similarly, a multi-center study showed that the incidence of venous thromboembolism in COVID-19 patients who were followed for 45 days after hospitalization was “relatively low”[29]. Moreover, Eswaran et al., reported that among 447 patients who were followed after

discharge from the hospital, only 2% developed vascular thromboembolism 30 days after discharge; and they concluded against the routine post-discharge thromboprophylaxis [69]. In light of these controversies, there is an urgent need for more extensive randomized clinical trials.

Management

General care

Greenhalgh et al., made recommendations for family physicians and general practitioners regarding long haulers [105]. They mentioned that in long haulers, symptoms should not be underestimated; for example, chest pain should be taken even more seriously. They have also recommended pulse oximetry and home-based assessment for all COVID-19 survivors, urging further investigation for those with oxygen saturation < 95%, and additional tests for evaluation of exertional desaturation for patients with resting oxygen saturation ≥ 96%. A 3% or more decrease in exertional oxygen saturation requires further cardiorespiratory assessment [105].

Because of the diversity of the affected populations' symptoms, a personalized and holistic approach to symptom management is recommended. Thus, we highlight the need for continuing medical education (CME) programs on long COVID, especially for general primary care practitioners. Training health care workers in managing their stress while enabling positivity and connectedness for patients is also critical. Poor mental health consequences are highly associated with social exclusion. Therefore, building hope and resilience, social connection, and peer supports are essential in managing psychological issues [134]. In a qualitative study on 43 health professionals, Ladds et al., [26] reported that the participants repeatedly mentioned the role of social media in feeling better and diminishing their anxiety/stress and stigma when communicating with others and with their colleagues about their symptoms.

Pharmacological options

As hypothesized above, the core mechanism that possibly leads to chronic symptoms is an ongoing inflammatory state and oxidative stress. If proven, non-steroid anti-inflammatory drugs (NSAIDs), corticosteroids, and antioxidants such as CoQ10 could be possible approaches to management [109, 124].

Considering the nature of multisystem inflammatory syndrome in children (MIS-C), four initial treatment domains, including supportive care, empirical broad-spectrum antibiotics, anti-inflammatory agents, and anticoagulants are suggested. Anti-inflammatory management aims to reduce tissue inflammation to prevent or slow down the progression of coronary artery aneurysms [121].

Regarding anti-inflammatory agents, high dose IVIG and aspirin are advised as in Kawasaki disease [164]. However, there has been a debate over the administration of steroids in MIS-C. More recent studies suggest the use of corticosteroids based on each patient's condition guided by a multidisciplinary team [121]. Agents that target inflammatory molecules such as IL-1 [165], IL-6 [166], and TNF-α [167] are also suggested for the management of MIS-C.

While these medications might be protective on some occasions, these drugs' pros and cons should be weighed before prescribing due to the possible adverse effects. Metastasio et al., in their case study, reported using Kratum (Mitragyna speciosa) in their patient resulted in early recovery from the acute COVID-19 syndromes, including body pain, fatigue, and malaise, which are challenging for patients/physicians to deal with [168]. The therapeutic benefits of the plant are possibly related to the fact that it is a rich source of mitragynine, and the related metabolite 7-hydroxymitragynine[169]. Further studies may reveal the herbals' benefit in long COVID haulers, especially for those with contraindications for NSAIDs. The harms and benefits of over-the-counter vitamins and supplements are unknown [134]. Although this is an early systematic review in the field, our qualitative assessment of the literature does not support prophylactic use of the anticoagulants for COVID-19 survivors; this requires multinational large-scale cohorts RCTs.

Role of physical and mental rehabilitation

Post-acute care is usually defined as the care provided following release from the hospital; however, here we extend this concept further to those surviving from an acute phase COVID-19, whether or not the patient had been admitted to a hospital. We recommend that the local public health authorities should develop adaptive post-acute COVID-19 care centers that specifically work on the palliative care of COVID-19 long haulers. Importantly, the vulnerable populations such as those in nursing homes, residential care centers, refugees, and asylum seekers should not be neglected [107]. As long COVID has a multisystem involvement, it has been suggested that a broad range of rehabilitation disciplines would be beneficial [128]. Cough and breathlessness are common. If there is no sign of superinfection or low oxygen saturation, breathing control exercise could help. The role of graded exercise in fatigue management is still a source of debate, and in long COVID patients it should be considered cautiously [134]. Myalgia Encephalomyelitis (ME) Association on post-viral fatigue syndrome (PVFS) highlighted the role of a multidisciplinary approach in managing chronic fatigue; it included resting, activity management,

mental well-being, nutrition, and adequate sleep [78]. Also, based on the experience of post-infectious fatigue syndrome induced by Q-fever, it was generally thought the cognitive-behavioral therapy (CBT) could be beneficial in the management of post-infectious fatigue syndrome [170]; however, a recent study by Vink et al., reanalyzed the results of "Qure study" and showed that CBT was neither helpful in that regard nor possibly in the post-infectious fatigue syndrome of COVID-19 [119].

Another point to consider is early rehabilitation; the current definition of the recovery from COVID-19 is misleading as it mentions 3 weeks or without an episode of fever. We suggest that full recovery should be considered when the post-acute symptoms are adequately addressed; in doing so, Belli et al., in their study showed that the majority of their study population had a very severe degree of disability (dependency) at the time of discharge, demonstrated by Barthel index ≤ 60, requiring early rehabilitation [52]. Barthel Index is used to assess performance in activities of daily life (ADLs). In a report of the Italian cohort of post-acute COVID-19 patients, all of the included participants were grade 4 or 5 on the mMrc dyspnea scale, suggesting dyspnea during even minimal activities, and only a few of them could perform the 6-min walk test (6MWT) [45].

For those discharged from the hospital, Sun et al., recommend aerobic exercises, balance training, breathing training, and resistance strength training (start with low intensity and gradually raise the duration and intensity) as being beneficial in early recovery [123]. In a case series, Ferraro et al., recruited 7 post-acute infectious patients. All of the participants underwent a tailored rehabilitation intervention twice a day, each time for half an hour, for 6 days a week. In the beginning, 6 of 7 patients had fatigue, and 1 of them had an extreme sense of exertion. Following rehabilitation, 5 of 7 were without fatigue, and the remaining 2 had only a light sense of exertion. Besides, at the beginning of the study, all 7 patients had a deficient physical performance using the metrics of 6 MWT and 10 MWT. In this regard, the authors found a considerable improvement in outcomes of all patients, especially in 2 cases [71]. Liu et al., did a prospective 6-week respiratory rehabilitation, quasi-experimental study, with 72 post-acute COVID-19 patients discharged from the hospital (36 with and 36 without respiratory rehabilitation). They found that 6-week respiratory rehabilitation improved their respiratory function tests, their level of anxiety, and their quality of life in the elderly patients post-acute phase COVID-19 (all P-values < 0.05) [60].

We would also like to highlight the development of more relevant functional assessment tools for COVID-19 survivors. For example, in spite of the broad use of 6 MWT in long COVID-related literature, it has been criticized as it shows "floor effects" because of respiratory failure and dyspnea in the acute phase, especially for discharged from ICU. Concerning this, Rivera-Lillo et al., suggested using 1-min sit and stand test instead of 6 MWT in the general population [171]. Also, Curci et al., suggested Chelsea Critical Care Physical Assessment Tool (CPAx) for those discharged from the ICU [172].

When to return to usual activities?

The crucial question is: "when can the survivors return to usual pre-infection activities?". There is a paucity of evidence concerning this issue; however, we believe that this decision should also include the patients' occupation/activity and should be made on a one-by-one basis. For example, additional follow-up tests may be warranted in the case of competitive athletes who wishes to return to the field. A recent expert consensus recommended that mildly symptomatic athletes, besides 2 weeks of convalescence, should have a normal electrocardiogram and transthoracic echocardiography prior to returning to competitive sports [173]. In their review, Mitrani et al., [120] mentioned that there is no guideline to help physicians deal with the cardiac COVID-19 long haulers in their follow-up to rapidly diagnose complications such as arrhythmias or cardiomyopathies. There is an absolute need to screen for residual cardiac involvement in the convalescent phase of acute cardiac injury and for long-term sequelae of "post–COVID-19 cardiac syndrome". The issue could become more complicated with a lack of proper assessment tools; Starekova et al., in a study of the utility of cardiac MRI as a screening tool among 145 asymptomatic or mildly symptomatic athletes who survived COVID-19, concluded that cardiac MRI is not useful in the cardiac assessment of the survivors [63].

Salman et al., propose a protocol for returning to the usual physical activity for the COVID-19 survivors [131]. There are several concerns about how and when the COVID survivors should start their physical activity/exercise. Some potential risks, including cardiac, pulmonary, and psychiatric, have to be stratified and considered before advising the return to physical activity. Besides, the physicians should consider patients' pre-illness baseline physical activities before any recommendation. Those with persistent symptoms or a history of severe COVID-19 or cardiac involvement of COVID (e.g., myocarditis) are recommended to consult their medical doctor before returning to physical activities.

Also, Salman et al., recommended waiting at least a week after being asymptomatic to resume exercise. Moreover, the first 2 weeks of exercise should be minimal exertion, with gradual progression. The self-monitoring of the signs/symptoms and mood using a diary is highly recommended in all steps. For example, suppose patients felt fatigued or unable to feel recovered one hour or a day after exercise; in that

case, they should step back to the prior activity level and seek medical advice when unsure.

Concluding comments and further suggestion

We found many discrepancies and lacunae in the myriad of papers available on the subject with data based on isolated cases and lacking the numerical strength for reliable data analysis. We found only one randomized clinical trial. We found a significant void of global collaborative studies on COVID 19 patients, their clinical presentation, management and long-term effects of the disease. We need a global consensus on the nomenclature of the long COVID 19 syndrome with a clear definition of the timeline to differentiate between prolonged symptomatic infection and actual post-recovery COVID 19 syndrome. Likewise, the diagnostic criteria need to be clearly established based on the severity of infection. More research is needed to focus on the pathophysiology of this complicated ailment. The clinical presentation needs to be analyzed between the spectrum of age, gender, race and concurrent comorbidities. Long-term follow-up has to be established with a clear focus on identifying the risk factors that predispose certain individuals to more complications versus others and a timeline for repeat testing or intervention and rehabilitation.

The unique pattern of morbidity and mortality that spans across a wide spectrum of demographics mandates that a more detailed, holistic approach is dedicated to the research of COVID 19 and its long-term effects.

After about 12 months following the declaration of the SARS-COV-2 pandemic by the World Health Organization, mysteries about this new virus, including the extent that the infection could cause long and persistent symptoms, are still not clear. There are also debates regarding the definition of prolonged disease, its diagnosis criteria, and its management. We highlight that the burden of the long COVID is overgrowing as more individuals become affected by the disease. Investigations in this field require considerable funding support and research investment. Also, we strongly suggest patient tracking via disease registries, similar to cancer registries.

Unfortunately, there is a wide gap in the literature related to the long-term COVID, which may reflect the need for long-term multi-national studies with adequate funding. This would allow for extensive subgroup analyses involving a wide range of ages, ethnicities, occupations, gender, and socioeconomic status. These studies will bring a more precise definition and symptom categorization for the long COVID. We also highlight the need for more rigorous research and developing special guidelines in particular populations such as those with comorbidities and those with the risk of specific complications, such as competitive athletes. As stress is considered to play a role in the progression of the long COVID, the health care workers, as front-liners, are possibly more prone to have higher stress/anxiety and may experience a more symptomatic long COVID, which requires attention and further research [42, 58].

Moreover, unique guidelines need to be developed for particular occupations and activities, such as professional athletes, in whom the long COVID may be associated with more severe and potentially fatal consequences. We also highlight the need to support the vulnerable population by allocating financial and human resources to establish and reinforce telemedicine and in-person long COVID clinics. Finally, SARS-COV-2 has not been with us for long enough time for us to have a realistic estimation of the long-term picture of the post-infectious state; with the emergence of new studies, subsequent updated reviews are expected to appear soon.

To fill the above gaps, we present the following suggestions:

Definition and management of the evolving nature of the disease: World Health Organization did well in naming the COVID-19 for standardizing the literature; there is also a need to develop a timeline for COVID-19, and appropriate action plans in managing this complex disease. In that regard, recovery from COVID-19 is far from just being tested negative or following a limited predetermined period; a consensus on the definition of full recovery should be reached. In addition, the diversity of symptoms requires a more stringent categorization of symptoms; this will help the treatment and rehabilitation programs.

Long-term patient follow-up and global data-sharing: more long-term follow-up of the cross-country populations is recommended. Long-term studies should include all COVID-19 patients, even those with mild symptoms.

Investing in recovery support, including mental health and psychosocial support: since many of these patients have impaired performance in their daily tasks and suffer from mental health symptoms, launching an in-person or online portal based on peer groups is crucial.

Building capacity and knowledge base of health care workers: to deal more efficiently, we highlight the role of continuing medical education (CME) courses in developing competencies regarding attitudes, skills, and knowledge, especially for primary care practitioners.

Personalized and more organized clinical management approach: since individual patients might experience specific symptoms, the need for personalized holistic management is notable.

Developing innovative assessment tools for further studies: since this is a new disease that affects all organs, developing newer functional metric tools to address its long-term impact on the mental and physical health status of the survivors is of paramount importance.

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Author contributions HA and MH conceptualized the study. NG, BB and MK led the literature review with contributions from BR, JM, AAP, LMM, SP, MH, AA and HA. MH led the data analysis with contribution from HA, LM and AA. All authors contributed to the development of the analysis plan, collection and analysis of primary data, data interpretation, and critically reviewed the revised initial draft of the manuscript. All authors have read and approve the final draft.

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Declarations

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