

Review

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Review

Unveiling Long COVID: General Perceptions and Challenges for Diagnosis and Management

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Abstract: On March 11, 2020, the World Health Organization (WHO) declared a pandemic caused by SARS-CoV-2, raising global health concerns. Reports of persistent and new symptoms following the acute phase of infection highlighted the complexities of recovery and prompted the investigation of what is now termed long COVID. Officially recognized by the WHO in October 2021, long COVID presents various health implications, though terminology—such as post-COVID syndrome and post-acute sequelae of COVID-19 (PASC)—remains inconsistent, complicating diagnostic standardization. Long COVID affects an estimated 10% to 30% of SARS-CoV-2 infected individuals, with common symptoms including fatigue, dyspnea, cognitive dysfunction, and joint pain, all of which significantly impair quality of life. Public perception is influenced by factors like education and health history, while misinformation and stigma hinder accurate diagnosis and treatment. The absence of biomarkers and overlap with other post-viral syndromes further complicate clinical recognition. Experts emphasize the need for refined diagnostic criteria and integrated strategies combining biomedical research, public policy, and educational initiatives to improve clinical management, address healthcare inequalities, and mitigate the impacts of long COVID. This review unveils state of art and knowledge gaps to raise discussion leading to better clinical decision-making and public awareness related to long COVID.

Keywords: long COVID; post-COVID syndrome; public perception; persistent symptoms; knowledge gaps; health policy

1. Introduction

Long COVID, also referred to as post-COVID syndrome or long COVID syndrome, is a complex condition characterized by persistent symptoms that continue or emerge after the acute phase of SARS-CoV-2 infection, even in mild and asymptomatic cases [1]. These symptoms can persist for weeks or months and affect various body systems, complicating the recovery process for patients [2,3]. The most common symptoms include fatigue, dyspnea, cognitive dysfunction, chest pain, and joint pain [4,5].

Research by Sudre [6] indicates that long COVID affects, on average, between 10% and 30% of individuals who have had COVID-19. Estimates of long COVID prevalence range from 2.0% to 53% (7.5% to 53% in adults and 2% to 3.5% in pediatric cases) [7]. These variations reflect not only diverse methodologies but also a lack of consensus on the operational definition of the condition. Methodological differences include variations in diagnostic criteria, populations studied, and symptom measurement approaches. This wide range underscores the need for standardization in definitions and study methods to achieve more accurate and globally comparable estimates. Various studies suggest that prevalence is higher among women, older individuals, and those with pre-existing conditions [8–10]; however, in countries with limited healthcare access, the prevalence may

be underestimated, complicating a uniform global assessment [11]. Furthermore, observed discrepancies highlight the urgency for additional research to clarify the true magnitude of long COVID across different epidemiological and socioeconomic contexts.

Long COVID extends beyond physiological effects, significantly impacting the societal, emotional, and financial dimensions of individuals, who often struggle to recognize and attribute their symptoms to the condition. Many individuals encounter obstacles in obtaining diagnoses and assistance within healthcare systems [7,12]. Marginalized populations, including informal workers, face substantial challenges in diagnosing and managing long COVID due to their limited access to formal healthcare systems. Financial and institutional barriers hinder their ability to seek medical care, while job insecurity and the lack of employment support exacerbate recovery difficulties, reinforcing the socioeconomic impacts of the condition. These barriers can lead to underreporting of cases and significant delays in diagnosis, perpetuating inequality in access to treatment and long-term medical follow-up [7].

Public perception regarding long COVID plays a crucial role in seeking medical intervention and adhering to therapeutic regimens. Misinformation and stigma associated with the condition often hinder diagnosis and the initiation of treatment, exacerbating physical, emotional, and social ramifications [13]. To address these challenges, investment in educational initiatives and integrated public health strategies is imperative to raise awareness and adapt healthcare systems to meet the unique needs of affected individuals [2]. These strategies can improve the quality of life for these individuals and reduce pressure on medical services [2,13]. Besides, there is a lack of understanding regarding the mechanisms underlying long COVID and its similarities to other post-viral syndromes may contribute to public confusion and misconceptions [2,14]. Additionally, the overlap of symptoms with other prolonged viral infections, such as sequelae from Epstein-Barr and influenza infections, complicates diagnosis and creates uncertainties surrounding optimal management of long COVID [15].

The aim in this review is to examine factors that shape societal perception of long COVID, particularly given the rising prevalence of cases characterized by persistent and incapacitating symptoms. Objectives also include the evaluation of remaining knowledge gaps related to long COVID, such as the absence of diagnostic biomarkers and symptom heterogeneity, which hinder clinical identification of the condition and directly affect patients' perceptions and trust in their diagnoses. Understanding these factors is crucial to inform future research, public policies, and educational initiatives, ultimately enhancing public awareness and improving clinical management and patient support.

2. Material and Methods

Publication period: Studies published between January 2020 and December 2024 were included, considering the relevance of the pandemic period for understanding long COVID and the increase in publications related to the topic during this period.

Databases: The search was carried out in the PubMed, Web of Science and SciELO databases, chosen for their relevance to the medical literature, interdisciplinary scope, public health, biomedicine, social sciences and for allowing access to publications from different regions and languages. The selection of these databases was based on their ability to index high-quality studies, covering regional and international publications that allow for contextual and comparative analysis of the data. In addition, these databases include a diversity of languages and address different methodological approaches, ensuring the inclusion of literature that reflects the multiple dimensions of long COVID. Relevant studies found outside these platforms were considered upon explicit inclusion in the search criteria.

Language: Articles published in English and Portuguese were selected, with the aim of allowing an accessible and regionally representative analysis, while recognizing the limitation of excluding other languages.

Thematic focus: Studies addressing prevalence, symptoms, underlying mechanisms, social impacts, and public perception of long COVID were prioritized, considering their relevance to answer the research questions and identified knowledge gaps.

Robust methodology: Only studies with clear designs and consistent methodologies were included. Anecdotal reports and studies with low methodological quality were excluded to ensure the validity of the conclusions.

Scientific relevance: Studies that had a significant impact on the current literature and that contributed to expanding the understanding of long COVID were selected, prioritizing those that addressed critical gaps in scientific knowledge.

Descriptors and search terms: Long COVID, post COVID condition, public perception, prolonged viral infections, persistent symptoms and knowledge gaps.

Analysis and interpretation: A critical analysis of the information collected was carried out, identifying patterns, trends, gaps in knowledge and conflicts between studies. The data were interpreted according to their specific perspective and context.

3. Long Covid Overview

Long COVID, also known as post-acute sequelae of SARS-CoV-2, is a complex and multifaceted condition that affects a subset of individuals infected with the SARS-CoV-2 virus, the causative agent of COVID-19. This condition is characterized by the persistence of symptoms for an extended duration, often lasting several months or even years after the initial infection has resolved [16,17].

The primary symptoms associated with long COVID include fatigue, shortness of breath, cognitive dysfunction, and a wide range of other physical and neurological manifestations [18,19]. These symptoms can significantly impact the quality of life for affected individuals, with some experiencing substantial declines in overall health and well-being [16].

To diagnose long COVID, healthcare providers typically rely on a comprehensive clinical evaluation that includes a thorough medical history, physical examination, and various diagnostic tests [19]. These tests may encompass imaging studies, such as chest X-rays or CT scans, to assess lung damage, as well as neurological and cognitive assessments to evaluate the impact on the nervous system. Additionally, laboratory tests may be conducted to rule out other underlying conditions or to identify potential biomarkers associated with long COVID [16,17,20].

3.1. Prevalence and Symptom Variability

Recent studies have highlighted the prevalence of long COVID, with community-based surveys indicating that 15%-18% of patients continue to experience symptoms beyond the initial 4-week period, and 8%-17% beyond 12 weeks [21,22]. In a population-based study, 15.9% of participants reported new or worsened symptoms at least 90 days after infection, with higher prevalence linked to specific acute symptoms [22]. Moreover, a global cohort study found that the prevalence of long COVID was notably higher in high-income countries compared to low- and middle-income countries, suggesting disparities in health outcomes and support systems [11]. The risk of developing long COVID is particularly high among those who experienced more severe illness, with estimates indicating a more than twofold increase in risk for individuals who required hospitalization or admission to intensive care units [19].

The symptoms associated with long COVID are highly diverse, encompassing a range of physiological and neurological manifestations. Respiratory complications, such as persistent breathlessness and pulmonary fibrosis, have been widely documented, underscoring the lasting impact of COVID-19 on respiratory health [19,23]. Extrapulmonary effects, including reduced exercise tolerance, frailty, and neuromuscular dysfunction, further highlight the systemic nature of the condition [19].

Differences in reported variability are attributed to a lack of consensus on diagnostic criteria, as well as methodological variations and differences in populations studied [25,26]. Additionally,

regional disparities, such as lower recognition and underreporting in countries with limited healthcare access, exacerbate this complexity [35].

3.2. Public Perception of Long COVID

The perception of long COVID can be influenced by various factors, including education level, age, health history, and access to information about the condition [18,24]. Individuals with higher levels of education may be better equipped to understand the complex and evolving nature of long COVID, as research indicates that more educated populations tend to have a more nuanced comprehension of health conditions [25]. This may lead to a more informed and less anxious perception of long COVID compared to those with limited educational backgrounds, who may struggle with the intricacies of the condition.

Age is another significant factor that shapes perceptions of long COVID. Older adults, who are generally more vulnerable to severe outcomes from COVID-19, may view long COVID as a more substantial threat, while younger individuals might underestimate the potential long-term implications of the disease. Furthermore, individuals with pre-existing health conditions, such as respiratory or cardiovascular diseases, may be more attuned to the potential long-term effects of COVID-19, resulting in heightened awareness and concern regarding long COVID [19,20].

3.3. Impact of Media and Social Networks

The COVID-19 pandemic has profoundly impacted public health and society [26]. The role of media and social networks in shaping public understanding and perception of long COVID is crucial, as both accurate information and misinformation can significantly influence people's knowledge and attitudes toward this syndrome [26].

Research has shown that social media usage has increased dramatically during the pandemic, leading to the dissemination of both reliable information and misinformation about COVID-19 and its long-term effects [27]. Social media platforms have become primary sources of health information for many individuals, and the abundance of content—some of which may be inaccurate or misleading—has contributed to what has been termed an "infodemic" [28,29].

Studies indicate that social media is often utilized as a primary source of health information, particularly in contexts where access to formal medical resources is limited. For example, analyses of Twitter data have revealed prevalent discussions of symptoms such as "brain fog" and fatigue, contributing to the collective recognition of long COVID manifestations. However, content posted on social media may include unverified information, creating confusion and fueling misinformation [31].

For instance, users of platforms like TikTok have demonstrated less knowledge of COVID-19 guidelines, which may extend to misconceptions about long COVID symptoms [30]. Conversely, another study utilizing Twitter data analyzed discussions about long COVID, revealing prevalent symptoms such as brain fog and fatigue, thereby demonstrating how social media can facilitate understanding of long COVID experiences [31]. Overall, the relationship between social media use and knowledge of long COVID is complex, necessitating targeted public health interventions to mitigate misinformation and improve understanding [32].

Thus, social media represents a critical space for shaping public perceptions of long COVID, highlighting the need to balance the dissemination of accurate information with the mitigation of misinformation. Strategic engagement by healthcare institutions on these platforms can play a vital role in educating the public and enhancing health responses.

3.4. Scientific Knowledge Gaps about Long COVID

The COVID-19 pandemic has left an indelible mark on the global health landscape, and the emergence of long COVID has become a significant area of concern. The clinical spectrum of long COVID is characterized by a diverse array of symptoms that often persist long after the initial

infection has resolved [33,34]. However, the underlying mechanisms and long-term prognosis of this condition remain poorly understood, leading to significant gaps and controversies in current scientific research [5,24].

One of the primary challenges in understanding long COVID is the lack of consensus on the pathophysiological mechanisms driving persistent symptoms. Hypothesized mechanisms include end-organ damage, specific symptom clusters, and potential autoimmune responses, but the precise pathways remain elusive [35]. The heterogeneity of long COVID presentations further complicates efforts to establish a coherent schema linking SARS-CoV-2 infection to the diverse array of persistent symptoms [35].

Additionally, the duration of long COVID is another aspect that remains highly debated. While some individuals may experience a gradual recovery, others may suffer from recurring or worsening symptoms, leading to a prolonged and unpredictable course of the disease [5].

Limitations in current scientific research on long COVID can be attributed to several factors, including the evolving nature of the disease and the absence of a clear, universally accepted definition. These challenges have hampered the development of standardized diagnostic criteria and effective treatment approaches [25,33,34]. Furthermore, the paucity of well-characterized clinical cohorts and the need for more rigorous scientific investigations have impeded progress in understanding the underlying mechanisms and risk factors associated with long COVID [36].

Alterations in the immune systems of individuals with long COVID have been widely documented, revealing complex immune profiles and persistent inflammatory responses. Studies indicate that patients with long COVID exhibit elevated levels of various leukocytes, including lymphocytes, eosinophils, and monocytes, which correlate with the duration and severity of symptoms [49]. Additionally, distinct inflammatory groups have been identified, such as limited and systemic immune activation, which are associated with clinical variables like age and vaccination status [50]. Furthermore, immune dysregulation is evident through intensified antibody responses not only to SARS-CoV-2 but also to other viruses, suggesting a compromised viral control mechanism [51]. Single-cell RNA sequencing has shown changes in immune cell populations over time, indicating ongoing challenges in virus clearance and possible chronic complications [52]. Overall, these findings underscore the intricate immune alterations that characterize long COVID, affecting a significant portion of the global population [53].

In patients with long COVID, persistent oxidative stress and mitochondrial dysfunction significantly contribute to cellular damage and metabolic changes, alongside immune dysregulation. Evidence indicates that mitochondrial dysfunction leads to impaired cellular energy metabolism, characterized by increased glycolysis and oxidative phosphorylation, disrupting normal cellular functions and promoting apoptotic activity [54,55]. Additionally, the metabolic profiles of patients with long COVID reveal low levels of amino acids and triglycerides, suggesting mitochondrial stress and altered metabolic pathways linked to chronic fatigue syndrome [56]. The interaction between oxidative stress and metabolic disorders exacerbates symptoms such as fatigue and cognitive disturbances, highlighting the need for targeted therapeutic strategies that address these underlying metabolic issues [57,58]. Therefore, understanding these mechanisms is crucial for developing effective interventions for long COVID.

3.5. Consequences of Lack of Specific Knowledge and Confusion with Other Viral Infections

The ambiguity surrounding long COVID has significantly contributed to public misconceptions regarding its severity and impact. Research indicates that long COVID manifests as a diverse array of over 200 symptoms, complicating diagnosis due to a lack of understanding of its underlying mechanisms [37,38]. Furthermore, the interplay of comorbidities and immune dysregulation has been identified as critical in understanding the trajectory of long COVID, necessitating multidisciplinary approaches for effective management [39]. The absence of a standardized definition and clear prognostic factors perpetuates skepticism surrounding the condition, making it difficult to recognize

the debilitating effects of long COVID on quality of life [37]. Therefore, continued research is essential to bridge these gaps and enhance public understanding of this emerging health challenge.

Prolonged symptoms following viral infections, such as those seen in influenza and Epstein-Barr virus (EBV), exhibit notable similarities with long COVID, potentially leading to confusion among patients and healthcare providers. Both conditions are characterized by a range of persistent symptoms, including fatigue, cognitive impairment, and musculoskeletal pain, which can last for months or even years post-infection [40,41].

For instance, studies indicate that post-viral fatigue is a common feature in both long COVID and post-EBV conditions, with chronic symptoms reported in a significant percentage of affected individuals [41]. Furthermore, the pathophysiological mechanisms underlying these syndromes may overlap, involving immune dysregulation and systemic effects that complicate diagnosis and treatment [42]. The cumulative prevalence of long COVID symptoms is reported to be significantly higher than that of other post-viral syndromes; however, the symptomatology often overlaps, necessitating careful clinical evaluation to differentiate between these conditions [40,43].

Vivaldi [44] compared the long-term symptom profiles of SARS-CoV-2 and other acute respiratory infections (ARIs), highlighting the substantial and diverse symptom burden associated with both types of infections. Findings showed that both SARS-CoV-2 and non-COVID-19 ARIs resulted in a wide range of persistent symptoms and reductions in health-related quality of life (HRQoL). However, individuals with SARS-CoV-2 infection exhibited a significantly higher prevalence of certain symptoms compared to those with non-COVID-19 ARIs, including taste and smell disturbances, dizziness, hair loss, unusual sweating, heart palpitations, and memory problems.

Approximately 22% of participants with either SARS-CoV-2 or non-COVID-19 ARIs fell into the category of severe symptoms, underscoring the significant impact of these infections. Neurocognitive symptoms, such as memory problems and difficulty concentrating, were particularly prominent in individuals with SARS-CoV-2 infection. While some symptoms, including coughing and taste or smell disturbances, diminished after 12 weeks, others persisted, with more severe acute infections associated with a higher prevalence and intensity of ongoing symptoms.

Latent class analysis (LCA) identified three symptom severity clusters for SARS-CoV-2: mild (45%), moderate (32%), and severe (22%). Individuals in the severe group were characterized by a predominance of neurocognitive symptoms and were more likely to report suspected long COVID. Similar severity-based clusters were observed for non-COVID-19 ARIs, with some individuals in the severe category misattributing their symptoms to long COVID. These findings suggest that the severity of symptoms, rather than the type of infection, may be a critical determinant of long-term impact.

The study emphasizes the need for greater recognition and understanding of long-term sequelae associated with both SARS-CoV-2 and other ARIs. Persistent symptoms following non-COVID-19 ARIs may be underdiagnosed, highlighting the importance of extending research and clinical attention beyond long COVID. While the study underscores the value of severity-based symptom clusters in informing clinical care and predicting recovery trajectories, it also calls for further investigation into the mechanisms underlying these conditions to improve diagnosis and treatment.

The study's strengths include its large, community-based cohort, which captured a broad spectrum of infection severities, and the use of a contemporaneous control group to contextualize findings. However, limitations such as reliance on self-reported symptoms, potential recall bias, and the lack of pathogen-specific data for non-COVID-19 ARIs should be addressed in future research. Overall, the findings highlight the extensive reach of long COVID and the overlooked burden of other respiratory infections, underscoring the need for comprehensive approaches to post-acute care.

3.6. Implications for Diagnosis and Treatment

Differentiating long COVID from other similar syndromes poses significant challenges for healthcare providers and patients, impacting the perceived legitimacy of the condition. Long COVID is characterized by a diverse array of persistent symptoms affecting multiple organ systems,

complicating diagnosis, as these symptoms often overlap with those of other post-viral syndromes, such as chronic fatigue syndrome (ME/CFS) [45,46]. The presence of comorbidities and immune dysregulation further blurs the lines, as autoantibodies and cytokine imbalances can mimic or exacerbate symptoms of other conditions [39]. This diagnostic ambiguity can lead to skepticism regarding the legitimacy of long COVID, as patients may struggle to have their experiences validated within the medical community [46].

The lack of diagnosis and recognition of long COVID can have far-reaching consequences. Patients may encounter significant challenges in accessing appropriate healthcare and support, leading to delays in treatment and prolonged recovery processes. Furthermore, the absence of robust epidemiological data on the prevalence and burden of long COVID hinders the development of targeted interventions and resource allocation, ultimately impacting the overall public health response [11].

Moreover, the evolving nature of diagnostic criteria and the reliance on subjective evidence from patients contribute to the ongoing debate regarding long COVID's recognition as a distinct clinical entity, necessitating further research and multidisciplinary approaches for effective management [47,48]. Scientific evidence underscores the urgent need for increased awareness, improved diagnostic tools, and the development of comprehensive healthcare strategies to address the challenges posed by long COVID [39,48].

4. Concluding Remarks

The literature observations, in this study, underscore the inherent complexity of long COVID, both in terms of its clinical definition and its broader social and public health implications. As a multifaceted condition, long COVID encompasses a wide range of persistent symptoms affecting multiple body systems, complicating diagnosis and clinical management. The lack of specific biomarkers and standardized diagnostic criteria contributes to underreporting and hinders recognition of its severity, particularly in populations with limited access to healthcare services.

Public perception of long COVID emerges as a critical factor influencing both the pursuit of medical care and adherence to treatment. However, conflicting information, misinformation, and stigma continue to negatively affect how this condition is understood and managed. This situation underscores the need for educational campaigns designed to enhance understanding of long COVID, reduce stigma, and promote early diagnosis and effective treatment.

Furthermore, the similarities between long COVID and other post-viral syndromes, such as those associated with Epstein-Barr virus and influenza, highlight the challenges faced by healthcare providers and patients in differentiating these conditions. This overlap may impact the perceived legitimacy of long COVID, restricting adequate resource allocation for its management. Investment in research aimed at exploring distinctive features and underlying pathophysiological mechanisms is essential to overcome these barriers.

The knowledge gaps identified emphasize the need of collaborative efforts to develop multidisciplinary approaches that integrate biomedical research, health policies, and educational interventions. Such efforts have the potential to improve clinical management of long COVID and strengthen healthcare systems in addressing similar conditions.

Finally, the data highlight that effectively addressing the implications of long COVID requires actions that extend beyond the medical realm, incorporating social and economic dimensions. Investments in public awareness, psychological support, and workplace adaptations can mitigate the prolonged impact of the disease and promote a more comprehensive recovery for affected individuals. It is imperative to continue exploring the intersections between research, clinical practice, and public policy to tackle the challenges posed by long COVID effectively.

Abbreviations

The following abbreviations are used in this manuscript:

MDPI Multidisciplinary Digital Publishing Institute

DOAJ	Directory of open access journals
TLA	Three letter acronym
LD	Linear dichroism
WHO	Whorld Health Organization
PASC	Post-COVID syndrome
CT scan	Computed tomography scan
EBV	Epstein-Bar Virus
ARIs	Acute respiratory infections
HRQoL	Health-related quality of life
LCA	Latent class analysis
ME/CFS	Mialgic encephalomyelitis/chronic fatigue syndrome

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