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Review Article

Long-term pulmonary and extra-pulmonary consequences of COVID-19: A comprehensive review of current evidence and future perspectives

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Abstract

The global impact of the coronavirus disease 2019 (COVID-19) pandemic has been significant, affecting countless individuals worldwide. The existence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to considerable levels of illness and mortality. While considerable attention has been devoted to the immediate handling of COVID-19, there is a growing concern about the long-term effects of this disease. The recent studies have brought to light various complexities associated with COVID-19, encompassing both respiratory and non-respiratory problems such as lung scarring, heart diseases, neurological effects, and psychological consequences. The purpose of this review is to provide a comprehensive understanding of the persistent repercussions of COVID-19. It presents a summary of recent studies that have examined the frequency and severity of these complications, as well as an exploration of the potential mechanisms that contribute to their development. Specifically, it delves into the role of immune dysregulation, prolonged inflammation, and dysfunction of blood vessel linings in the origin of these complications. Moreover, the clinical significance of these long-term consequences is discussed, including their potential impact on healthcare systems and society as a whole. Our review highlights the necessity for continuous monitoring and management of patients diagnosed with COVID-19, along with the importance of conducting follow-up studies over an extended period to determine the most effective strategies for prevention and treatment of these complications.

Keywords: COVID-19, consequence, SARS-CoV-2, pulmonary, complication

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent responsible for the ongoing coronavirus disease 2019 (COVID-19) pandemic, has had a significant and far-reaching impact on global health. Its influence has been experienced worldwide, with millions of documented cases and hundreds of thousands of deaths [1]. While the initial focus has been on effectively addressing and mitigating the immediate consequences of COVID-19, concerns have arisen regarding the potential long-term effects of this disease. Recent investigations have unveiled various complications associated with COVID-19 that extend well beyond the respiratory system. These complications encompass pulmonary fibrosis, cardiovascular ailments,

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neurological manifestations, and even psychological repercussions [2-5]. The emerging body of evidence emphasizes the necessity for a comprehensive understanding of the multi-organ impact of this illness, necessitating ongoing research and proactive measures to tackle its long-term consequences.

The primary aim of this extensive review is to present a thorough analysis of the existing evidence concerning the extended pulmonary and extra-pulmonary consequences resulting from COVID-19. Recent research findings that have shed light on the occurrence and severity of these complications were consolidated, and the potential mechanisms that contribute to their emergence were delved. Specifically, the involvement of immune dysregulation, chronic inflammation, and endothelial dysfunction in the development of these complications were examined.

Pulmonary consequences

COVID-19 can give rise to various pulmonary complications, encompassing pulmonary fibrosis, restrictive and obstructive lung disease, pulmonary vascular disease, chronic cough, and dyspnea [2, 6-9]. Pulmonary fibrosis is a prevalent consequence of COVID-19, with certain studies indicating a prevalence rate of up to 50% among survivors [6, 10]. It can lead to permanent scarring of lung tissue, resulting in diminished lung function and breathlessness. Restrictive and obstructive lung disease may also manifest, impeding the capacity of the lungs to expand or contract and causing breathing difficulties. Furthermore, COVID-19 can provoke pulmonary vascular disease, such as pulmonary embolism, due to its association with hypercoagulability [7]. Chronic cough and dyspnea are likewise widespread, with certain studies reporting that these symptoms persist in up to 60% of individuals who have recovered from COVID-19 [11].

Pulmonary fibrosis

Pulmonary fibrosis, a recognized complication of COVID-19, can potentially manifest within a few weeks following the initial illness, as supported by available evidence [12]. In a study involving 113 patients, it was discovered that 33% exhibited radiological indications of pulmonary fibrosis on chest computed tomography (CT) scans three months after being discharged [13]. Another study, which involved 70 patients and conducted chest CT scans six months post-discharge, found that 40% displayed signs of pulmonary fibrosis [14]. Moreover, postmortem examinations have revealed evidence of pulmonary fibrosis in individuals who succumbed to COVID-19 [15]. These findings strongly suggest that pulmonary fibrosis represents a significant long-term complication resulting from COVID-19.

Restrictive and obstructive lung disease

COVID-19 can cause both restrictive and obstructive lung disease [16]. A study of 1,655 COVID-19 patients found that 17.5% had restrictive lung disease and 11.2% had obstructive lung disease on pulmonary function tests three months post-discharge [17]. Another study of 57 COVID-19 patients found that 35% had reduced diffusion capacity, a measure of gas exchange in the lungs [18]. These findings suggest that COVID-19 can result in significant long-term lung function abnormalities.

Pulmonary vascular disease

COVID-19 has been associated with the development of pulmonary vascular disease, such as pulmonary embolism [19]. A study of 1,288 COVID-19 patients found that 20% had evidence of pulmonary embolism on chest CT scans [18]. Another study of 184 COVID-19 patients found that 20% had evidence of pulmonary vascular disease on pulmonary angiography [20]. These findings suggest that COVID-19 can result in significant long-term vascular complications in the lungs.

Chronic cough and dyspnea

COVID-19 has the potential to induce enduring symptoms, such as a lingering cough and difficulty breathing, even among individuals who experienced a mild or asymptomatic infection [21]. A research investigation involving 143 individuals who had contracted COVID-19 revealed that 44% of them experienced persistent symptoms, including coughing, shortness of breath, and

fatigue, even three months after being discharged [22], while another study, which observed 177 COVID-19 patients, discovered that 50% of them continued to experience persistent symptoms one year after being discharged [23].These findings strongly indicate that COVID-19 can lead to significant and prolonged respiratory complications. An overview of the lasting pulmonary effects resulting from COVID-19 is provided in **Table 1**.

Table 1. Long-term pulmonary consequences of COVID-19

Consequences	Prevalence (range)	Severity	Mechanisms	Sources
Pulmonary fibrosis	4–13%	Moderate-severe	Dysregulated immune response, inflammation	[21, 24, 25]
Pulmonary hypertension	Unknown	Unknown	Endothelial dysfunction	[26]
Chronic obstructive pulmonary disease (COPD)	Unknown	Unknown	Airway injury, inflammation, fibrosis	[2]
Diffusion impairment	10–30%	Mild-moderate	Alveolar damage, inflammation	[27, 28]
Chronic fatigue syndrome	Unknown	Moderate-severe	Unknown	[29]

Extra-pulmonary consequences

COVID-19 has the potential to cause various complications beyond the lungs, encompassing cardiovascular disease, neurological effects, and psychological consequences [3, 4, 30-33]. Among these complications, cardiovascular disease stands out as a significant concern in COVID-19, particularly for older individuals with pre-existing cardiovascular conditions, as it can lead to myocardial injury, arrhythmias, and heart failure [30, 34]. Additionally, neurological sequelae, including stroke, encephalopathy, and peripheral neuropathy, have been observed and likely attributed to the neurotropic nature of the SARS-CoV-2 virus [4, 31, 35].

Cardiovascular disease

Numerous investigations have documented an elevated susceptibility to cardiovascular complications in individuals suffering from COVID-19. These complications comprise myocardial injury, arrhythmias, and thromboembolic events [36, 37]. In a comprehensive analysis involving a substantial number of hospitalized COVID-19 patients, it was observed that approximately 20% of the patients exhibited signs of myocardial injury, which in turn correlated with an increased mortality risk [38]. Although the precise mechanisms underlying the cardiovascular complications associated with COVID-19 are not entirely elucidated, potential factors include direct viral-induced damage to the myocardium, endothelial dysfunction, and hypercoagulability [39].

Neurological sequelae

Neurological symptoms frequently occur in individuals diagnosed with COVID-19, encompassing manifestations like headaches, dizziness, confusion, and impaired cognition [35]. Numerous studies have further documented heightened instances of severe neurological complications, including stroke, encephalitis, and Guillain-Barré syndrome [40, 41]. Although the precise mechanisms behind COVID-19-related neurological complications are still not entirely comprehended, potential factors could involve direct viral invasion, hypoxia, immune-mediated harm, or thromboembolic incidents [42].

Psychological impacts

COVID-19, along with the accompanying isolation and quarantine protocols, can exert considerable psychological effects on patients, healthcare professionals, and the overall populace. Numerous studies have documented elevated levels of anxiety, depression, and post-traumatic stress disorder among individuals afflicted with COVID-19 as well as healthcare workers [36, 37]. Furthermore, the societal and economic upheaval resulting from the pandemic may engender enduring impacts on mental well-being [38]. An overview of the enduring non-pulmonary consequences of COVID-19 is provided in **Table 2**.

Table 2. Long-term extra-pulmonary consequences of COVID-19

Consequences	Severity	Mechanisms	Sources
Cardiovascular complications	Moderate-severe	Inflammation, endothelial dysfunction, hypercoagulability	[35, 39, 40]
Neurological complications	Moderate-severe	Neuroinflammation, microvascular injury, hypercoagulability	[41-43]
Renal complications	Moderate-severe	Direct viral infection, endothelial dysfunction, hypercoagulability	[44-46]
Gastrointestinal complications	Moderate-severe	Direct viral infection, inflammation, endothelial dysfunction	[22, 47, 48]
Hematological complications	Moderate-severe	Hypercoagulability, inflammation, direct viral infection	[35, 49, 50]
Psychological complications	Moderate-severe	Stress, anxiety, depression, post-traumatic stress disorder	[18, 51, 52]
Endocrine complications	Moderate-severe	Direct viral infection, inflammation, endothelial dysfunction	[53-55]
Musculoskeletal complications	Mild-moderate	Immobility, inflammation, myopathy	[56, 57]
Skin manifestations	Mild-moderate	Immune dysregulation, direct viral infection, inflammation	[58, 59]

Pathogenesis of long-term consequences

The etiology of long-term pulmonary and extra-pulmonary complications in COVID-19 is intricate and likely encompasses immune dysregulation, persistent inflammation, and dysfunction of the endothelium [60-63].

An unbalanced immune response to SARS-CoV-2 infection can give rise to a cytokine storm, which induces systemic inflammation and damage to multiple organs [60]. Prolonged inflammation can also lead to tissue damage and scarring, contributing to the development of pulmonary fibrosis and other enduring complications [61]. Endothelial dysfunction, characterized by injury to the lining of blood vessels, can result in blood clot formation and vascular complications [60, 61].

Immune dysregulation

Immune deregulation, recognized as one of the primary mechanisms implicated in the emergence of long-lasting complications arising from COVID-19, is characterized by an excessive inflammatory response, distinguished by increased cytokine production and activation of immune cells, including T cells and macrophages. This dysregulation of the immune system can lead to tissue damage and fibrosis, ultimately resulting in enduring complications such as pulmonary fibrosis [2, 26-29].

Numerous investigations have explored the connection between immune deregulation and persistent pulmonary outcomes linked to COVID-19. Huang *et al.* [14] conducted a study that revealed a correlation between elevated levels of cytokines like IL-6, IL-8, and TNF-alpha and the development of pulmonary fibrosis in individuals severely affected by COVID-19. Similarly, studies indicating that increased levels of cytokines such as IL-6 and IL-8 were associated with the emergence of pulmonary vascular disease in patients with COVID-19 [28, 29, 36-38].

Chronic inflammation

Chronic inflammation has been implicated in the onset of long-lasting complications resulting from COVID-19. The excessive inflammatory reaction observed in COVID-19 can persist beyond the acute phase of the illness, leading to persistent inflammation and subsequent harm to tissues. This persistent inflammation is linked to the progression of pulmonary fibrosis, cardiovascular disease, and other enduring complications [41].

Numerous studies have examined the association between persistent inflammation and long-term complications stemming from COVID-19. Huang *et al.* [43] conducted a study that unveiled a connection between heightened levels of C-reactive protein (CRP), an indicator of inflammation, and the development of pulmonary fibrosis in patients with severe COVID-19. Similarly, Wang *et al.* established a link between elevated CRP levels and the occurrence of cardiovascular disease in patients with COVID-19 [45].

Endothelial dysfunction

Endothelial dysfunction, characterized by injury to the inner lining of blood vessels, has also been implicated in the emergence of long-term complications of COVID-19. COVID-19 can cause direct harm to endothelial cells, as well as triggering the coagulation system and the release of pro-inflammatory cytokines, resulting in endothelial dysfunction and damage to the blood vessels. This can lead to pulmonary vascular disease, cardiovascular disease, and other enduring complications [43].

Multiple studies have documented the correlation between endothelial dysfunction and persistent complications arising from COVID-19. According to a study conducted by Libby and Lüscher, an examination of lung tissue from individuals who died from COVID-19 revealed significant damage to the blood vessel lining and the formation of blood clots [44]. Similarly, Zhang *et al.* conducted a study that showed COVID-19 patients had elevated levels of markers associated with endothelial dysfunction, such as von Willebrand factor and soluble thrombomodulin. These markers were found to be linked to the development of pulmonary vascular disease [51].

Implications of long-term COVID-19

The long-term consequences of COVID-19 have significant implications for patients, healthcare systems, and society. The impact on healthcare systems is substantial, with the potential for a large number of patients requiring ongoing management for long-term complications [64]. Societal impacts include the potential loss of productivity and increased healthcare costs associated with managing these complications.

For patients, the long-term effects of COVID-19 can be profound, with many experiencing ongoing symptoms and disability that significantly impact their quality of life. The psychological impacts of COVID-19 and its long-term effects should not be underestimated. Many survivors report ongoing anxiety, depression, and post-traumatic stress disorder [2].

The potential for long-term complications underscores the need for comprehensive follow-up care for patients with COVID-19. As the pandemic continues, healthcare providers must be prepared to manage a large number of patients with ongoing health needs. The development of new treatment strategies and clinical guidelines for managing long-term complications will be critical for optimizing patient outcomes [14].

One important consideration for managing long-term complications is the need for multidisciplinary care. Patients may require input from a range of healthcare professionals, including respiratory therapists, physiotherapists, occupational therapists, and mental health professionals. Close collaboration between healthcare providers will be essential for providing holistic care and optimizing patient outcomes [16].

Additionally, there are significant ramifications for public health policy. The enduring consequences of COVID-19 emphasize the necessity of continuous surveillance and monitoring of disease prevalence and occurrence. Precise data regarding the lasting consequences of COVID-19 will be crucial in guiding public health policy decisions and distributing resources effectively [12, 13, 63, 64].

Ultimately, the enduring impacts of COVID-19 emphasize the requirement for sustained investment in research to gain a deeper comprehension of the development of these complications and to identify effective measures for prevention and treatment. Conducting comprehensive, large-scale studies over an extended period will be indispensable in identifying individuals at the highest risk of long-term complications and devising targeted interventions to mitigate their effects [11, 30, 31].

Impacts on healthcare system

The long-term pulmonary and extra-pulmonary complications of COVID-19 have significant implications for healthcare systems. As patients recover from acute COVID-19, they may continue to require medical care for ongoing complications [22, 45, 46, 48]. This may include pulmonary rehabilitation, cardiovascular risk reduction, and psychological support. The burden of caring for these patients could place a strain on healthcare systems already stretched thin by the pandemic [47].

Societal impacts

In addition to the impacts on healthcare systems, the long-term consequences of COVID-19 also have significant societal implications. Many patients may experience disability or decreased quality of life due to ongoing symptoms and complications [49]. This could have a ripple effect on families, communities, and the economy as a whole. Moreover, the psychological impacts of COVID-19 could have a lasting effect on individuals and society at large [48].

Management of long-term consequences

Pulmonary rehabilitation

Individuals afflicted with COVID-19 have the potential to experience pulmonary fibrosis, a condition that may result in long-lasting respiratory issues and diminished ability to engage in physical activity. The implementation of pulmonary rehabilitation has shown promise in enhancing the ability to partake in exercise, alleviating breathlessness, and enhancing overall quality of life for these patients. In a recent investigation, it was discovered that a pulmonary rehabilitation program lasting twelve weeks demonstrated significant advancements in exercise capacity and breathlessness among individuals with pulmonary fibrosis arising after a COVID-19 infection [50].

Cardiovascular risk reduction

COVID-19 is linked to a heightened likelihood of cardiovascular disease, encompassing myocardial injury, myocarditis, and thrombotic incidents. It is imperative to effectively address cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, in these individuals. Moreover, administering anticoagulation therapy may be crucial to avert thrombotic events. A recent investigation revealed a correlation between anticoagulation therapy and reduced risk of mortality during hospitalization in COVID-19 patients with elevated D-dimer levels [35].

Psychological support

COVID-19 can exert substantial psychological effects on patients, encompassing anxiety, depression, and post-traumatic stress disorder. The provision of psychological support, such as cognitive-behavioral therapy and mindfulness-based stress reduction, could prove beneficial for these individuals. A recent investigation revealed that an internet-based cognitive-behavioral therapy initiative exhibited efficacy in alleviating symptoms of anxiety and depression among individuals recuperating from COVID-19 [51].

Future perspectives

Ongoing monitoring and follow-up studies

Conducting long-term follow-up studies is essential for comprehending the complete range of pulmonary and extra-pulmonary implications caused by COVID-19. These studies play a critical role in recognizing individuals with the highest vulnerability to developing these complications and guiding the creation of preventive and management approaches. Numerous ongoing investigations are currently in progress, such as the COVID-19 Host Genetics Initiative, which endeavors to identify genetic elements linked to disease susceptibility and outcomes [18].

Development of prevention and treatment strategies

There is a critical necessity for the implementation of effective strategies to diminish the enduring consequences of COVID-19. Current inquiries are focused on the creation of vaccinations and antiviral remedies that can prevent and cure COVID-19, while concurrently exploring efficient methodologies to address the long-lasting complexities associated with this ailment. It is noteworthy to mention that recent studies have uncovered that respiratory rehabilitation possesses the ability to amplify pulmonary function and improve the overall welfare of individuals affected by COVID-19 [52].

Importance of global cooperation and funding

Global collaboration and financial support play a vital role in combatting COVID-19 and its enduring ramifications. The World Health Organization has emphasized the need for enhanced investment in research and development to gain a deeper understanding of pathogenesis of COVID-19 and to devise efficient strategies for prevention and treatment [53]. It is imperative for researchers and healthcare providers worldwide to collaborate closely in order to tackle the intricate challenges brought about by this pandemic.

Conclusion

In conclusion, COVID-19 is a complex ailment that can give rise to a variety of lasting respiratory and non-respiratory complications. These complications carry significant implications for patients, healthcare systems, and society as a whole. The development of these complications involves the disruption of the immune system, chronic inflammation, and dysfunction of the endothelial cells. Consequently, continuous monitoring and management of patients diagnosed with COVID-19 are necessary.

To mitigate the long-term consequences of COVID-19, it is imperative to establish strategies for prevention and management. Among these strategies, pulmonary rehabilitation, reduction of cardiovascular risks, and provision of psychological support hold promise in ameliorating the enduring effects of this disease.

Furthermore, it is vital to conduct follow-up studies on an ongoing basis to identify individuals who are at the highest risk of experiencing long-term complications and to develop effective strategies for prevention and treatment. Global cooperation and funding are indispensable in these endeavors, as they are crucial for addressing the enduring impact of COVID-19 on global health. Ultimately, the development of efficient prevention and treatment strategies will help diminish the impact of COVID-19 on both individuals and society.

Ethics approval

Not required.

Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

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