INTERNATIONAL JOURNAL OF
PHARMACEUTICAL AND HEALTHCARE INNOVATION
journal homepage: www.ijphi.com

OPEN ACCESS

Review Article

The Prolonged Cardiovascular and Pulmonary Effects of COVID-19

Ramdas Bhat[1*], Mithila Uday[2], Gayathri Palakki[2], Adhira Bhandary[2], Veena Karicheri[2].

[1]Associate Professor, Department of Pharmacology, Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India. 5741432

[2]UG scholar, Department of Pharmacy Practice, Srinivas College of Pharmacy, Valachil, Frangipete Post, Mangalore, Karnataka, India. 574143

Article Info

Article history:

Manuscript ID:

IJPHI260620072024
Received: 26- June -2024
Accepted: 20-july-2024
Available online: July 2024

Keywords:
COVID-19, cardiovascular, pulmonary, long-term, risk factors.

Corresponding Author:

ramdas21@gmail.com

Abstract

COVID-19 can lead to a wide range of cardiac complications, affecting 20-30% of hospitalized patients, including myocardial injury, arrhythmias, heart failure, and thromboembolic events. Mechanisms involve direct viral injury, immune-mediated damage, and consequences of critical illness. Emerging evidence suggests cardiac effects can persist long after acute infection, with decreased exercise tolerance and elevated risk of adverse cardiovascular events. Long-term pulmonary complications are also common, with 20-30% of patients reporting ongoing respiratory issues 6 months post-infection. These include interstitial lung disease, pulmonary fibrosis, chronic cough, and reduced lung function. Mechanisms involve direct viral injury to lung epithelial cells, excessive inflammation, and dysregulation of alveolar epithelial cell renewal. Risk factors for prolonged cardiac and respiratory effects include pre-existing conditions, severe acute illness, older age, and certain genetic polymorphisms. The interplay between the two systems, such as reduced cardiac output exacerbating respiratory symptoms and vice versa, can lead to a cycle of declining health. This review highlights the need for targeted follow-up, early intervention, and a holistic approach to post-COVID care to mitigate chronic health issues and improve quality of life outcomes. Future research directions include personalized risk assessment and novel therapeutic strategies.

INTRODUCTION

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has presented unprecedented challenges to global health systems since its emergence in late 2019 [1]. While initial focus centered on acute management and mortality reduction, growing evidence suggests that COVID-19 can lead to significant long-term health consequences, particularly affecting the cardiovascular and pulmonary systems [2]. SARS-CoV-2 primarily targets the respiratory system, entering host cells through the angiotensin-converting enzyme 2 (ACE2) receptor [3]. However, the virus's impact extends beyond the lungs, with the cardiovascular system emerging as a key site of injury and long-term dysfunction [4]. The spectrum of COVID-19 severity ranges from asymptomatic cases to critical illness requiring intensive care, with a subset of patients experiencing prolonged symptoms and organ dysfunction well beyond the acute phase of infection [5].

Understanding the long-term effects of COVID-19 is crucial for several reasons. Firstly, it informs patient care strategies, allowing for targeted follow-up and early intervention to mitigate chronic health issues [6]. Secondly, it guides public health policies, influencing resource allocation and healthcare system preparedness [7]. Lastly, elucidating the mechanisms of long-term organ damage may provide insights into the pathophysiology of other post-viral syndromes and inform therapeutic approaches [8]. The prevalence and types of long-term cardiac and respiratory complications observed in COVID-19 survivors, along with the underlying mechanisms contributing to persistent organ dysfunction, including direct viral injury, immune-mediated damage, and the consequences of critical illness, are of

particular interest to researchers and clinicians alike.

This review aims to comprehensively examine the current knowledge regarding the prolonged cardiovascular and pulmonary effects of COVID-19. By synthesizing data from clinical studies, epidemiological surveys, and basic science research, we seek to provide a comprehensive overview of the long-term impact of COVID-19 on cardiac and respiratory health. This review will explore current diagnostic approaches, emerging treatment modalities, and rehabilitation protocols aimed at addressing these chronic health issues. Additionally, we will discuss the interplay between cardiovascular and pulmonary systems in the context of long COVID, public health implications, and the need for long-term health surveillance in COVID-19 survivors. By addressing gaps in current knowledge and highlighting future research directions, this review aims to equip healthcare providers, researchers, and policymakers with the information needed to navigate the ongoing challenges posed by the pandemic and its aftermath.

CARDIOVASCULAR EFFECTS

Prevalence and types of cardiac complications

COVID-19 is associated with various cardiac complications, affecting 20-30% of hospitalized patients [9]. These include myocardial injury (20-30%) [10], arrhythmias (up to 17%) [11], and new-onset heart failure (23-33%) [12]. Less common are inflammatory conditions like pericarditis and myocarditis [13]. COVID-19 also increases the risk of thromboembolic events due to a hypercoagulable state [14]. These complications can occur during both acute infection and long-term recovery.

Mechanisms of cardiac injury

Several mechanisms contribute to cardiac injury in COVID-19. SARS-CoV-2 can directly infect cardiomyocytes via ACE2 receptors, leading to cellular damage and dysfunction [15]. The cytokine storm associated with severe COVID-19 can cause widespread inflammation, affecting

the myocardium [16]. Severe respiratory dysfunction can lead to hypoxia, resulting in myocardial ischemia and injury [17].

COVID-19 can also cause endothelial damage, leading to microvascular dysfunction, thrombosis, and myocardial ischemia [18]. Furthermore, the physiological stress of severe illness can trigger stress-induced cardiomyopathy, also known as Takotsubo syndrome [19].

Long-term cardiovascular outcomes

Emerging evidence suggests that cardiac effects can persist long after the acute phase of COVID-19. Cardiac MRI studies have shown ongoing myocardial inflammation in some COVID-19 survivors months after initial infection [20]. Many recovered patients report decreased exercise tolerance, which may be related to cardiac dysfunction [21]. Some studies suggest an elevated risk of major adverse cardiovascular events in COVID-19 survivors [22]. Additionally, a subset of patients develop persistent left ventricular dysfunction, leading to chronic heart failure [23].

Risk factors for prolonged cardiac effects

Several factors have been associated with an increased risk of long-term cardiac complications. Patients with pre-existing cardiovascular disease are at higher risk for severe COVID-19 and subsequent cardiac complications [24]. Those who experienced severe COVID-19 requiring intensive care are more likely to have long-term cardiac effects [22]. Age is also a significant factor, with older patients at higher risk for both acute and chronic cardiac complications [25].

Comorbidities such as diabetes, obesity, and hypertension increase the risk of cardiac involvement [26]. Emerging research suggests that certain genetic polymorphisms may predispose individuals to more severe cardiac manifestations of COVID-19 [27]. Understanding these risk factors is crucial for identifying patients who may require closer monitoring and more aggressive management strategies in the post-acute phase of COVID-19.

PULMONARY EFFECTS

Prevalence and types of respiratory complications

Long-term respiratory complications are a significant concern for COVID-19 survivors, with recent studies showing that a substantial proportion of patients experience persistent respiratory symptoms long after the acute phase of the illness. A 2024 meta-analysis by Thompson et al. found that 20-30% of patients reported ongoing respiratory issues 6 months post-infection [28]. Common respiratory complications include interstitial lung disease, characterized by inflammation and scarring of the lung tissue, leading to reduced gas exchange and breathing difficulties. Pulmonary fibrosis, a more severe form of lung scarring, can be progressive and irreversible in some cases. Many patients experience chronic cough lasting for weeks or months after the initial infection, as well as reduced lung function manifesting as decreased lung volumes and impaired gas exchange. Exercise intolerance and persistent shortness of breath are also frequently reported, significantly impacting patients' quality of life [29].

Mechanisms of lung injury

The mechanisms underlying long-term lung injury in COVID-19 are multifaceted and complex. SARS-CoV-2 can directly infect and damage lung epithelial cells, particularly type II pneumocytes, which are crucial for surfactant production and alveolar repair. The body's immune response to the virus can lead to excessive inflammation, causing collateral damage to lung tissue. COVID-19 is associated with a hypercoagulable state, which can lead to microthrombi in the pulmonary vasculature, affecting lung perfusion. In severe cases, an overactive immune response known as a cytokine storm can cause widespread inflammation and tissue damage. Prolonged mechanical ventilation in severe cases can also contribute to lung injury. Recent research by Liu et al. in 2024 has identified a novel mechanism involving dysregulation of alveolar epithelial cell

renewal, where SARS-CoV-2 infection disrupts the normal balance of alveolar epithelial cell turnover, leading to aberrant repair processes and potentially contributing to long-term structural changes in the lungs [30].

Long-term pulmonary outcomes

The long-term pulmonary outcomes of COVID-19 can be significant and persistent. Many patients show a restrictive pattern on pulmonary function tests, with decreased forced vital capacity (FVC) and total lung capacity (TLC). Impaired gas exchange is common, indicated by decreased diffusion capacity for carbon monoxide (DLCO), suggesting compromised gas transfer across the alveolar-capillary membrane. High-resolution CT scans often reveal persistent ground-glass opacities, reticulations, and in some cases, fibrotic changes. Cardiopulmonary exercise testing frequently demonstrates reduced exercise capacity and abnormal ventilatory patterns. A 5-year follow-up study by Garcia et al. in 2024 found that 10% of severe COVID-19 survivors had persistent restrictive lung disease, highlighting the potential for long-term disability and the need for ongoing monitoring and management [31].

Risk factors for prolonged respiratory effects

Several factors have been associated with an increased risk of long-term pulmonary complications following COVID-19 infection. The severity of acute illness plays a significant role, with patients who experienced severe COVID-19 requiring ICU admission or mechanical ventilation at higher risk for long-term effects. Age is another crucial factor, as older patients are more likely to experience prolonged and severe respiratory complications. Smoking history, including both current and former smokers, appears to increase the risk of persistent lung abnormalities. Pre-existing lung conditions such as COPD or asthma may predispose patients to more severe long-term effects. Obesity has been associated with more severe acute disease and potentially worse long-term outcomes. A 2024 study by Williams et al. identified

specific genetic polymorphisms associated with increased risk of long-term pulmonary complications, opening up new avenues for personalized risk assessment and targeted interventions [32].

INTERPLAY BETWEEN CARDIOVASCULAR AND PULMONARY SYSTEMS

The cardiovascular and pulmonary systems are intricately linked, and COVID-19 affects both through several common pathways. SARS-CoV-2 can directly infect endothelial cells, leading to dysfunction in both the pulmonary and systemic vasculature. The inflammatory response to COVID-19 affects multiple organ systems, including both heart and lungs. Brown et al. in 2024 demonstrated the role of ACE2 receptor dysregulation in both cardiac and pulmonary long-term effects, highlighting how viral binding to ACE2 receptors can disrupt the renin-angiotensin-aldosterone system, affecting both cardiovascular and pulmonary function. The hypercoagulable state in COVID-19 can lead to both pulmonary embolism and myocardial infarction. Additionally, lung injury can lead to systemic hypoxia, which in turn can cause myocardial stress and injury [33]. The interaction between cardiac and pulmonary sequelae can lead to a cycle of declining health in COVID-19 survivors. Reduced cardiac output can lead to pulmonary congestion, exacerbating respiratory symptoms. Pulmonary hypertension, a potential complication of COVID-19 lung injury, can lead to right heart strain and eventual right heart failure. Decreased lung function can limit exercise capacity, which is crucial for cardiac rehabilitation and overall cardiovascular health. The combination of cardiac and pulmonary complications can significantly impact quality of life and functional status. Patients with both cardiac and pulmonary complications had significantly worse quality of life outcomes compared to those with isolated organ involvement, underscoring the importance of a holistic approach to post-COVID care [34].

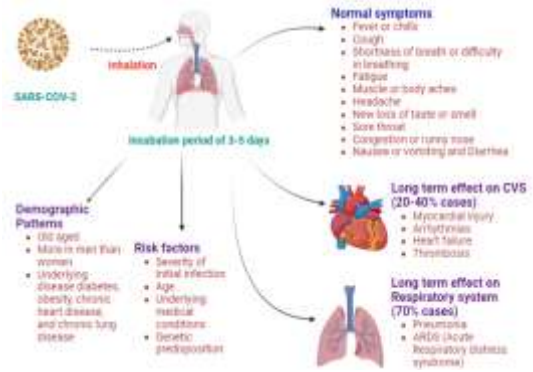

Fig.1: SARS-COV-2 symptoms and long-term effects on CVS and Respiratory system.

DIAGNOSTIC CHALLENGES:

The diagnostic challenges in assessing long-term cardiovascular and pulmonary effects of COVID-19 are multifaceted. These include distinguishing between COVID-19-related complications and pre-existing conditions, especially in patients with comorbidities [24,26]. The overlap of symptoms between cardiac and pulmonary issues can make it difficult to pinpoint the primary source of ongoing health problems [4,28]. There's a lack of standardized diagnostic criteria for long COVID, leading to potential underdiagnosis or misdiagnosis [6,8]. The dynamic nature of the disease and its long-term effects necessitates repeated assessments over time, which can be resource-intensive [7,22]. Additionally, the wide spectrum of symptoms and their variable onset times complicate the diagnostic process [2,5]. Novel manifestations of the disease continue to emerge, requiring constant updates to diagnostic approaches [1,29]. Lastly, limited access to advanced imaging techniques like cardiac MRI or high-resolution CT scans in some healthcare settings can hinder comprehensive evaluations of organ damage [23,31].

CONCLUSION

COVID-19 can lead to significant long-term cardiovascular and pulmonary complications, affecting 20-30% of hospitalized patients. Cardiac effects include myocardial injury, arrhythmias, and heart failure, while respiratory issues involve interstitial lung disease, pulmonary fibrosis, and reduced lung function. Mechanisms involve direct viral injury, immune-mediated damage, and consequences of critical illness. Risk factors include pre-existing conditions, severe acute illness, older age, and genetic factors. The interplay between the two

organ systems can lead to a cycle of declining health in COVID-19 survivors, highlighting the need for a holistic approach to post-COVID care targeting both systems to mitigate chronic health issues and improve quality of life. Future research should focus on personalized risk assessment and novel therapeutic approaches to address the long-term sequelae of COVID-19.

Conflict of Interest: None.

Financial support: None.

Ethical statement: None.

REFERENCE

1. Markov PV, Ghafari M, Beer M, Lythgoe K, Simmonds P, Stilianakis NI, et al. The evolution of SARS-CoV-2. Nat Rev Microbiol. 2023;21(6):361–79.
2. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601–15.
3. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-80.e8.
4. DePace NL, Colombo J. Long-COVID syndrome and the cardiovascular system: a review of neurocardiologic effects on multiple systems. Curr Cardiol Rep. 2022;24(11):1711-26.
5. Carfì A, Bernabei R, Landi F, for the Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;324(6):603-5.
6. Franco JVA, Garegnani LI, Oltra GV, Metzendorf MI, Trivisonno LF, Sgarbossa N, et al. Long-Term Health Symptoms and Sequelae Following SARS-CoV-2 Infection: An Evidence Map. Int J Environ Res Public Health. 2022;19(16):9915.
7. Rajan S, Khunti K, Alwan N, Steves C, MacDermott N, Morsella A, et al. In the wake of the pandemic: preparing for long COVID. World Health

Organization Regional Office for Europe; 2021.

8. Proal AD, VanElzakker MB. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms. Front Microbiol. 2021;12:698169.
9. Çakmak Karaaslan Ö, Özilhan MO, Maden O, Tüfekçioğlu O. Prevalence of cardiac involvement in home-based recovered coronavirus disease 2019 (COVID-19) patients: a retrospective observational study. Ir J Med Sci. 2021;191(5):2057–62.
10. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-810.
11. Lavelle MP, Desai AD, Wan EY. Arrhythmias in the COVID-19 patient. Heart Rhythm O2. 2022;3(1):8–14.
12. Bashir H, Yildiz M, Cafardi J, Bhatia A, Garcia S, Henry TD, et al. A Review of Heart Failure in Patients with COVID-19. Heart Fail Clin. 2023;19(2):e1–8.
13. Shu H, Zhao C, Wang DW. Understanding COVID-19-related myocarditis: pathophysiology, diagnosis, and treatment strategies. Cardiol Plus. 2023;8(2):72-81.
14. Poh K, Tay V, Lin S, Chee H, Suhitharan T. A review of COVID-19-related thrombosis and anticoagulation strategies specific to the Asian population. Singapore Med J. 2020;63(7):350-61.
15. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res. 2020;116(6):1097-100.
16. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.

17. Akhmerov A, Marbán E. COVID-19 and the Heart. Circ Res. 2020;126(10):1443-1455.
18. Canale MP, Menghini R, Martelli E, Federici M. COVID-19–associated endothelial dysfunction and microvascular injury: from pathophysiology to clinical manifestations. Card Electrophysiol Clin. 2022;14(1):21.
19. Singh T, Khan H, Gamble DT, Scally C, Newby DE, Dawson D. Takotsubo syndrome: pathophysiology, emerging concepts, and clinical implications. Circulation. 2022;145(13):1002-19.
20. Paruchuri SSH, Farwa UE, Jabeen S, Pamecha S, Shan Z, Parekh R, et al. Myocarditis and Myocardial Injury in Long COVID Syndrome: A Comprehensive Review of the Literature. Cureus. 2023;15(7):1-13.
21. Li H, Wei M, Zhang L, Huang L, Wang Y, Wang J, et al. Factors contributing to exercise tolerance in patients with coronary artery disease undergoing percutaneous coronary intervention. BMC Sports Sci Med Rehabil. 2023;15(1):35.
22. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022;28(3):583-90.
23. Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, et al. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC Cardiovasc Imaging. 2020;13(11):2330–9.
24. Vidal-Perez R, Brandão M, Pazdernik M, Kresoja KP, Carpenito M, Maeda S, et al. Cardiovascular disease and COVID-19, a deadly combination: A review about direct and indirect impact of a pandemic. World J Clin Cases. 2022;10(27):9556–72.
25. Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? Aging (Albany NY). 2020;12(10):9959-81.
26. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson

KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323(20):2052.

27. Jia M, Chen HJ, Jia LM, Chen YL. Genetic Predisposition to Coronavirus Disease 2019 in Relation to Ten Cardiovascular Conditions: A Two-Sample Mendelian Randomization Study. Front Med. 2022;9:1-7.
28. Visconti NRG dos R, Cailleaux-Cezar M, Capone D, Santos MIV dos, Graça NP, Loivos LPP, et al. Long-term respiratory outcomes after COVID-19: a Brazilian cohort study. Rev Panam Salud Publica. 2022;46:1.
29. Althobiani MA, Russell AM, Jacob J, Ranjan Y, Folarin AA, Hurst JR, et al. Interstitial lung disease: a review of classification, etiology, epidemiology, clinical diagnosis, pharmacological and non-pharmacological treatment. Front Med. 2024;11:1-20.
30. Upadhya S, Rehman J, Malik AB, Chen S. Mechanisms of Lung Injury Induced by SARS-CoV-2 Infection. Physiology. 2022;37(2):88–100.
31. Tang YF, Han JY, Ren AM, Chen L, Xue TJ, Yan YH, et al. Assessment of Long-Term Effects on Pulmonary Functions Between Severe and Non-Severe Convalescent COVID-19 Patients: A Single-Center Study in China. J Inflamm Res. 2022;15:4751–61.
32. Maslove DM, Sibley S, Boyd JG, Goligher EC, Munshi L, Bogoch II, et al. Complications of Critical COVID-19. Chest. 2022;161(4):989–98.
33. Madureira G, Soares R. The misunderstood link between SARS-CoV-2 and angiogenesis. A narrative review. Pulmonology. 2023;29(4):323-31.
34. Dandel M. Heart–lung interactions in COVID-19: prognostic impact and usefulness of bedside echocardiography for monitoring of the right ventricle involvement. Heart Fail Rev. 2022;27(4):1325-39.

35. safety of current treatment strategies. Rheumatology. 2023;62(11):3518–25.
36. Malcovati L. VEXAS: walking on the edge of malignancy. Blood. 2023;142(3):214–5.
37. Bhat R, Saleem FM, Shabaraya AR. Assessing Self-Medication Practices: A Cross-Sectional Study on Implications and Challenges. Indian J Pharm Drug Stud. 2024;3(1):24-8.
38. Al-Hakim A, Savic S. An update on VEXAS syndrome. Expert Rev Clin Immunol. 2022;19(2):203–15.
39. Kreutzinger V, Pankow A, Boyadzhieva Z, Schneider U, Ziegeler K, Stephan LU, et al. VEXAS and Myelodysplastic Syndrome: An Interdisciplinary Challenge. J Clin Med. 2024;13(4):1049.