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Long-term covid outcomes and cardiovascular health: New pandemic after the pandemic?

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Abstract

The COVID-19 pandemic has had lasting global health effects, with many survivors experiencing persistent symptoms known as long COVID. Cardiovascular complications, including myocarditis, arrhythmias, and thromboembolic events, are among the most severe. However, the pathophysiology, risk factors, and optimal management strategies remain unclear, posing significant challenges for healthcare systems.

Studies estimate that 10–70% of COVID-19 survivors experience long-term symptoms, with cardiovascular manifestations among the most prevalent. Large cohort studies report increased risks of hypertension, heart failure, and major adverse cardiovascular events post-infection. Mechanisms such as viral persistence, immune dysregulation, endothelial dysfunction, and microvascular thrombosis are implicated. Retrospective and prospective analyses show an elevated incidence of myocardial infarction and stroke among COVID-19 survivors, particularly those hospitalized. Despite growing awareness, there are no standardized clinical guidelines for diagnosing or managing long COVID-related cardiovascular conditions.

Long COVID presents a substantial public health burden, particularly due to its cardiovascular effects. There is an urgent need for systematic screening, long-term monitoring, and targeted interventions to mitigate risks. Future research should focus on defining diagnostic criteria, identifying at-risk populations, and developing effective treatment strategies to improve post-COVID patient outcomes.

Keywords: Long COVID; Cardiovascular complications; Myocarditis; Arrhythmias; Thromboembolic events

1. Introduction

The COVID-19 pandemic has left a lasting impact on global health and economies, disrupting healthcare systems and causing significant mortality worldwide. By November 2023, over 770 million cases and nearly 7 million deaths had been reported globally by the World Health Organization (WHO), with Ukraine alone recording more than 5.5 million cases and over 100,000 deaths [1-2]. However, it is likely that these figures underestimate the true extent of the pandemic, particularly in regions with limited diagnostic capabilities and in populations where asymptomatic cases are common [3-5].

Since the early stages of the pandemic, the rate of recovery has risen substantially, driven by improvements in medical treatment, effective public health measures, and the rollout of preventive vaccinations [6]. This progress has given hope that the global healthcare system has managed to control the acute phase of the virus. Nevertheless, as more individuals recover from COVID-19, it has become evident that the virus can lead to persistent health issues, manifesting as long-

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term, systemic, and organ-specific complications. These post-acute conditions are emerging as a complex global health problem for the 21st century [6-8].

Studies show that many people who have survived COVID-19, including those with mild or asymptomatic cases, continue to experience a range of persistent symptoms, impacting their cardiovascular, pulmonary, neurological, and general health [9-10]. These long-lasting effects extend well beyond the initial infection period, influencing the quality of life for a considerable number of patients and posing new challenges for healthcare systems [3, 11].

Research indicates that between 10-15% [12] and up to 50-70% [13] of COVID-19 survivors report symptoms that last for six months, a year, or even longer. Cardiovascular symptoms, including chest pain, heart palpitations, and shortness of breath, are among the most common. Despite substantial ongoing research, gaps remain in our understanding of the epidemiology, diagnosis, and prevention of these cardiovascular complications. This is partly due to an incomplete understanding of the physiological and morphological changes that occur in the post-COVID state [6]. Moreover, the field lacks systematic data, unified terminology, and clinical definitions that can guide diagnosis and treatment.

Current research efforts are focused on understanding the pathophysiological mechanisms of long COVID, identifying high-risk groups, and developing effective prevention and treatment strategies. By addressing these challenges, healthcare systems can better respond to the ongoing burden of this "pandemic after the pandemic."

2. Results and discussion

2.1. Long COVID: Definition and Key Clinical Manifestations

For some individuals, COVID-19 can lead to prolonged health issues that significantly impact quality of life. According to data from the UK Office for National Statistics, approximately one in five people who tested positive for COVID-19 experienced persistent symptoms for five weeks or more. By January 2023, around 2 million individuals in the United Kingdom (3.1% of the population) reported ongoing symptoms that could not be attributed to other causes [14].

The terms “long COVID,” “post-COVID syndrome,” and “post-COVID conditions” emerged in public and medical discussions even before their official recognition. This development underscores the undeniable reality of prolonged health disturbances that persist even after the acute phase of the SARS-CoV-2 infection [15]. To support improved healthcare delivery and harmonize epidemiological and clinical research, the World Health Organization (WHO) introduced a provisional clinical definition for “long COVID” in October 2021. According to the WHO, long COVID is a condition experienced by patients with a history of probable or confirmed SARS-CoV-2 infection, which develops at least three months after the onset of symptoms, lasts for a minimum of two months, and cannot be explained by other diagnoses [16].

The UK’s National Institute for Health and Care Excellence (NICE) distinguishes between ongoing symptomatic COVID-19 (lasting between 4 and 12 weeks) and post-COVID syndrome (beyond 12 weeks) [17]. In contrast, the Centers for Disease Control and Prevention (CDC) in the United States refers to these cases as “post-COVID conditions,” encompassing symptoms that persist for at least four weeks after infection [18]. Some researchers further divide the post-acute phase into pre-12 months post-infection (post-COVID) and long COVID (lasting over a year) [3]. Despite differences in terminology and definitions, the general consensus is that common long COVID symptoms include fatigue, breathlessness, and cognitive dysfunction. These manifestations can be severe, leading to reduced physical capability and an inability to return to work, school, or normal daily activities [19].

Recent studies over the past two years indicate that long COVID is a multifaceted condition with diverse symptoms, including neurological, neuropsychiatric, pulmonary, gastrointestinal, and cardiovascular issues [20]. Among the most frequently reported neurological and neuropsychiatric symptoms are fatigue (29-58%), headaches (10-44%), and anxiety or depression (22-28%) [9, 21-22]. Pulmonary symptoms, such as shortness of breath or difficulty breathing (21-24%) and loss of taste or smell (12-15%), are also common among long COVID patients [23].

Cardiovascular manifestations include tachycardia, palpitations, chest pain [3], newly identified arrhythmias, heart failure, orthostatic hypotension, sustained hypertension [24], postural orthostatic tachycardia syndrome [25], myocarditis, pulmonary hypertension, and other potentially severe conditions [12].

The extensive number of symptoms reported after COVID-19 has prompted large-scale cohort, prospective, retrospective, and population-controlled studies aimed at understanding the clinical progression of long COVID, identifying at-risk patient groups, and developing strategies to manage these long-term effects. For example, the

German cohort study CORONA-MONITORING local (CoMoLo), which tracked participants over 452 days, found significant differences in quality of life and health indicators between those with confirmed or clinically suspected SARS-CoV-2 infection and those who were never infected [26]. In a large cohort study involving the US Department of Veterans Affairs (DVA) and its healthcare database, long-term cardiovascular outcomes in COVID-19 survivors included hypertension, arrhythmias (particularly tachycardia), circulatory disorders, chest pain, coronary artery atherosclerosis, and heart failure [27-28]. Notably, these cardiovascular conditions were more prevalent in hospitalized COVID-19 patients compared to non-hospitalized patients [27].

In another cohort study, patients who survived the first 30 days post-COVID-19 were at increased risk of cardiovascular disease for 12 months, including thrombotic complications (stroke, transient ischemic attack), arrhythmias (atrial fibrillation, sinus tachycardia or bradycardia, ventricular arrhythmias), pericarditis/myocarditis, ischemic heart disease (acute coronary syndrome, ischemic cardiomyopathy, angina), other conditions (acute or chronic heart failure, non-ischemic cardiomyopathy), and thromboembolic disorders (pulmonary embolism, deep vein thrombosis) [29]. Retrospective studies have shown that both hospitalized and non-hospitalized patients had a higher incidence of major adverse cardiovascular events (MACE) within 30 days to 4 months post-COVID-19 [30]. Ongoing multicenter prospective studies, such as the COVID-HEART study in the UK, have already demonstrated associations between COVID-19 and myocardial injury, thrombotic complications, and elevated cardiac biomarkers [31].

Over 50 long-term symptoms of COVID-19 have been documented in various large-scale studies [9, 32], and in some cases, more than 100 symptoms have been reported [33]. It is estimated that up to 80% of patients may experience one or more persistent symptoms, with approximately 30% reporting ongoing symptoms up to six months post-infection [9, 34]. However, the sheer volume of research conducted to date is still insufficient. There are currently no standardized clinical guidelines or official documents that address the definition, symptoms, and diagnosis of long COVID, leaving issues related to prevention and treatment largely unexplored [3, 9].

Beyond the nonspecific complaints and symptoms recognized in the WHO's October 2021 definition of long COVID, studies also report more severe and life-threatening cardiovascular conditions (e.g., myocardial infarction, stroke, acute heart failure), which, although they may be considered separate clinical entities, should be viewed as complications or long-term consequences of COVID-19. The lack of clear terminology, classification, clinical characterization, and understanding of the pathogenesis of these processes, along with the inability to assess risk, underscores the need for effective prevention and treatment strategies. This gap in medical science and clinical practice must be addressed urgently.

2.2. Mechanisms of Long-Term Consequences of COVID-19: Current Insights

Our review of the literature identifies several potential mechanisms underlying the long-term effects of SARS-CoV-2 infection, highlighting the complex interplay of viral, immune, and systemic factors.

2.2.1. Viral Persistence

SARS-CoV-2 RNA has been detected in tissues weeks and even months after acute infection, suggesting that viral reservoirs may contribute to chronic immune activation. For instance, Nature reported that SARS-CoV-2 RNA persists in multiple anatomical sites, including the brain, up to 230 days post-symptom onset, without significant inflammation outside respiratory tissues [34-36]. Circulating spike antigens have been identified in 60% of long COVID patients up to 12 months after diagnosis, supporting the theory of residual viral activity [37]. This persistence may trigger prolonged inflammation through pathogen-associated molecular patterns (PAMPs), exacerbating systemic dysregulation [36-37].

2.2.2. Reactivation of Latent Viruses

Dormant viruses like Epstein-Barr virus (EBV) can be reactivated by COVID-19, leading to symptoms such as chronic fatigue and immune hyperactivation. Studies indicate higher antibody responses to herpesviruses in long COVID patients compared to uninfected individuals, underscoring the role of viral reactivation [13, 38-39].

2.2.3. Autoimmunity and Immune Dysregulation

Viral infections are known to induce autoimmunity, and SARS-CoV-2 has been linked to elevated levels of autoantibodies targeting receptors such as ACE2, β2-adrenergic, and muscarinic M2 receptors [40-43]. These autoantibodies may contribute to symptoms like arrhythmias, hypertension, and inflammation in long COVID. Additionally, autoantibodies targeting tissues, endothelial cells, and coagulation factors have been reported, suggesting that immune dysregulation plays a significant role [43]. However, some studies argue that autoimmunity may not be a universal driver of long COVID [44].

2.2.4. Chronic Inflammation and Tissue Damage

Persistent inflammation following SARS-CoV-2 infection is a key mechanism behind long COVID. DAMPs released during tissue injury can trigger a cascade of inflammatory responses, potentially leading to organ dysfunction. Elevated cytokines such as IL-1β, IL-6, and TNF have been documented, alongside increased levels of CCL11, which is associated with cognitive impairments [45-48]. These findings underscore the role of systemic inflammation in perpetuating long-term symptoms.

2.2.5. Microthrombosis and Coagulation Abnormalities

Formation of microthrombi in small blood vessels is a hallmark of both acute and long COVID, contributing to ischemia, organ damage, and systemic dysfunction. Long-term alterations in blood cell size and oxygen delivery parameters have also been observed, complicating recovery in some patients [49-50]. These findings suggest that targeting microvascular thrombosis could provide therapeutic benefits.

2.2.6. Endothelial Dysfunction

Damage to endothelial cells during SARS-CoV-2 infection may result in prolonged vascular complications, including atherosclerosis, hypertension, and coronary artery disease. Studies report reduced capillary density and impaired angiogenesis in long COVID patients up to 18 months post-infection, indicating sustained endothelial injury [50-52].

2.2.7. Gut Microbiome Alterations

SARS-CoV-2 infection disrupts gut microbiome diversity, reducing beneficial bacterial populations and enriching pathogenic species. This dysbiosis is associated with increased gut permeability, systemic inflammation, and immune dysregulation, potentially contributing to long COVID symptoms [52-55].

2.2.8. Neurological Dysregulation

Dysfunction in neurological regulation has been implicated in persistent symptoms such as limb weakness, seizures, and sensory abnormalities. These findings suggest that SARS-CoV-2 may disrupt neural pathways, leading to chronic functional deficits [56].

These mechanisms reflect the multifactorial nature of long COVID, with overlapping processes such as immune dysregulation, vascular damage, and viral persistence contributing to a wide spectrum of symptoms. Further research is essential to clarify these pathways and develop effective treatments to mitigate long-term outcomes.

3. Cardiovascular Diseases as Long-Term Consequences of COVID-19

Understanding the cardiovascular impacts of COVID-19 is crucial for identifying and managing the complications that may arise after the acute phase of the disease. Retrospective cohort studies from Hong Kong and the UK, as well as one-year follow-ups using echocardiography and biomarkers, have raised concerns about the prevalence of cardiovascular sequelae in COVID-19 survivors. These sequelae include myocardial injury, myocarditis, acute coronary syndrome, arrhythmias, heart failure, cardiomyopathies, and cardiogenic shock [57-58]. Research from the U.S. adult population further highlights an elevated risk of adverse cardiovascular events and increased all-cause mortality following the acute phase of COVID-19 [59].

COVID-19 has significant effects on the cardiovascular system, as demonstrated by numerous studies. Hypoxia-induced myocardial injury, microvascular damage, and venous thromboembolism are commonly reported complications, resulting in microvascular ischemia, pulmonary embolism, acute right ventricular failure, and left ventricular dysfunction [59]. The mechanisms underlying these effects remain incompletely understood, but understanding the cardiovascular impacts of COVID-19 is essential for effective management and treatment strategies.

3.1. Myocarditis and Pericarditis

Myocarditis and pericarditis are notable cardiovascular complications associated with COVID-19 [29, 60-63]. While some retrospective studies, such as one involving 196,992 adults in Israel, found no significant association between COVID-19 and these conditions [60], others report increased rates of myocarditis and pericarditis during the acute phase of the disease [61]. Persistent myocarditis has been observed as part of long COVID, with symptoms ranging from asymptomatic inflammation to life-threatening heart failure [62]. A study involving 153,760 COVID-19 patients found a higher risk of cardiovascular diseases, including myocarditis and pericarditis, within 30 days post-infection [63].

3.2. Cardiac Dysautonomia and Arrhythmias

Cardiac dysautonomia and arrhythmias are frequently reported in long COVID [25, 64]. Conditions such as postural orthostatic tachycardia syndrome (POTS) and sinus tachycardia are common manifestations. Dysautonomia, characterized by autonomic nervous system dysfunction, has been linked to chronic systemic inflammation caused by COVID-19, which may exacerbate sympathetic nerve activity and lead to cardiovascular complications [65].

3.3. Ischemic Myocardial Damage and Microvascular Diseases

COVID-19 is associated with ischemic myocardial damage and microvascular complications [66-68]. Hypoxia, endothelial dysfunction, and thrombosis contribute to myocardial ischemia and long-term heart issues. Studies highlight the role of preexisting conditions such as hypertension, diabetes, and chronic kidney disease in increasing susceptibility to ischemic injury [67]. Persistent myocardial damage and fibrosis are reported in COVID-19 survivors, underscoring the need for continued monitoring [68].

3.4. Myocardial Fibrosis

Myocardial fibrosis, characterized by excessive extracellular matrix protein deposition, has been identified in patients with mild COVID-19 who experience persistent cardiac symptoms [69-70]. Non-hospitalized individuals with chronic symptoms have also shown signs of myocardial fibrosis, which may contribute to long-term cardiovascular complications [70].

3.5. Cardiomyopathy

COVID-19 has been linked to various forms of cardiomyopathy, including stress-induced (Takotsubo) cardiomyopathy and right ventricular arrhythmogenic cardiomyopathy [71-72]. The virus-induced myocardial damage, combined with systemic inflammation, can exacerbate cardiac dysfunction.

3.6. Heart Failure and Dysfunction

Hypoxia and myocardial injury caused by COVID-19 can lead to heart failure. Long-term complications include myocardial fibrosis and systolic dysfunction, which are reported in a significant number of patients post-COVID-19 [60, 73].

3.7. New-Onset Hypertension

COVID-19 has been associated with the development of new-onset hypertension, particularly in older adults, men, and individuals with preexisting cardiovascular conditions [74-75]. Research highlights the need to identify risk factors and implement strategies to prevent long-term hypertension in COVID-19 survivors.

3.8. Pulmonary Hypertension

While the link between COVID-19 and pulmonary hypertension remains under investigation, severe respiratory infections associated with COVID-19 can lead to pulmonary hypertension as a secondary complication [76]. Understanding these connections is critical for managing long-term cardiopulmonary outcomes.

3.9. Stroke and Pulmonary Embolism

COVID-19 significantly increases the risk of stroke and pulmonary embolism, reflecting the virus's impact on cardiovascular and cerebrovascular systems [77-80]. Studies report a higher prevalence of pulmonary embolism among COVID-19 patients, correlating with disease severity [77]. COVID-19-associated coagulopathy and immune-mediated hyperinflammation further increase the risk of thromboembolic events [78].

4. Conclusion

The COVID-19 pandemic has had profound global consequences, significantly impacting public health and continuing to do so. Symptoms persisting after recovery from acute SARS-CoV-2 infection have reached a scale now described as the "pandemic after the pandemic." In response, the WHO introduced the term "long COVID" in 2021, alongside related terms such as "post-COVID" and "post-COVID syndrome." However, these definitions remain vague, with no standardized diagnostic criteria, diagnostic methods, or treatment approaches for the long-term effects of COVID-19. This underscores the urgent need for further research into these areas.

Pathogenetic mechanisms contributing to long COVID are actively being studied, with notable progress in understanding links between health disorders and viral persistence, reactivation of latent pathogens, immune system dysregulation, autoimmunity, and microvascular thrombotic and endothelial dysfunctions. These findings represent complementary theories of the pathogenesis of long COVID, rather than contradictory ones, yet a unified concept explaining the condition remains elusive. Numerous large-scale studies emphasize the importance of focusing on cardiovascular consequences of COVID-19. These include myocarditis, pericarditis, acute and chronic heart failure, acute and chronic coronary syndromes, hypertension, arrhythmias, pulmonary embolism, cerebrovascular disorders, and cardiomyopathies. Considering the prevalence of cardiovascular diseases and their leading role in global mortality, these processes pose a significant threat to healthcare systems worldwide in the post-pandemic era.

Understanding the relationship between COVID-19 and cardiovascular diseases by elucidating the pathogenetic mechanisms, identifying risk factors and high-risk groups is essential. Only through this can we improve prevention and treatment strategies for cardiovascular complications of COVID-19 and achieve effective control over these processes on a global scale.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Lenz C, Slack MP, Shea KM, Reinert RR, Taysi BN, Swerdlow DL. Long-Term effects of COVID-19: A review of current perspectives and mechanistic insights. Crit Rev Microbiol. 2023;1-14. https://doi.org/10.1080/1040841x.2023.2190405

[2] World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Available from: https://covid19.who.int/. Accessed November 2, 2023.

[3] Lippi G, Sanchis-Gomar F, Henry BM. COVID-19 and its long-term sequelae: what do we know in 2023. Pol Arch Intern Med. 2023;16402. https://doi.org/10.20452/pamw.16402

[4] Lippi G, Mattiuzzi C, Henry BM. Uncontrolled confounding in COVID-19 epidemiology. Diagnosis. 2022;10(2):200-202. https://doi.org/10.1515/dx-2022-0128

[5] Msemburi W, Karlinsky A, Knutson V, Aleshin-Guendel S, Chatterji S, Wakefield J. The WHO estimates of excess mortality associated with the COVID-19 pandemic. Nature. 2023;613(7942):130-137. https://doi.org/10.1038/s41586-022-05522-2

[6] Kim Y, Bae S, Chang HH, Kim SW. Long COVID prevalence and impact on quality of life 2 years after acute COVID-19. Sci Rep. 2023;13(1):11207. https://doi.org/10.1038/s41598-023-36995-4

[7] Heidemann C, Sarganas G, Du Y, Gaertner B, Poethko-Müller C, Cohrdes C, et al. Long-term health consequences among individuals with SARS-CoV-2 infection compared to individuals without infection: results of the population-based cohort study CoMoLo Follow-up. BMC Public Health. 2023;23(1):1587. https://doi.org/10.1186/s12889-023-16524-8

[8] Hallek M, Adorjan K, Behrends U, Ertl G, Suttorp N, Lehmann C. Post-COVID syndrome. Dtsch Arztebl Int. 2023;120(4):48. https://doi.org/10.3238/arztebl.m2022.0409

[9] Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep. 2021;11(1):16144. https://doi.org/10.21203/rs.3.rs-266574/v1

[10] Jacobson KB, Rao M, Bonilla H, Subramanian A, Hack I, Madrigal M, et al. Patients with uncomplicated coronavirus disease 2019 (COVID-19) have long-term persistent symptoms and functional impairment similar to patients with severe COVID-19: a cautionary tale during a global pandemic. Clin Infect Dis. 2021;73(3):e826-e829. https://doi.org/10.1093/cid/ciab103

[11] Munblit D, Nicholson T, Akrami A, Apfelbacher C, Chen J, De Groote W, et al. A core outcome set for post-COVID-19 condition in adults for use in clinical practice and research: an international Delphi consensus study. Lancet Respir Med. 2022;10(7):715-724. https://doi.org/10.1016/S2213-2600(22)00169-2

[12] Nalbandian A, Desai AD, Wan EY. Post-COVID-19 condition. Annu Rev Med. 2023;74:55-64. https://doi.org/10.1146/annurev-med-043021-030635

[13] Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023;21(3):133-146. https://doi.org/10.1038/s41579-022-00846-2

[14] Bosworth MP, D. A. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 2 February 2023. Office for National Statistics. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/2february2023. Accessed February 2, 2023.

[15] Callard F, Perego E. How and why patients made Long Covid. Soc Sci Med. 2021;268:113426. https://doi.org/10.1016/j.socscimed.2020.113426

[16] Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis. 2022;22(4):e102-e107. https://doi.org/10.1016/s1473-3099(21)00703-9

[17] Shah W, Heightman M, O'Brien S. UK guidelines for managing long-term effects of COVID-19. Lancet. 2021;397(10286):1706. https://doi.org/10.1016/s0140-6736(21)00847-3

[18] Centers for Disease Control and Prevention. Post-Covid Conditions: Information for Healthcare Providers. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html. Accessed November 10, 2023.

[19] Parhizgar P, Yazdankhah N, Rzepka AM, Chung KYC, Ali I, Fur RLF, et al. Beyond acute COVID-19: A review of long-term cardiovascular outcomes. Can J Cardiol. 2023. https://doi.org/10.1016/j.cjca.2023.01.031

[20] Lai YJ, Liu SH, Manachevakul S, Lee TA, Kuo CT, Bello D. Biomarkers in long COVID-19: A systematic review. Front Med. 2023;10:1085988. https://doi.org/10.3389/fmed.2023.1085988

[21] Han, Q., Zheng, B., Daines, L., & Sheikh, A. (2022). Long-term sequelae of COVID-19: a systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. Pathogens, 11(2), 269. https://doi.org/10.3390/pathogens11020269

[22] Huang, L., Li, X., Gu, X., Zhang, H., Ren, L., Guo, L., ... & Cao, B. (2022). Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. The Lancet Respiratory Medicine, 10(9), 863-876. https://doi.org/10.1016/s2213-2600(22)00126-6

[23] Natarajan, A., Shetty, A., Delanerolle, G., Zeng, Y., Zhang, Y., Raymont, V., ... & Phiri, P. (2023). A systematic review and meta-analysis of Long COVID symptoms. Systematic reviews, 12(1), 1-19. https://doi.org/10.1186/s13643-023-02250-0

[24] Mitrani, R. D., Dabas, N., & Goldberger, J. J. (2020). COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors. Heart rhythm, 17(11), 1984-1990. https://doi.org/10.1016/j.hrthm.2020.06.026

[25] Blitshteyn, S., & Whitelaw, S. (2021). Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. Immunologic research, 69(2), 205-211. https://doi.org/10.1007/s12026-021-09185-5

[26] Heidemann, C., Sarganas, G., Du, Y., Gaertner, B., Poethko-M‚Äö√†√∂¬¨¨,à´ller, C., Cohrdes, C., ... & Scheidt-Nave, C. (2023). Long-term health consequences among individuals with SARS-CoV-2 infection compared to individuals without infection: results of the population-based cohort study CoMoLo Follow-up. BMC Public Health, 23(1), 1587. https://doi.org/10.1186/s12889-023-16524-8

[27] Al-Aly, Z., Xie, Y., & Bowe, B. (2021). High-dimensional characterization of post-acute sequelae of COVID-19. Nature, 594(7862), 259-264. https://doi.org/10.1038/s41586-021-03553-9

[28] St‚Äö√†√∂ohlberg, M., Reistam, U., Fedorowski, A., Villacorta, H., Horiuchi, Y., Bax, J., ... & Maisel, A. (2021). Post-COVID-19 tachycardia syndrome: a distinct phenotype of post-acute COVID-19 syndrome. The American journal of medicine, 134(12), 1451-1456. https://doi.org/10.1016/j.amjmed.2021.07.004

[29] Xie, Y., Xu, E., Bowe, B., & Al-Aly, Z. (2022). Long-term cardiovascular outcomes of COVID-19. Nature medicine, 28(3), 583-590. https://doi.org/10.1038/s41591-022-01689-3

[30] Logue, J. K., Franko, N. M., McCulloch, D. J., McDonald, D., Magedson, A., Wolf, C. R., & Chu, H. Y. (2021). Sequelae in adults at 6 months after COVID-19 infection. JAMA network open, 4(2), e210830-e210830. https://doi.org/10.1001/jamanetworkopen.2021.0830

[31] Stuber, M., & Baggish, A. L. (2023). Acute Myocardial Injury in the COVID-HEART Study: Emphasizing Scars While Reassuring Scares. Circulation, 147(5), 375-377. https://doi.org/10.1161/circulationaha.122.062508

[32] Hayes, L. D., Ingram, J., & Sculthorpe, N. F. (2021). More than 100 persistent symptoms of SARS-CoV-2 (long COVID): a scoping review. Frontiers in Medicine, 8, 750378. https://doi.org/10.3389/fmed.2021.750378

[33] Chen, C., Haupert, S. R., Zimmermann, L., Shi, X., Fritsche, L. G., & Mukherjee, B. (2022). Global prevalence of post-coronavirus disease 2019 (COVID-19) condition or long COVID: a meta-analysis and systematic review. The Journal of infectious diseases, 226(9), 1593-1607. https://doi.org/10.1093/infdis/jiac136

[34] Chen, B., Julg, B., Mohandas, S., & Bradfute, S. B. (2023). Viral persistence, reactivation, and mechanisms of long COVID. Elife, 12, e86015. https://doi.org/10.7554/elife.86015

[35] Buonsenso, D., Martino, L., Morello, R., Mariani, F., Fearnley, K., & Valentini, P. (2023). Viral persistence in children infected with SARS-CoV-2: current evidence and future research strategies. The Lancet Microbe. https://doi.org/10.1016/s2666-5247(23)00115-5

[36] Buonsenso, D., Piazza, M., Boner, A. L., & Bellanti, J. A. (2022, May). Long COVID: A proposed hypothesis-driven model of viral persistence for the pathophysiology of the syndrome. In Allergy and Asthma Proceedings (Vol. 43, No. 3, p. 187). OceanSide Publications. https://doi.org/10.2500/aap.2022.43.220018

[37] Swank, Z., Senussi, Y., Manickas-Hill, Z., Yu, X. G., Li, J. Z., Alter, G., & Walt, D. R. (2023). Persistent circulating severe acute respiratory syndrome coronavirus 2 spike is associated with post-acute coronavirus disease 2019 sequelae. Clinical Infectious Diseases, 76(3), e487-e490. https://doi.org/10.1093/cid/ciac722

[38] Viral reactivation and Long Covid. RTHM. (2023, October 20). https://rthm.com/articles/viral-reactivation-and-long-covid/

[39] Craddock V, Mahajan A, Spikes L, Krishnamachary B, Ram AK, Kumar A, Chen L, Chalise P, Dhillon NK. Persistent circulation of soluble and extracellular vesicle-linked Spike protein in individuals with postacute sequelae of COVID-19. J Med Virol. 2023 Feb;95(2):e28568. doi: 10.1002/jmv.28568

[40] Habibi, M. A., Nezhad Shamohammadi, F., Rajaei, T., Namdari, H., Pashaei, M. R., Farajifard, H., & Ahmadpour, S. (2023). Immunopathogenesis of viral infections in neurological autoimmune disease. BMC neurology, 23(1), 1-15. https://doi.org/10.1186/s12883-023-03239-x

[41] Su, Y., Yuan, D., Chen, D. G., Ng, R. H., Wang, K., Choi, J., ... & Heath, J. R. (2022). Multiple early factors anticipate post-acute COVID-19 sequelae. Cell, 185(5), 881-895. https://doi.org/10.1016/j.cell.2022.01.014

[42] Arthur, J. M., Forrest, J. C., Boehme, K. W., Kennedy, J. L., Owens, S., Herzog, C., ... & Harville, T. O. (2021). Development of ACE2 autoantibodies after SARS-CoV-2 infection. PloS one, 16(9), e0257016. https://doi.org/10.1371/journal.pone.0257016

[43] Wallukat, G., Hohberger, B., Wenzel, K., F,Äö√†√∂¬¨,à´rst, J., Schulze-Rothe, S., Wallukat, A., ... & M,Äö√†√∂¬¨,à´ller, J. (2021). Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. Journal of Translational Autoimmunity, 4, 100100. https://doi.org/10.1016/j.jtauto.2021.100100

[44] Wang, E. Y., Mao, T., Klein, J., Dai, Y., Huck, J. D., Jaycox, J. R., ... & Ring, A. M. (2021). Diverse functional autoantibodies in patients with COVID-19. Nature, 595(7866), 283-288. https://doi.org/10.1038/s41586-021-03631-y

[45] Klein, J., Wood, J., Jaycox, J., Dhodapkar, R. M., Lu, P., Gehlhausen, J. R., ... & Iwasaki, A. (2023). Distinguishing features of Long COVID identified through immune profiling. Nature, 1-3. https://doi.org/10.1101/2022.08.09.22278592

[46] Peluso MJ, Lu S, Tang AF, Durstenfeld MS, Ho HE, Goldberg SA, et al. Markers of immune activation and inflammation in individuals with postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection. J Infect Dis. 2021;224(11):1839-1848. doi:10.1093/infdis/jiab490.

[47] Schultheiü C, Willscher E, Paschold L, Gottschick C, Klee B, Henkes SS, et al. From online data collection to identification of disease mechanisms: the IL-1Œ≤, IL-6 and TNF-Œ± cytokine triad is associated with post-acute sequelae of COVID-19 in a digital research cohort. medRxiv. 2021. doi:10.1101/2021.11.16.21266391.

[48] Fern√°ndez-Casta√±eda A, Lu P, Geraghty AC, Song E, Lee MH, Wood J, et al. Mild respiratory SARS-CoV-2 infection can cause multi-lineage cellular dysregulation and myelin loss in the brain. bioRxiv. 2022. doi:10.1101/2022.01.07.475453.

[49] Pretorius E, Vlok M, Venter C, Bezuidenhout JA, Laubscher GJ, Steenkamp J, Kell DB. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. Cardiovasc Diabetol. 2021;20(1):1-18. doi:10.1186/s12933-021-01359-7.

[50] Ambrosino P, Sanduzzi Zamparelli S, Mosella M, Formisano R, Molino A, Spedicato GA, et al. Clinical assessment of endothelial function in convalescent COVID-19 patients: a meta-analysis with meta-regressions. Ann Med. 2022;54(1):3233-3248. doi:10.1080/07853890.2022.2136403.

[51] Patel MA, Knauer MJ, Nicholson M, Daley M, Van Nynatten LR, Martin C, et al. Elevated vascular transformation blood biomarkers in Long-COVID indicate angiogenesis as a key pathophysiological mechanism. Mol Med. 2022;28(1):122. doi:10.1186/s10020-022-00548-8.

[52] Osiaevi I, Schulze A, Evers G, Harmening K, Vink H, K√ºmpers P, et al. Persistent capillary rarefication in long COVID syndrome. Angiogenesis. 2023;26(1):53-61. doi:10.1007/s10456-022-09850-9.

[53] Xiang H, Liu QP. Alterations of the gut microbiota in coronavirus disease 2019 and its therapeutic potential. World J Gastroenterol. 2022;28(47):6689. doi:10.3748/wjg.v28.i47.6689.

[54] Sun Z, Song ZG, Liu C, Tan S, Lin S, Zhu J, et al. Gut microbiome alterations and gut barrier dysfunction are associated with host immune homeostasis in COVID-19 patients. BMC Med. 2022;20(1):24. doi:10.1186/s12916-021-02212-0.

[55] de Nies L, Galata V, Martin-Gallausiaux C, Despotovic M, Busi SB, Snoeck CJ, et al. Altered infective competence of the human gut microbiome in COVID-19. Microbiome. 2023;11(1):46. doi:10.1101/2022.10.20.512999.

[56] Teodoro T, Chen J, Gelauff J, Edwards MJ. Functional neurological disorder in people with long COVID: A systematic review. Eur J Neurol. 2023;30(5):1505-1514. doi:10.1111/ene.15721.

[57] Salamanna F, Veronesi F, Martini L, Landini MP, Fini M. Post-COVID-19 syndrome: the persistent symptoms at the post-viral stage of the disease. A systematic review of the current data. Front Med. 2021;392. doi:10.3389/fmed.2021.653516.

[58] Lam ICH, Wong CKH, Zhang R, Chui CSL, Lai FTT, Li X, et al. Long-term post-acute sequelae of COVID-19 infection: a retrospective, multi-database cohort study in Hong Kong and the UK. EClinicalMedicine. 2023;60. doi:10.1016/j.eclinm.2023.102000.

[59] Matejova G, Radvan M, Bartecku E, Kamenik M, Koc L, Horinkova J, et al. Cardiac sequelae after COVID-19: Results of a 1-year follow-up study with echocardiography and biomarkers. Front Cardiovasc Med. 2022;9:1067943. doi:10.3389/fcvm.2022.1067943.

[60] Czeisler M√â, Ibrahim SA. Cardiovascular Risks in Patients With Post-COVID-19 Condition. JAMA Health Forum. 2023;4(3):e224664-e224664. doi:10.1001/jamahealthforum.2022.4664.

[61] Fairweather, D., Beetler, D. J., Di Florio, D. N., Musigk, N., Heidecker, B., & Cooper Jr, L. T. (2023). COVID-19, myocarditis and pericarditis. Circulation research, 132(10), 1302-1319. https://doi.org/10.1161/circresaha.123.321878

[62] Tuvali, O., Tshori, S., Derazne, E., Hannuna, R. R., Afek, A., Haberman, D., ... & George, J. (2022). The incidence of myocarditis and pericarditis in post COVID-19 unvaccinated patients-a large population-based study. Journal of clinical medicine, 11(8), 2219. https://doi.org/10.3390/jcm11082219

[63] Rohun, J., Dorniak, K., Faran, A., Kocha,âà√ëska, A., Zacharek, D., & Dani,âà√áowicz-Szymanowicz, L. (2022). Long COVID-19 myocarditis and various heart failure presentations: a case series. Journal of Cardiovascular Development and Disease, 9(12), 427. https://doi.org/10.3390/jcdd9120427

[64] Chadda, K. R., Blakey, E. E., Huang, C. L. H., & Jeevaratnam, K. (2022). Long COVID-19 and postural orthostatic tachycardia syndrome-is dysautonomia to be blamed?. Frontiers in Cardiovascular Medicine, 9, 860198. https://doi.org/10.3389/fcvm.2022.860198

[65] Allendes, F. J., D,àö,â†az, H. S., Ortiz, F. C., Marcus, N. J., Quintanilla, R., Inestrosa, N. C., & Del Rio, R. (2023). Cardiovascular and autonomic dysfunction in long-COVID syndrome and the potential role of non-invasive therapeutic strategies on cardiovascular outcomes. Frontiers in Medicine, 9, 1095249. https://doi.org/10.3389/fmed.2022.1095249

[66] Izquierdo-Marquis,àö¬∞, A., Cubero-Gallego, H., Aparisi, ,àö√Ö., Vaquerizo, B., & Ribas-Barquet, N. (2022). Myocardial injury in COVID-19 and its implications in short-and long-term outcomes. Frontiers in Cardiovascular Medicine, 9, 901245. https://doi.org/10.3389/fcvm.2022.901245

[67] Bonow, R. O., Fonarow, G. C., O'Gara, P. T., & Yancy, C. W. (2020). Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA cardiology, 5(7), 751-753. https://doi.org/10.1001/jamacardio.2020.1105

[68] Puntmann, V. O., Martin, S., Shchendrygina, A., Hoffmann, J., Ka, M. M., Giokoglu, E., ... & Nagel, E. (2022). Long-term cardiac pathology in individuals with mild initial COVID-19 illness. Nature medicine, 28(10), 2117-2123. https://doi.org/10.1038/s41591-022-02000-0

[69] Krishnan, A., Ellenberger, K. A., Phetsouphanh, C., Kelleher, A. P., Matthews, G. V., Darley, D. R., & Holloway, C. J. (2022). Myocardial fibrosis occurs in non-hospitalised patients with chronic symptoms after COVID-19. International Journal of Cardiology. Heart & Vasculature, 39. https://doi.org/10.1016/j.ijcha.2022.100964

[70] Lampropoulos, C. E., Mavrogeni, S., Dervas, A., Manios, E., Chatzidou, S., Kontogiannis, C., ... & Papaioannou, I. (2021). Myocardial fibrosis after COVID-19 infection and severe sinus arrest episodes in an asymptomatic patient with mild sleep apnea syndrome: A case report and review of the literature. Respiratory Medicine Case Reports, 32, 101366. https://doi.org/10.1016/j.rmcr.2021.101366

[71] Omidi, F., Hajikhani, B., Kazemi, S. N., Tajbakhsh, A., Riazi, S., Mirsaeidi, M., ... & Nasiri, M. J. (2021). COVID-19 and cardiomyopathy: a systematic review. Frontiers in cardiovascular medicine, 8, 695206. https://doi.org/10.3389/fcvm.2021.695206

[72] Khalid, Y., Dasu, N., & Dasu, K. (2020). A case of novel coronavirus (COVID-19)-induced viral myocarditis mimicking a Takotsubo cardiomyopathy. HeartRhythm case reports, 6(8), 473-476. https://doi.org/10.1016/j.hrcr.2020.05.020

[73] Arrigo, M., Jessup, M., Mullens, W., Reza, N., Shah, A. M., Sliwa, K., & Mebazaa, A. (2020). Acute heart failure. Nature Reviews Disease Primers, 6(1), 16. https://doi.org/10.1038/s41572-020-0151-7

[74] Zhang, V., Fisher, M., Hou, W., Zhang, L., & Duong, T. Q. (2023). Incidence of new-onset hypertension post-COVID-19: comparison with influenza. Hypertension, 80(10), 2135-2148. https://doi.org/10.1161/hypertensionaha.123.21174

[75] Vyas, P., Joshi, D., Sharma, V., Parmar, M., Vadodariya, J., Patel, K., & Modi, G. (2023). Incidence and predictors of development of new onset hypertension post COVID-19 disease. Indian Heart Journal. https://doi.org/10.1016/j.ihj.2023.06.002

[76] Burger, C. D., DuBrock, H. M., Cartin-Ceba, R., Moss, J. E., Shapiro, B. P., & Frantz, R. P. (2021, December). Topic-based, recent literature review on pulmonary hypertension. In Mayo Clinic Proceedings (Vol. 96, No. 12, pp. 3109-3121). Elsevier. https://doi.org/10.1016/j.mayocp.2021.05.026

[77] Maron, B. A. (2023). Revised definition of pulmonary hypertension and approach to management: a clinical primer. Journal of the American Heart Association, 12(8), e029024. https://doi.org/10.1161/JAHA.122.029024

[78] Martin, A. I., & Rao, G. (2020). COVID-19: a potential risk factor for acute pulmonary embolism. Methodist DeBakey Cardiovascular Journal, 16(2), 155. https://doi.org/10.14797/mdcj-16-2-155

[79] Gul, M. H., Htun, Z. M., de Jesus Perez, V., Suleman, M., Arshad, S., Imran, M., ... & Morris, P. E. (2023). Predictors and outcomes of acute pulmonary embolism in COVID-19; insights from US National COVID cohort collaborative. Respiratory Research, 24(1), 1-12. https://doi.org/10.1186/s12931-023-02369-7

[80] Katsoularis, I., Fonseca-Rodr,àö,â†guez, O., Farrington, P., Jerndal, H., Lundevaller, E. H., Sund, M., ... & Connolly, A. M. F. (2022). Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19: nationwide self-controlled cases series and matched cohort study. bmj, 377. https://doi.org/10.1136/bmj-2021-069590