"WHAT'S TAKING SO LONG?"
WHAT WE KNOW ABOUT LONG COVID-19 SO FAR.

Richard II Dela Rosa[1]

[1]Master's student Molecular Mechanisms of Disease, Radboud university medical center, Nijmegen, the Netherlands

Abstract

Emerging cases of chronic illness after the acute phase of COVID-19, commonly called "Long COVID," have shed light on the long-term negative consequences of SARS-CoV-2 infections. There is increasing concern that even patients with mild initial symptoms may develop a variety of multiorgan symptoms with disabling consequences. Some groups of people appear to be more susceptible to persistent illness with risk factors including 1) higher age, 2) asthma, 3) low levels of certain immunoglobulins, and/or 4) multiple symptoms during primary SARS-CoV-2 infection. Among those affected with Long COVID, symptoms are commonly associated with the brain, lungs, and circulatory system. Due to the complex nature of Long COVID, treatment regimens mainly involve symptom management and burden alleviation. Therefore, it is crucial to uncover the pathophysiology and epidemiology of Long COVID to improve diagnostics, monitoring, treatment, and public health policies.

An increasing amount of people experience lingering symptoms after recovering from COVID-19, shedding light on the virus's real toll on the human body. Post-acute COVID-19 syndrome, commonly referred to as Long COVID, is defined as persistent complications beyond 4 weeks from the onset of symptoms [1]. Current estimates suggest that 10 to 25% of recovered patients with mild or severe COVID-19 symptoms experience some degree of chronic illness [2]. Months after recovery, a number of patients have not even regained pre-COVID-19 physical and mental capabilities due to significant symptom burden [3]. The persistence of long-term symptoms, some even debilitating, emphasizes that the negative consequences of SARS-CoV-2 infections go beyond acute symptoms, hospitalizations, and deaths.

Why does it happen and who is at risk?

There is insufficient information available to pinpoint the cause and pathophysiology of Long COVID. It is uncertain whether the virus persists in patients with Long COVID, or whether the long-term symptoms are caused by direct virus-induced damage to the organs during infection [4]. Some even suggest that Long Covid might be caused by indirect immune-related damage [4]. However, one of the leading theories is that SARS-CoV-2 infection can cause a hyperactive immune response which may trigger autoimmunity and other immune disorders [1, 5].

While the exact mechanisms of Long COVID are unknown, we do know that certain groups of people are more susceptible to these chronic symptoms. A 1-year cohort study showed that people with higher age, a history of asthma, low levels of certain immunoglobulins, and/or multiple symptoms during primary infection had an increased risk of Long COVID [6]. However, recent evidence indicates that vaccinations significantly reduce the risk of Long COVID [7]. A study of UK adults obtained self-reported data from previously recovered COVID-19 patients who are either fully vaccinated, partially vaccinated, or unvaccinated [8]. The findings show that individuals with full vaccinations from AstraZeneca, Janssen, Moderna, or Pfizer are 50% less likely to have COVID symptoms lasting 28 days post-infection compared to unvaccinated people [8]. Although breakthrough infections could still lead to Long COVID, it is clear that vaccinations are valuable beyond just preventing infections.

Although COVID-19 has often been described as a respiratory disease, Long COVID patients exhibit diverse symptoms affecting multiple organ systems [1, 9]. The following sections aim to give an overview of some of the most prominent organs affected by COVID-19 and current strategies employed to treat them. It should be pointed out that the following studies were performed in the context of different SARS-CoV-2 variant surges, so it remains unclear whether Long COVID risk is associated with different variants.

Brain

It has been reported that COVID-19 may affect both the brain's function and structure. Cognitive dysfunction occurs in an estimated 70% of people with Long COVID across multiple studies – making it one of the most common symptoms [2]. These cognitive issues manifest themselves through brain fog, reduced concentration, and/or memory loss [1]. It is important to note that most Long COVID studies only include self-reported results on cognitive issues, which may be susceptible to bias [2]. Thus, more research on quantifying cognition after the acute phase of COVID-19 is needed to provide more robust insights into Long COVID and its effects on cognition [2]. Moreover, the distinct loss of smell and taste symptoms in infected individuals can persist. Multiple studies observed that ~10% of hospitalized patients had impaired taste and smell six months after discharge [1]. This was similarly observed in home-isolated young adults aged 16-30 years in Norway, where 28% (17/61 individuals) had impaired loss of taste and smell after six months [10].

Interestingly, a recent longitudinal study involving UK Biobank participants (aged 51-81) sheds light on the possibility that COVID-19 influences brain structure [11]. Imaging analyses were conducted on 401 participants who had mild COVID-19 and they found that the overall brain size had decreased, ranging from 0.2% to 2.0% in participants [11]. Notably, affected parts of the brain included the grey matter in olfactory- and memory-associated regions and markers of tissue damage were found in regions connected to the

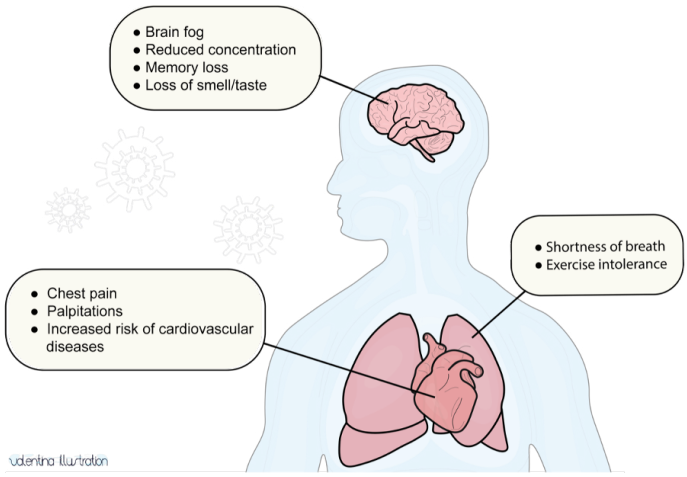

Figure 1: *Common Long COVID symptoms associated with the brain, lungs, and heart.*

primary olfactory cortex [11]. Since this was only an observational study, a causal relationship between the structural changes and cognitive dysfunction remains to be elucidated [12].

Lungs

SARS-CoV-2 infects cells along the respiratory system in the early stages of infection, while using them to replicate itself and spread quickly to other cells [13]. Shortness of breath, an initial symptom affecting the lungs, has been reported to linger even after testing virus negative in both hospitalized and non-hospitalized people [14]. However, health providers and researchers are puzzled to find that some Long COVID individuals who experience breathlessness test normally in routine tests such as computed tomography (CT) scans and lung function tests [15].

An initial small-scale study by Fergus Gleeson, a radiology professor at the University of Oxford, employed an uncommon method to check for lung abnormalities that are otherwise undetectable in Long COVID patients who had mild and severe symptoms [16]. Instead of using CT scans, a patient inhales a non-toxic gas called xenon, followed by a magnetic resonance imaging (MRI) scan [16]. This visualizes signs of lung damage by highlighting regions where gas exchange is inefficient [16]. Indeed, the detailed scans found that those who experienced breathlessness as a Long COVID symptom had impaired oxygen uptake compared to healthy controls [16]. Gleeson mentions that the degree of lung damage he saw in Long COVID patients was larger than anticipated [16, 17]. Moving forward, a larger study is being prepared to validate the findings and determine if the lung damage is irreversible or resolves over time [17].

For some people, however, lung problems post-COVID-19 manifest themselves only during strenuous activities, such as exercise. Among those who have persistent exercise intolerance after COVID-19, a study found that there was a significant reduction in peak oxygen consumption and also a hyper ventilatory response during exercise compared to healthy individuals [18].

Overall, it can be observed that insufficient oxygen consumption is a trend among individuals with Long COVID. As such, studies exploring exact mechanisms on how COVID-19 alters lung function are crucial to developing effective interventions.

Heart and circulatory system

Symptoms with cardiac origins have also been observed in Long COVID patients. In an international online survey of 3,762 patients who still had symptoms seven months after infection, ~86% of the respondents reported experiencing chest pains, palpitations, and/or fainting [19]. The high prevalence of cardiac symptoms in Long COVID patients led researchers to investigate underlying abnormalities in the heart and blood vessels. Although further research is needed, initial studies show that circulatory-related symptoms may be due to chronic inflammation, which damages nerve fibres that normally help control circulation or microscopic blood clots [9, 20]. Both these mechanisms reduce oxygen delivery to various tissues in the body, thus limiting aerobic capacity and causing severe fatigue [21].

Beyond chronic symptoms from COVID-19, a study involving a cohort of 153,760 individuals showed that individuals 30 days post-infection were at an increased risk of cardiovascular disease [22]. Compared to healthy controls, recently recovered individuals had higher incidence ratios of cardiovascular outcomes such as cerebrovascular disorders, dysrhythmias, pericarditis, myocarditis, heart failure, and thromboembolic disease [22]. Increased risks and burdens were apparent in both hospitalized and non-hospitalized individuals, although at different levels [22]. However, a concerning fact is that the risk was elevated even for those who are below 65 years and lacked risk factors such as obesity and diabetes [22, 23]. The findings of this large study can help healthcare providers in forming new protocols for COVID-19 aftercare, such as cardiovascular monitoring [22].

Treatments and interventions

Chronic illnesses after a viral infection are not unique to SARS-CoV-2, therefore Long COVID is not completely surprising. Better-known post-viral syndromes include Guillain-Barré syndrome and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), both associated with various viruses such as the Epstein-Barr virus and human immunodeficiency virus (HIV) [4, 24]. However, Long COVID-19 is unique due to the relatively high number of affected patients and its multi-organ involvement [4]. The diversity of symptoms and unknown mechanisms of Long COVID has made it difficult to develop effective drug treatments and evidence-based interventions [4].
At present, there is great emphasis on managing symptoms and increasing physical activity in affected individuals [25]. Diverse symptoms varying from patient to patient would need multiple specialists as well, which can be troublesome for both patients and health institutions. To address this problem, some have adopted an integrated approach to ensure more refined logistics and patient care through setting up centres for treatments that specialize in Long COVID [4]. In Radboudumc, for example, a COVID-19 aftercare outpatient clinic has been established to aggregate clinicians with different specialties [26]. This allows them to deploy tailor-made interventions to Long COVID patients and monitor for other symptoms as well [26].

Conclusion

As we enter the third year of the pandemic, we are beginning to witness the long-term effects of chronic illnesses associated with COVID-19. This article only tackled some of the most common organs that are affected in individuals with Long COVID. However, chronic symptoms have also been found to affect the gastrointestinal system, pancreas, and other organs [27, 28]. Aside from displaying immediate and noticeable symptoms, there is accumulating evidence that COVID-19 increases the risk for an array of conditions such as diabetes and ischemic attacks [22, 28].

Due to the complexity and multisystem involvement of Long COVID, we are left with more questions than answers regarding the nature of this condition. The rapid evolution of the virus and absent sequencing data from routine diagnostics make it difficult to study whether different variants are associated with different risks to develop Long COVID. Moreover, multiethnic and age representation need to be considered for future studies to reach more accurate and representative conclusions [29].

The emergence of Long COVID challenges the thought that this virus is just your common cold. Vaccines curb severe impacts of SARS-CoV-2 infection, but cases of Long COVID in breakthrough infections suggest that the effects of this pandemic are far from over. Albeit at different probabilities, it is still possible to develop Long COVID for both vaccinated and unvaccinated people. The sheer number of Long COVID cases and an increased risk for multiple diseases may aggravate the problems of already overstretched public health systems. It is therefore imperative to gain further understanding of the epidemiology of Long COVID and chronic health effects of SARS-CoV-2 infection. This may serve to improve health policies and adapt healthcare towards diagnosing and treating long-term patients effectively [4].

Acknowledgements

RAMS would like to thank Prof. dr. Ronald van Rij for providing feedback to the author of this article. RAMS would also like to thank Daphne Oligascher, BSc for reviewing this article.

References

1. Nalbandian, A., *et al.* Post-acute COVID-19 syndrome. *Nature Medicine* **27**, 601-615 (2021).
2. Guo, P., *et al.* COVCOG 2: Cognitive and Memory Deficits in Long COVID: A Second Publication From the COVID and Cognition Study. *Frontiers in Aging Neuroscience* **14**(2022).
3. Davis, H.E., *et al.* Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* **38**, 101019 (2021).
4. Anonymous. Meeting the challenge of long COVID. *Nature Medicine* **26**, 1803-1803 (2020).
5. Ducharme, J. Researchers Are Getting Closer to Understanding Long COVID. But Treatments Are Likely Still a Ways Off. *Time*. https://time.com/6153259/what-causes-long-covid/ (2022).
6. Cervia, C., *et al.* Immunoglobulin signature predicts risk of post-acute COVID-19 syndrome. *Nature Communications* **13**(2022).
7. Ducharme, J. Can Breakthrough Infections Lead to Long COVID? For an Unlucky Few, Yes. *Time*. https://time.com/6102534/breakthrough-infections-long-covid/ (2021).
8. Antonelli, M., *et al.* Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *The Lancet Infectious Diseases* **22**, 43-55 (2022).
9. Novak, P., *et al.* Multisystem Involvement in Post-Acute Sequelae of Coronavirus Disease 19. *Annals of Neurology* **91**, 367-379 (2022).
10. Blomberg, B., *et al.* Long COVID in a prospective cohort of home-isolated patients. *Nature Medicine* **27**, 1607-1613 (2021).
11. Douaud, G., *et al.* SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* (2022).
12. Morelle, R. Scans reveal how Covid may change the brain. *BBC News*. https://www.bbc.com/news/health-60591487 (2022).
13. Ni, W., *et al.* Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Critical Care* **24**(2020).
14. National Heart, L., And Blood Institute. COVID-19 and the Lungs. https://www.nhlbi.nih.gov/coronavirus (2021).
15. Press Association. Lung Abnormalities Found in Long Covid Patients With Breathing Issues. *Bloomberg*. https://www.bloomberg.com/news/articles/2022-01-29/long-covid-patients-with-breathing-issues-lung-abnormalities-now-found (2022).
16. Grist, J.T., *et al.* The Investigation of Pulmonary Abnormalities using Hyperpolarised Xenon Magnetic Resonance Imaging in Patients with Long-COVID. *medRxiv*. (ed.^(eds. (2022).
17. Ghosh, P. Covid-19: Lung damage 'identified' in study. *BBC News*. https://www.bbc.com/news/health-55017301 (2020).
18. Singh, I., *et al.* Persistent Exertional Intolerance After COVID-19. *Chest* **161**, 54-63 (2022).
19. Raman, B., *et al.* Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. *European Heart Journal* **43**, 1157-1172 (2022).
20. Pretorius, E., *et al.* Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. *Cardiovascular Diabetology* **20**(2021).
21. Keller, J. How Long Covid Exhausts the Body. *The New York Times*. https://www.nytimes.com/interactive/2022/02/19/science/long-covid-causes.html (2022).
22. Xie, Y., *et al.* Long-term cardiovascular outcomes of COVID-19. *Nature Medicine* ***28**, 583-590* (2022).
23. Sidik, S.M. https://www.nature.com/articles/d41586-022-00403-0. in *Nature News*, Vol. 602 (2022).
24. Westermeier, F., *et al.* Editorial: Current Insights Into Complex Post-infection Fatigue Syndromes With Unknown Aetiology: The Case of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Beyond. *Frontiers in Medicine* **9**(2022).
25. Anonymous. Long Covid: What is it and what are the symptoms? *BBC News*. https://www.bbc.com/news/health-57833394 (2022).
26. Anonymous. Meet Bram van der Borst. https://www.radboudumc.nl/verwijzers/nieuws/bram-van-den-borst (2022)
27. Weng, J., *et al.* Gastrointestinal sequelae 90 days after discharge for COVID-19. *The Lancet Gastroenterology & Hepatology* **6**, 344-346 (2021).
28. Narayan, K.M.V. & Staimez, L.R. Rising diabetes diagnosis in long COVID. *The Lancet Diabetes & Endocrinology* (2022).
29. Anonymous. Long COVID and kids: more research is urgently needed. *Nature*. https://www.nature.com/articles/d41586-022-00334-w (2022).