Manual Therapy, Posturology & Rehabilitation Journal
ISSN: 2236-5435

REVIEW

COVID-19 and lung function: a comprehensive review of long-term implications and therapeutic interventions

Luis F. R. Jacomossi-Oliveira[1], Miriã C. Oliveira[1], Isabela L. Costa[1], João P. R. Afonso[1], Adriano L. Fonseca[1], Shayra K. A. Souza[2], Bruna M. R. Silva[2], Aline C. Oliveira[1], Maria Eduarda M. Lino[1], Barbara O. Moura[1], Marilúcia M. Carrijo[1], Larissa R. Alves[1], Luís V. F. Oliveira[1], Rodolfo P. Vieira[1].

[1]Human Movement and Rehabilitation Post-Graduation Program, Evangelical University of Goiás - UniEVANGÉLICA, Anápolis (GO), Brazil.
[2]Scientific Initiation Program, Evangelical University of Goiás, (UniEVANGELICA), Anápolis (GO), Brazil.

ABSTRACT:

Background: As the scientific community grapples with the increasing symptomatology stemming from COVID-19, it is becoming increasingly evident that this systemic disease extends beyond its acute respiratory manifestations. While the world was still grappling with the immediate consequences of the pandemic, such as pneumonia, pulmonary thromboembolism, and heightened cardiovascular risk, a series of questions arose concerning the long-term sequelae. The mechanisms and implications of these sequelae remain elusive. **Objective:** This review explores the impact of COVID-19 on lung function and underscores the significance of thorough assessment and treatment for post-COVID-19 patients, often referred to as Post-Acute Sequelae of COVID-19 (PACS). COVID-19, caused by SARS-CoV-2, exerts its primary effects on the respiratory system and can lead to chronic complications affecting various organ systems. **Methods:** We carried out searches in three main databases and gray literature, in English, without date restrictions. **Results:** Lung function assumes a pivotal role, as a substantial number of patients report persistent dyspnea and other respiratory symptoms even after recovery from the acute infection. These lingering symptoms significantly impair patients' quality of life and functional capacity. This study underscores the necessity of precise assessments of lung function, encompassing pulmonary function tests and computed tomography scans, to identify abnormalities and guide treatment strategies. Moreover, we emphasize the vital role of therapeutic interventions and multidisciplinary rehabilitation programs aimed at enhancing the quality of life for PACS patients. **Final Considerations:** While there exist recommendations for post-COVID-19 rehabilitation, further research is imperative to validate the effectiveness of these interventions and establish a robust evidence base. In summary, this review underscores the enduring impact of COVID-19 on lung function and underscores the importance of individualized care and ongoing research efforts to cater to the needs of post-COVID-19 patients.

Keywords: COVID-19, lung function, post-COVID-19 sequelae.

Corresponding author: Rodolfo V Paula.
E-mail: rodrelena@yahoo.com.br

Received: 02 March, 2023.
Accepted: 10 Mar, 2023.
Published: 22 Dec, 2023.

BACKGROUND

The COVID-19 pandemic marked a historic event with profound impacts on global public health, society at large, and the global economy[1]. Since the initial diagnosis of the first COVID-19 cases, the SARS-CoV-2 virus, responsible for COVID-19, prompted immediate public health responses in numerous countries. These responses initially emphasized non-pharmaceutical interventions as pivotal measures to curtail the transmission of the virus[1, 2]. As the pandemic rapidly disseminated worldwide, the scientific and medical community shifted its focus beyond the immediate management of the disease to a deeper exploration of its enduring consequences[2]. While initial efforts predominantly centered on prevention and the development of vaccines against

COVID-19, the challenges and post-recovery sequelae remain insufficiently elucidated, representing a critical facet of pandemic management[3].

As the scientific community grapples with the escalating symptomatology induced by COVID-19, it is increasingly apparent that this systemic ailment transcends its acute respiratory manifestations[4]. While the world was still grappling with the immediate repercussions of the pandemic, including pneumonia, pulmonary thromboembolism, and an elevated risk of cardiovascular events, a slew of questions emerged concerning the protracted sequelae, the underlying mechanisms, and their clinical implications, all of which remain shrouded in uncertainty[4,5]. Upon a comprehensive investigation of the COVID-19 landscape, it becomes evident that it is imperative not only to analyze the virus's initial transmission dynamics and the implemented public health measures but also to gain insights into the enduring effects on various organ systems such as the heart, lungs, muscles, and others[6-8]. This comprehension is pivotal for public health, clinical practice, and ongoing research efforts, as it challenges us to holistically grasp and address the sustained repercussions of this pandemic on population health[8].

The significance of lung function in the context of post-COVID-19 symptoms, particularly persistent dyspnea, assumes paramount importance in comprehending and addressing the challenges faced by survivors of the disease[9]. Recent studies indicate that a substantial proportion of individuals who recuperate from COVID-19 continue to report chronic dyspnea and other respiratory symptoms even several months after their initial infection[10,11]. Lung function is pivotal in this scenario, as it directly influences a patient's capacity to perform daily activities and, consequently, their overall quality of life[12]. Dyspnea, in particular, is a multifaceted symptom that can initiate a cycle of reduced activity and functional impairment, culminating in an inability to carry out fundamental daily tasks[13]. Therefore, discerning the disparities in lung function between patients with persistent dyspnea and those without is crucial for unraveling the mechanisms underpinning this symptom and for devising effective management strategies aimed at enhancing the quality of life for COVID-19 survivors[13].

Furthermore, it is indispensable to acknowledge the fundamental role of lung function in enhancing the overall quality of life for individuals in the process of recovering from COVID-19. Effective respiratory function is essential for the execution of routine activities and even engaging in physical exercise[12]. Consequently, preserving and optimizing lung function is of paramount importance to enable patients to maintain an active and independent lifestyle following their recovery from the disease[13]. This care not only facilitates physical recuperation but also substantially contributes to psychological well-being, as the ability to perform everyday activities is intricately linked to self-esteem and a sense of normalcy[14]. In summary, the assessment and monitoring of lung function occupy a central position in the comprehensive management of post-COVID-19 patients, with the overarching goal of not only alleviating persistent symptoms such as dyspnea but also enhancing their overall quality of life and functional capabilities[14].

This article aims to comprehensively review the key alterations in lung function associated with COVID-19, spanning from acute changes during the infection to the long-term respiratory complications following recovery. The article seeks to contribute

to a profound understanding of the respiratory challenges inherent to the disease and advance clinical approaches in this regard.

Pathophysiology of SARS-CoV-2 Infection

COVID-19, caused by SARS-CoV-2, is a viral disease characterized by a unique pathophysiology[15]. SARS-CoV-2 belongs to the coronavirus family, a group of single-stranded RNA viruses known to cause diseases in both humans and animals[15]. Moreover, the clinical symptoms of COVID-19 bear similarities to those of other viral respiratory diseases, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), which were also attributed to coronaviruses[16,17].

The process of SARS-CoV-2 infection initiates with the invasion of respiratory tract cells, including nasal and bronchial epithelial cells and pneumocytes. This invasion is facilitated by the viral spike (S) protein, which binds to the angiotensin converting enzyme 2 (ACE2) receptor on the surface of host cells[18]. This mechanism of viral entry elicits an inflammatory response that involves both the innate and adaptive immune systems. Consequently, T cells and lymphocytes may undergo cell death, resulting in lymphopenia in some patients[18]. Additionally, infection can compromise the barrier function of pulmonary alveoli, leading to thickening of alveolar walls and the development of a pulmonary angioedema syndrome dependent on bradykinin[19]. Furthermore, COVID-19 is associated with disorders related to blood clotting and the formation of microthrombi, increasing the risk of thrombotic complications[20,21].

These pathological characteristics encompass lung barrier impairment, widespread inflammation, and coagulation abnormalities, collectively contributing to the emergence of severe and potentially fatal symptoms in COVID-19 patients. These symptoms may include Acute Respiratory Distress Syndrome (ARDS), disseminated intravascular coagulation (DIC), and multiple organ dysfunction[22,23]. It is crucial to underscore that comprehending the intricate and diverse mechanisms underpinning COVID-19 plays a pivotal role in the development of effective strategies for treating and managing this disease.

Impact of COVID-19 on Lung and Respiratory Function

COVID-19, stemming from the SARS-CoV-2 coronavirus, exerts profound effects on the lung and respiratory function of afflicted individuals. Following initial infection within the upper respiratory tract, the virus continues its replication within the lower airways and alveolar epithelial cells, setting off a hyperinflammatory immune response that culminates in tissue damage and vascular permeability[24,25]. This cascade of events can result in persistent lung injury, a phenomenon observed in a substantial proportion of patients even months after the acute phase of COVID-19[26,27].

The chronic lung injuries associated with COVID-19 share similarities with the mechanisms underlying pulmonary fibrosis. These entail an adaptive immune response influenced by Transforming growth factor-β (TGF- β), the activation of fibroblast cells, the demise of alveolar epithelial cells, and structural alterations in the basal lamina. These processes can lead to lung tissue stiffening and alveolar collapse[28, 29].

Furthermore, prior investigations into infections caused by other coronaviruses, such as SARS and MERS, along with the swine-like Influenza A virus (H1N1), have also uncovered links to lung restriction, diminished oxygen diffusion capacity, and pathological changes discernible through chest computed tomography (CT scans)[30,31].

Recent research has underscored the significant impact of COVID-19 on lung and respiratory function. A substantial number of survivors of the disease report enduring symptoms, including persistent dyspnea, manifesting approximately 2 to 3 months post-initial infection[32,33]. Dyspnea, characterized by the sensation of breathlessness, is a multifaceted symptom that not only compromises the quality of life but also serves as an independent marker of morbidity and mortality in the general population[34]. It is noteworthy that some symptoms, such as dyspnea and fatigue, seem to persist for several months after recovery in approximately 50% of cases[34,35]. The persistence of dyspnea can trigger a debilitating cycle wherein patients eschew physical activities due to discomfort, leading to deconditioning and a subsequent decline in functional capacity. Ultimately, this can culminate in an inability to perform even basic daily tasks[37].

Furthermore, it is crucial to acknowledge the significant role played by racial and ethnic disparities in this context. Studies have illuminated racial biases and ethnic disparities in COVID-19 infections and hospitalizations, with Hispanic populations shouldering a disproportionate burden of the disease[38]. This may be attributed, at least in part, to higher rates of comorbidities such as diabetes and obesity, which independently correlate with the severity of COVID-19[39].

Long-term Respiratory Complications

The term "long COVID" made its debut in May 2020 to describe the persistence of diverse symptoms in certain individuals following the acute phase of COVID-19 infection[40]. Initially, a clear definition for this condition was lacking. However, in December 2020, the National Institute for Health and Care Excellence (NICE) introduced a distinction between "ongoing symptomatic COVID-19" (referring to symptoms occurring between 4 and 12 weeks post-acute COVID-19) and "post-COVID syndrome -19" (referring to symptoms manifesting 12 weeks after the onset of the disease)[41]. In alignment with this classification, the World Health Organization (WHO) outlined "Post-Condition COVID-19" in October 2021, characterized by symptoms persisting for a minimum of 2 months after SARS-CoV-2 infection, occurring 3 months post the onset of the acute illness, and lacking an explanation through alternative diagnoses[42]. The term "long COVID" serves as an umbrella concept encompassing this wide array of symptoms persisting after the recovery from COVID-19.

"Long COVID," also recognized as "post-acute sequelae of COVID-19," represents a multisystemic condition marked by the enduring presence of severe symptoms subsequent to SARS-CoV-2 infection. These symptoms traverse multiple bodily systems, encompassing the cardiovascular, metabolic, neurological, and autonomic domains. They also encompass conditions such as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and dysautonomia, exemplified by disorders like postural orthostatic tachycardia syndrome (POTS)[43-46].

The treatment of long COVID presents challenges due to its multifaceted nature. Hypotheses concerning its pathogenesis span virus persistence within tissues, immune system dysregulation, reactivation of latent pathogens, and other contributing factors. Consequently, continued research is imperative to attain a deeper comprehension of long COVID and facilitate the development of efficacious treatments[47].

Assessment of Lung Function in Patients with COVID-19

The evaluation of lung function in post-COVID-19 patients assumes a pivotal role in the detection and ongoing monitoring of the respiratory and functional consequences stemming from the disease. As elucidated in medical literature[48-50], COVID-19 can give rise to a spectrum of pulmonary complications, encompassing widespread destruction of the alveolar epithelium, the formation of hyaline membranes, capillary damage, proliferation of fibrous tissue within alveolar septa, and the consolidation of lung tissue. These pathophysiological events can culminate in pulmonary fibrosis and/or chronic pulmonary hypertension.

To gain an objective understanding of the repercussions of COVID-19 infection on the respiratory system, it is imperative to conduct comprehensive respiratory function assessments[51]. Pulmonary function tests (PFTs), inclusive of spirometry, diffusing capacity measurement, and lung volume quantification, frequently serve as valuable tools for the identification of deviations from normal lung function[52]. Furthermore, the assessment of respiratory muscle function and airway resistance can complement these tests, affording a more holistic perspective of lung characteristics[52].

Chest CT also assumes a critical role in the evaluation of pulmonary complications, and clinical guidelines stipulate that individuals with severe COVID-19 pneumonia should undergo complete pulmonary function tests (PFTs) approximately 12 weeks following their discharge[53]. The identification of anomalies in both lung function and CT scans may indicate the necessity for referral to specialists in interstitial lung diseases[53].

Preliminary investigations suggest that post-COVID-19 patients may manifest restrictive or obstructive patterns as well as impaired diffusion capacity[54]. Moreover, there are reports of these abnormalities persisting for months or even years following hospital discharge[54]. Consequently, the ongoing assessment of lung function is indispensable for early diagnosis and the adequate monitoring of these patients.

In summation, the assessment of lung function assumes a critical role in the identification and monitoring of respiratory and functional sequelae in post-COVID-19 patients. It is through these assessments that we can enhance our comprehension of the disease's impact on the lungs and provide the requisite treatment and support to facilitate the proper recovery of patients.

Therapeutic and Rehabilitation Approaches

Recent studies underscore the significance of therapeutic interventions and treatments designed for patients grappling with the lingering effects of COVID-19, known as PACS (Post-Acute Sequelae of COVID-19)[55,56]. A substantial portion of individuals who have recovered from acute SARS-CoV-2 infections may develop PACS, a multifaceted and heterogeneous health condition[55].

Given the scale of this health issue and the increasing population of COVID-19 survivors worldwide, it is imperative to channel our efforts towards comprehending and addressing the needs of these patients.

Therapeutic interventions and rehabilitation programs play a pivotal role in enhancing the quality of life for individuals with PACS[57]. These multidisciplinary programs encompass precise assessments of physical and cognitive impairments, pain management, fatigue mitigation, enhancement of respiratory function, monitoring of exercise capacity, and tailored recommendations for reintegrating into daily activities[58-61]. Effective coordination among healthcare professionals, including physiotherapists, occupational therapists, neuropsychologists, and other specialists, is indispensable to address the diverse clinical manifestations of PACS[57].

Furthermore, therapeutic interventions aim to provide relief and rehabilitation across various domains, encompassing respiratory, physical, and cognitive functions. It is imperative to emphasize the need for clear and standardized guidelines for the clinical management of these patients, highlighting the pivotal role of rehabilitation and the provision of personalized care to cater to individual needs[62].

Despite the existence of recommendations for post-COVID-19 rehabilitation, the effectiveness of these interventions remains unconfirmed through clinical studies. Consequently, future research must persist in evaluating the efficacy of these rehabilitation programs to furnish robust evidence supporting their widespread adoption. Enhancing the quality of life and functional capabilities of post-COVID-19 patients stands as a paramount objective, with therapeutic interventions serving as a crucial component in this endeavor.

FINAL CONSIDERATIONS

The COVID-19 pandemic has reverberated throughout global health, underscoring the paramount importance of lung function. COVID-19 has not merely affected patients during the acute infection but has also left enduring respiratory sequelae in a substantial number of survivors, including chronic dyspnea and functional limitations. The assessment of lung function has emerged as a pivotal tool for the detection and ongoing monitoring of these sequelae, thereby instigating the necessity for rehabilitation programs and tailored therapeutic approaches. Nevertheless, future research must persist in delving into the underlying causes of pulmonary sequelae and in crafting effective treatment strategies. These efforts are aimed at enhancing the quality of life for post-COVID-19 patients and mitigating the long-term consequences of this unprecedented pandemic.

Authors' contribution: Conceptualization, R.P.V, L.F.R.J.O., and L.V.F.O.; Methodology, M.C.O., J.P.R.A., R.P.V., I.L.C, and L.V.F.O.; Project administration R.P.V., and L.V.F.O Investigation, L.F.R.J.O., A.L.F., S.K.A.S., B.M.R.S., A.C.O., R.P.V., and L.V.F.O; Data curation, M.E.M.L., B.O.M., M.M.C., M.C.O., J.P.R.A., and, L.V.F.O; Formal analysis, R.P.V, L.F.R.J.O., B.O.M., and L.V.F.O.; Supervision, R.P.V., L.R.A., L.V.F.O.; Writing-original draft, R.P.V, L.F.R.J.O., and L.V.F.O.; Writing-review and edit, R.P.V., and L.V.F.O. All authors have read and approved the final version of the manuscript

Financial support: This research received no external funding.

Funding: R.P.V. received grants from Research Productivity, modality PQII; process no. 313299/2018-8 of Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (local acronym CNPq), L.V.F.O. received grants from Research Productivity, modality PQII; process no. 310241/2022-7 of Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (local acronym CNPq), Brazil. J.P.R.A. and, M.C.O. receives a grant from the Fundação de Amparo a Pesquisa do Estado de Goias (FAPEG), (GO), Brazil.

REFERENCES

1. Ball S, Banerjee A, Berry C, Boyle JR, Bray B, Bradlow W, et al. Monitoring indirect impact of COVID-19 pandemic on services for cardiovascular diseases in the UK. Heart. 2020;106(24):1890-1897.
2. Chow EJ, Uyeki TM, Chu HY. The effects of the COVID-19 pandemic on community respiratory virus activity. Nat Rev Microbiol. 2023;21(3):195-210.
3. Sullivan SG, Carlson S, Cheng AC, Chilver MB, Dwyer DE, Irwin M, et al. Where has all the influenza gone? The impact of COVID-19 on the circulation of influenza and other respiratory viruses, Australia, March to September 2020. Euro Surveill. 2020;25(47):2001847.
4. Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J. 2020;1;41(32):3038-3044.
5. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020;1;116(10):1666-1687.
6. Mangion K, Morrow A, Bagot C, Bayes H, Blyth KG, Church C, et al. The Chief Scientist Office Cardiovascular and Pulmonary Imaging in SARS Coronavirus disease-19 (CISCO-19) study. Cardiovasc Res. 2020;1;116(14):2185-2196.
7. Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, et al. Global evaluation of echocardiography in patients with COVID-19. Eur Heart J Cardiovasc Imaging. 2020;1;21(9):949-958
8. Gualtieri P, Falcone C, Romano L, Macheda S, Correale P, Arciello P, et al.Body Composition Findings by Computed Tomography in SARS-CoV-2 Patients: Increased Risk of Muscle Wasting in Obesity. Int J Mol Sci. 2020;30;21(13):4670.
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;9;11(1):16144.
10. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;11;324(6):603-605.
11. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol. 2023;93(2):1013-1022.
12. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;15;187(4):347-65.
13. Ahmed I, Mustafaoglu R, Yeldan I, Yasaci Z, Erhan B. Effect of Pulmonary Rehabilitation Approaches on Dyspnea, Exercise Capacity, Fatigue, Lung Functions, and Quality of Life in Patients With COVID-19: A Systematic Review and Meta-analysis. Arch Phys Med Rehabil. 2022;103(10):2051-2062.
14. Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, Solis-Navarro L, Burgos F, Puppo H, et al. Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis. Pulmonology.

2021;27(4):328-337.

15. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;25;324(8):782-793.
16. Zhong NS, Zheng BJ, Li YM, Poon, Xie ZH, Chan KH, et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet. 2003;25;362(9393):1353-8..
17. Ochani R, Asad A, Yasmin F, Shaikh S, Khalid H, Batra S, et al. COVID-19 pandemic: from origins to outcomes. A comprehensive review of viral pathogenesis, clinical manifestations, diagnostic evaluation, and management. Infez Med. 2021;1;29(1):20-36.
18. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;16;181(2):271-280.e8.
19. van de Veerdonk FL, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Brüggemann RJ, et al. Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. Elife. 2020;27;9:e57555.
20. Teimury A, Khameneh MT, Khaledi EM. Major coagulation disorders and parameters in COVID-19 patients. Eur J Med Res. 2022;15;27(1):25.
21. Chen AT, Wang CY, Zhu WL, Chen W. Coagulation Disorders and Thrombosis in COVID-19 Patients and a Possible Mechanism Involving Endothelial Cells: A Review. Aging Dis. 2022;1;13(1):144-156.
22. Merad M, Blish CA, Sallusto F, Iwasaki A. The immunology and immunopathology of COVID-19. Science. 2022;11;375(6585):1122-1127.
23. Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. Eur Heart J. 2022;14;43(11):1157-1172.
24. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;25;324(8):782-793.
25. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-469.
26. Lerum TV, Aaløkken TM, Brønstad E, Aarli B, Ikdahl E, Lund KMA, et al. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. Eur Respir J. 2021;29;57(4):2003448.
27. Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, et al. Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. Eur Respir J. 2021;29;57(4):2003481.
28. Ferreira-Gomes M, Kruglov A, Durek P, Heinrich F, Tizian C, Heinz GA, et al. SARS-CoV-2 in severe COVID-19 induces a TGF-β-dominated chronic immune response that does not target itself. Nat Commun. 2021;30;12(1):1961.
29. Gralinski LE, Bankhead A, Jeng S, Menachery VD, Proll S, Belisle SE, et al. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. mBio. 2013;6;4(4):e00271-13.
30. Hui DS, Joynt GM, Wong KT, Gomersall CD, Li TS, Antonio G, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax. 2005;60(5):401-9.
31. Hsieh MJ, Lee WC, Cho HY, Wu MF, Hu HC, Kao KC, et al. Recovery of pulmonary functions, exercise capacity, and quality of life after pulmonary rehabilitation in survivors of ARDS due to severe influenza A (H1N1) pneumonitis. Influenza Other Respir Viruses. 2018;12(5):643-648.
32. Carfì A, Bernabei R, Landi F. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;11;324(6):603-605.
33. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and

health-related quality of life after hospitalization for COVID-19. J Infect. 2020;81(6):e4-e6.

34. Bellan M, Soddu D, Balbo PE, Baricich A, Zeppegnom P, Avanzi GC, et al. Respiratory and psychophysical sequelae among patients with COVID-19 four months after hospital discharge. JAMA Netw. Open 2021;4:e2036142.
35. Besnier F, Bérubé B, Malo J, Gagnon C, Grégoire CA, Juneau M, et al. Cardiopulmonary Rehabilitation in Long-COVID-19 Patients with Persistent Breathlessness and Fatigue: The COVID-Rehab Study. Int J Environ Res Public Health. 2022;31;19(7):4133.
36. Motiejunaite J, Balagny P, Arnoult F, Mangin L, Bancal C, Vidal-Petiot E, et al. Hyperventilation as one of the mechanisms of persistent dyspnoea in SARS-CoV-2 survivors. Eur Respir J. 2021;26;58(2):2101578.
37. Budhwar N, Syed Z. Chronic Dyspnea: Diagnosis and Evaluation. Am Fam Physician. 2020;1;101(9):542-548.
38. Mackey K, Ayers CK, Kondo KK, Saha S, Advani SM, Young S, et al. Racial and Ethnic Disparities in COVID-19-Related Infections, Hospitalizations, and Deaths : A Systematic Review. Ann Intern Med. 2021;174(3):362-373.
39. Giannouchos, Theodoros V, et al. Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an analysis of 89,756 laboratory–confirmed COVID-19 cases. Medrxiv. 2020-06.
40. Higgins V, Sohaei D, Diamandis EP, Prassas I. COVID-19: from an acute to chronic disease? Potential long-term health consequences. Crit Rev Clin Lab Sci. 2021;58(5):297-310.
41. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nat Med. 2021 Apr;27(4):626-631.
42. WHO. A clinical CAS definition of post COVID condition by a Delphy consensus. World health Organization (WHO); 2021.
43. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022;28(3):583-590.
44. Mancini DM, Brunjes DL, Lala A, Trivieri MG, Contreras JP, Natelson BH. Use of Cardiopulmonary Stress Testing for Patients With Unexplained Dyspnea Post-Coronavirus Disease. JACC Heart Fail. 2021;9(12):927-937.
45. Kedor C, Freitag H, Meyer-Arndt L, Wittke K, Hanitsch LG, Zoller T, et al. A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity. Nat Commun. 2022;30;13(1):5104.
46. Larsen NW, Stiles LE, Shaik R, Schneider L, Muppidi S, Tsui CT, et al. Characterization of autonomic symptom burden in long COVID: A global survey of 2,314 adults. Front Neurol. 2022;19;13:1012668.
47. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023;21(3):133-146.
48. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;15;395(10223):497-506.
49. Ñamendys-Silva SA. ECMO for ARDS due to COVID-19. Heart Lung. 2020;49(4):348-349.
50. Qiao Z, Liu D, Fu F, Ye A, Hu C. Clinical Characterizations and Radiological Findings of COVID-19: A 4 Case Report. Curr Med Imaging. 2022;18(14):1536-1539.
51. Sirayder U, Inal-Ince D, Kepenek-Varol B, Acik C. Long-Term Characteristics of Severe COVID-19: Respiratory Function, Functional Capacity, and Quality of Life. Int J Environ Res Public Health. 2022;23;19(10):6304.
52. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J. 2020;18;55(6):2001217.
53. Lee JH, Yim JJ, Park J. Pulmonary function and chest computed tomography abnormalities 6-12 months after recovery from COVID-19: a systematic review and meta-analysis. Respir Res. 2022;6;23(1):233.
54. Frija-Masson J, Debray MP, Gilbert M, Lescure FX, Travert F, Borie R, et al. Functional characteristics of patients with SARS-CoV-2 pneumonia at 30 days post-infection. Eur Respir J. 2020;6;56(2):2001754.

55. Montani D, Savale L, Noel N, Meyrignac O, Colle R, Gasnier M, et al. Post-acute COVID-19 syndrome. Eur Respir Rev. 2022;9;31(163):210185.
56. Hockele LF, Sachet Affonso JV, Rossi D, Eibel B. Pulmonary and Functional Rehabilitation Improves Functional Capacity, Pulmonary Function and Respiratory Muscle Strength in Post COVID-19 Patients: Pilot Clinical Trial. Int J Environ Res Public Health. 2022;12;19(22):14899.
57. Fugazzaro S, Contri A, Esseroukh O, Kaleci S, Croci S, Massari M, et al. Rehabilitation Interventions for Post-Acute COVID-19 Syndrome: A Systematic Review. Int J Environ Res Public Health. 2022;24;19(9):5185.
58. Jimeno-Almazán A, Pallarés JG, Buendía-Romero A, Martínez-Cava A, Franco-López F, Sánchez-Alcaraz Martínez BJ, et al. Post-COVID-19 Syndrome and the Potential Benefits of Exercise. Int. J. Environ. Res. Public Health. 2021;18,5329.
59. Rooney S, Webster A, Paul L. Systematic Review of Changes and Recovery in Physical Function and Fitness After Severe Acute Respiratory Syndrome-Related Coronavirus Infection: Implications for COVID-19 Rehabilitation. Phys Ther. 2020;28;100(10):1717-1729.
60. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br J Sports Med. 2020;54(16):949-959.
61. Scheiber B, Spiegl C, Wiederin C, Schifferegger E, Schiefermeier-Mach N. Post-COVID-19 Rehabilitation: Perception and Experience of Austrian Physiotherapists and Physiotherapy Students. Int J Environ Res Public Health. 2021;18;18(16):8730.
62. Maley JH, Alba GA, Barry JT, Bartels MN, Fleming TK, Oleson CV, et a. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of breathing discomfort and respiratory sequelae in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). PM R. 2022;14(1):77-95..