

Pneumologia

Lung function assessment following SARS-CoV-2 infection: past, present and future?

Daniela Robu Popa^{1,2,#}, Raluca Ioana Arcana^{1,2,*}, Radu Adrian Crișan Dabija^{1,2}, Andreea Zabara², Mihai Lucian Zabara^{1,3,5}, Andrei Cernomaz^{1,4}, Oana Melinte^{1,#}, Antigona Trofor^{1,2,#}

¹ Department of Internal Medicine – Pneumology “Grigore T. Popa” University of Medicine and Pharmacy, Iași, Romania

² Clinical Hospital of Pulmonary Diseases, Iași, Romania

³ Department of Surgery, “St. Spiridon” Emergency Hospital, Iași, Romania

⁴ Department of Bronchial Endoscopy, Regional Institute of Oncology, Iași, Romania

⁵ Department of Surgery, “Grigore T. Popa” University of Medicine and Pharmacy, Iași, Romania

Abstract

English:

The impact of COVID-19 on lung function is an indisputable reality that has posed major management problems to all categories of specialists who have treated patients with SARS-CoV-2 infection. This disease presents an impressive multisystemic feature, in correlation with clinical, paraclinical, imaging and functional heterogeneity. Although most COVID-19 cases have a complete resolution, the evolution of vulnerable patients (elderly or people with multiple comorbidities such as cardiovascular, metabolic, renal, neoplastic or respiratory problems) or those with moderate to severe forms of the disease can be slower or even unfavourable. Recent data in the literature have shown that many of these patients return to hospital due to symptoms and respiratory dysfunction more than 6–12 months after the acute viral episode, highlighting the need for rigorous evaluation and further pulmonary function testing among patients with a history of COVID-19 to anticipate the appearance of long-term respiratory functional sequelae.

Keywords

COVID-19 • lung function • respiratory sequelae

Impactul asupra funcției pulmonare secundar infecției cu SARS-CoV-2: trecut, prezent și viitor?

Rezumat

Romanian:

Impactul COVID-19 asupra funcției pulmonare este o realitate incontestabilă care a pus probleme majore de management tuturor categoriilor de specialiști care au tratat pacienți cu infecție SARS-CoV-2. Această boală prezintă o caracteristică multisistemică impresionantă, în corelație cu heterogenitatea clinică, paraclinică, imagistică și funcțională. Deși cele mai multe cazuri au o rezoluție completă, evoluția pacienților vulnerabili (vârstnici sau cu multiple comorbidități, cum ar fi cele cardiovasculare, metabolice, renale, neoplazice, dar și respiratorii) sau a formelor moderat-severe ale bolii, poate fi mai lentă sau chiar nefavorabilă. Datele recente din literatura de specialitate au arătat că mulți dintre acești pacienți se întorc la spital pentru simptome și disfuncții respiratorii la mai mult de 6-12 luni de la episodul viral acut, subliniind necesitatea unei evaluări riguroase și a unor teste suplimentare ale funcției pulmonare în rândul pacienților cu antecedente de COVID-19, pentru a putea anticipa apariția sechelelor funcționale respiratorii pe termen lung.

Cuvinte-cheie

COVID-19 • funcția pulmonară • sechele respiratorii

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, initially reported in Wuhan, China, in

December 2019, continues to remain one of the most important global public health problems at this time, with

[#]PhD Student

*Corresponding author: Raluca Ioana Arcana

E-mail: raluca.dospinescu@yahoo.com

Open Access. © 2022 Popa et al., published by Sciendo

 This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 License.

645,630,482 diagnosed cases and more than 6,6 million deaths. In Romania, 3,298,738 cases were registered, of which over 67,289 were deaths (1).

The clinical picture of coronavirus disease 2019 (COVID-19) can vary considerably, from completely asymptomatic forms of SARS-CoV-2 infection to forms of viral pneumonia that require hospitalisation and can evolve unfavourably towards the development of acute respiratory distress syndrome (ARDS) (2).

Although the clinical, paraclinical, imaging and morphopathological aspects of the acute phase of the disease have been studied in detail, the long-term consequences of COVID-19 still require attention, being constantly updated with the latest news in the field, to master this exceptional global health situation (3).

The concept of post-acute COVID-19 (long COVID) integrates the persistence of symptoms such as dyspnoea and fatigue more than 3 weeks after infection with SARS-CoV-2. The development of a possible chronic post-COVID-19 syndrome appears when clinical-paraclinical, radiological and functional changes persist more than 12 weeks after the acute viral episode. In addition, the impairment of lung function may persist at distance (6–12 months); thus, a careful follow-up of the evolution of patients who had moderate and severe forms of the disease is necessary to identify possible complications that may occur and to minimise long-term effects (4,5).

The main complications that can occur related to COVID-19 are cardiological (myocarditis, arrhythmias), respiratory (pulmonary fibrosis, pulmonary arterial hypertension), metabolic (hyperglycaemia, dyslipidaemia), musculoskeletal (reactive arthritis) or psychiatric (depression, post-traumatic stress syndrome) (6).

Data from the literature are quite heterogeneous regarding patients with post-COVID-19 syndrome. The most commonly reported symptoms were fatigue (31%–58%), sleep disturbances (11%–44%), breathlessness (24%–40%), psychological distress (12%–35%), cough (7%–29%) and anosmia-dysgeusia (10%–22%). However, it was observed that there is not always a direct relationship between the symptoms described by the patient and the imaging and functional aspects of the case. There are situations with persistent symptoms and discrete imaging aspects, as well as imaging and functional changes in patients without alarming symptoms, especially if they have other associated comorbidities (7).

Currently, the mortality and severity rates associated with COVID-19 are decreasing, but the specialists in the medical field are starting to face another category of patients with post-COVID-19 syndrome, whose evolution can be complicated by the appearance of pulmonary fibrosis sequelae, with significant and irreversible functional impairment (8).

The pulmonary tropism of this infection is reflected in lung imaging lesions, changes in pulmonary function tests and respiratory symptoms, which are present not only in the acute phase but also weeks or even months after the acute infectious episode. There are many studies involving the rapid diagnosis, development and pathogenesis of acute COVID-19, but still little is known about the long-term changes of the disease on patients. The long-term persistence of these changes is one of the unknown factors of this disease, as well as their corresponding degree of resolution.

Lung function assessment after COVID-19

Exploring the respiratory system through lung function tests and imaging techniques in patients who have had severe forms of SARS-CoV-2 infection should represent an important step in the follow-up of these patients, which can help better understand the long-term pulmonary sequelae and how to manage them.

Pulmonary function testing is a key element in the management of patients with post-COVID-19 syndrome. The most important changes in pulmonary function observed among these patients are as follows: a restrictive pulmonary disorder with increased lung elastic recoil, objectified by decreases in forced vital capacity (FVC) and increases in the forced expiratory volume in the first second (FEV1)/FVC ratio; aspects that may suggest a certain degree of pulmonary fibrosis after COVID-19; obstructive pulmonary disorder (with FEV1/FVC ratio below 0.7); and the reduced diffusing capacity of the lungs for carbon monoxide (DLCO) (9).

Although most cases of SARS-CoV-2 infection have a complete resolution, in some cases, such as vulnerable patients (those with comorbidities and the elderly), the evolution can be slower or even unfavourable. Severe forms of COVID-19 can evolve towards the development of ARDS, and the risk of irreversible morphofunctional changes is significant (2).

Among the most important predisposing factors for subsequent respiratory impairment are advanced age and the presence of cardiovascular (arterial hypertension, chronic heart failure), metabolic (diabetes mellitus, metabolic syndrome, obesity) and neoplastic or respiratory (obstructive and restrictive lung diseases) comorbidities. Moreover, patients with pre-existing lung disease were reported to have more persistent symptoms after the acute infectious episode, such as persistent fatigue according to a study by Blomberg et al. (10).

Another study by Munblit et al. (11) has confirmed that patients with pre-existing asthma and a history of SARS-CoV-2 infection tend to have long-term neurological, mood and

behavioural changes, whereas chronic pulmonary disease was shown to be associated with chronic fatigue. Previous studies have shown that clinicians should take into account the persistence of symptoms after SARS-CoV-2 infection and recommend a series of further investigations to identify possible lung lesions (12).

In a meta-analysis that evaluated 38 studies involving 3062 COVID-19 patients, the incidence rate of respiratory failure or ARDS was 19.5% in hospitalised patients. Moreover, from imaging aspects, lesions limited to a single lung were reported in 25.8% of the patients, whereas 75.7% of patients had lesions involving bilateral lungs (13).

According to a study performed by Eksombatchai et al. (14), patients who developed severe forms of COVID-19 are at greater risk of developing pulmonary fibrosis than patients who had mild and moderate forms of the disease. At 60 days after the acute viral episode, the study observed the following: 9.2% of patients had obstructive ventilatory dysfunction, 8% had restrictive ventilatory dysfunction and 13.8% had residual fibrotic lesions on chest X-Ray examination, all these changes being present, especially among patients who had severe forms of COVID-19.

Studies designed to evaluate the evolution of patients following SARS-CoV-2 infection can provide key information. A study conducted in China showed that respiratory functional changes in patients with post-COVID-19 syndrome occur in more than 25% of patients, regardless of the presence or absence of respiratory symptoms at the time of examination. Furthermore, it was observed that there was a significant correlation between the level of D-dimers and the degree of impairment of DLCO (5).

It seems that the degree of decreasing DLCO is in direct correlation with the degree of severity of COVID-19, being a more sensitive predictor than FVC or total lung capacity (TLC). In addition, it was pointed that an association exists between the decrease in DLCO and changes in the 6-min walk test (15).

In a study conducted in Wuhan, China, the clinical, radiological and respiratory functional evolution of 1733 patients at 6 months after the diagnosis of SARS-CoV-2 infection was analysed. Persistence of symptoms was observed in 76% of patients, and more than 50% of them had radiological changes, and in 56% of patients who required high-flow oxygen therapy, non-invasive or invasive ventilation during hospitalisation showed decreased DLCO. In addition, respiratory functional changes could be correlated with imaging changes (3).

In the current medical practice, it has been observed that there was a significant increase in the addressability of patients with post-COVID-19 syndrome with persistent symptoms, such as dyspnoea, fatigue, sleep disorder, difficulty concentrating or cough. A meta-analysis showed that the prevalence of persistent dyspnoea did not

significantly decrease until 1 year after acute COVID-19. In this context, it is worth mentioning the fact that dyspnoea is a subjective symptom that can result from various pathological mechanisms and can have multiple aetiologies (16).

For example, some studies using cardiopulmonary exercise tests have demonstrated that persistent dyspnoea after COVID-19 was mostly due to deconditioning or dysfunctional breathing such as hyperventilation (17,18).

This aspect of persistent symptoms after COVID-19 was investigated in a study carried out in Central America which observed that persistent respiratory symptoms were also associated important respiratory functional changes (47% of all patients with persistent dyspnoea presented a restrictive ventilatory pattern) and a significant decrease in the quality of life (19).

Post-COVID-19 lung damage can occur more than 6 months after infection, or even longer, according to a study by Bardakci et al. (20). In 30.5% of cases, it was observed that there was a decrease in FEV₁, with a statistically significant correlation with the patient's perception regarding the performance of daily activities, vitality and general state of health. In addition, in 45.8% of cases, a decrease in FVC and changes in the 6-min walk test were noticed in 23.2% of cases, highlighting the need for monitoring the evolution of these patients.

On the other hand, even if some of the patients who have had COVID-19 pneumonia tend to have a restrictive pattern in pulmonary function tests immediately after the acute infection, studies show that the pulmonary function tends to improve over time, over the course of a 6- to 12-month period (21). One study by Steinbeis et al. (22) found that disease severity was correlated with pulmonary restriction and reduced DLCO. However, interestingly enough, in these patients with a restrictive pattern and reduced carbon monoxide diffusion, the values improved over a period of 12 months as follows: TLC from 68.92 to 76.95, DLCO from 60.18 to 68.98 and KCO from 81.28 to 87.80 (percent predicted values; $P = 0.002, 0.045, 0.0002$ and 0.0005).

The result of a persistent pulmonary restrictive pattern and reduced DLCO can represent a consequence of SARS-CoV-2 infection, especially in patients who experienced severe forms of the disease. The mechanisms also seem to be different according to disease severity: in patients with very severe pulmonary injury, the predominant mechanism is impairment of diffusion reflected by a decrease in both DLCO and KCO. In patients who experienced milder disease, the primary mechanism was found to be the loss of the ventilated area, with a decrease in DLCO (22).

However, the prevalence and persistence of pulmonary sequelae post-COVID-19 remain quite unclear, with the existing results in the literature being quite heterogeneous. A meta-analysis published in 2022 has underlined the impairment of DLCO as the most frequently encountered

change in lung function, both 6 months and 12 months after the acute viral episode, those changes having a higher prevalence among patients with critical acute COVID-19 (pooled prevalence 35%, 95% confidence interval [CI] 30%–41%) with a prevalence of 39% (95% CI: 34%–45%) and 31% (95% CI: 21%–40%) in the 6-month and 12-month follow-up studies, respectively ($P = 0.115$).

Restrictive pulmonary dysfunction, as demonstrated by reduced FVC and/or TLC, was less frequent than impaired diffusion capacity (pooled prevalence 8%, 95% CI: 6%–11%); however, as mentioned earlier, its prevalence was lower after 12 months than after 6 months (5% [95% CI: 3%–7%] vs 13% [95% CI: 8%–19%], $P = 0.006$). On follow-up chest computed tomography (CT), the prevalence of persistent ground-glass opacities (GGOs) and pulmonary fibrosis did not decrease over time (8).

Pulmonary fibrosis secondary to COVID-19

Understanding and correctly identifying persistent respiratory changes after SARS-CoV-2 infection can be often challenging and misleading. Findings such as interstitial lung disease (ILD) and various other parenchymal abnormalities have been reported in patients with a history of SARS-CoV-2 infection. Pulmonary fibrosis post-COVID-19 defines the persistence of different patterns of fibrotic changes identified on computer tomography, after the acute episode, usually accompanied by impaired pulmonary function tests (23).

There are a series of risk factors associated with the development of pulmonary fibrosis in patients with COVID-19 such as age – especially in individuals older than 65 years; male individuals; smokers; those with comorbidities such as diabetes, chronic lung and cardiovascular diseases; those with chronic alcoholism, those with disease severity – the more severe, the higher the risk for persistent lung injury and the higher the length of intensive care unit (ICU) stay and mechanical ventilation (23,24).

It seems that there is a correlation between the impairment of DLCO and the increased level of fibrogenesis markers, such as matrix metalloproteinases (MMPs) and periostin. MMP-7, MMP-1 and periostin were found elevated in patients with severe COVID-19 compared to those with moderate disease. Early fibrotic changes found in CT scan were associated with higher levels of MMP7, MMP1 and periostin, which could explain fibrotic persistent changes in such patients (25).

Another proposed theory for the development of fibrotic changes is that in COVID-19, pulmonary macrophages tend to develop a profibrotic phenotype, resembling idiopathic pulmonary fibrosis, causing extensive pulmonary tissue remodelling and scarring (26).

A multicentre prospective cohort study analysed the evolution at 3 months after the discharge of 103 patients with COVID-19. Twenty-five percent of all patients had GGOs, and 19% had parenchymal bands (the latter being suggestive of a possible evolution towards pulmonary fibrosis). These aspects were more frequently encountered among patients admitted to the ICU and who had required non-invasive or invasive ventilation. In addition, 25% of the patients presented low DLCO. Approximately half of the patients described persistent dyspnoea more than 3 months after the acute viral episode (27). SARS-CoV-2 infection is characterised by a multisystemic involvement, but the lungs remain the most affected. The morphopathological changes at this level are multiple, and the most frequent changes include diffuse alveolar damage (DAD), bronchiolitis, alveolitis and interstitial fibrosis. The changes described in these patients who presented diffuse alveolar lesions were the presence of multinucleated giant cells, intraalveolar fibrin, hyaline membranes, organising connective tissue of interalveolar septa, inflammatory multinuclear cells and perivascular lymphocytic inflammation (28,29).

Progression from the initial acute phase to lung fibrosis can be due to excessive formation of the extracellular matrix, with dense collagen deposition, and thickening of the alveolar walls. The pattern these changes create can resemble nonspecific interstitial pneumonitis (23).

However, other patterns were also identified. For example, a study by Myall et al. (30) that aimed to identify long-term pulmonary lesions in patients with COVID-19 found that 6 weeks after the acute infectious episode, parenchymal abnormalities persist. The predominant radiological pattern was consistent with an organising pneumonia-like pattern with bilateral subpleural ground-glass infiltrates distributed in the middle and inferior regions of the lung.

Post-COVID-19 syndrome and small airway disease

Although the impairment of diffusion capacity of CO is the most frequently encountered change in lung function after COVID-19, some patients show evidence of small airway disease on pulmonary function tests and air trapping on thoracic CT.

In a study conducted by Franquet et al. (31), it was observed that air trapping was the most common abnormality (77%), more common than GGOs (40%), reticulations (38%) or traction bronchiectasis (19%).

In addition, it seems that this change was more frequent and more important among patients who presented severe forms of COVID-19. In a study of 205 patients previously hospitalised for COVID-19 pneumonia, air trapping was seen on expiratory CT in 29% of cases, with significantly higher

quantitative measures of air trapping in severe pneumonia than in the mild pneumonia groups (32).

Regarding the follow-up of patients with a history of SARS-CoV-2 infection, it is recommended impulse oscillometry (IOS) should be used to objectivise possible small airway disease sequelae. IOS is a simple technique that does not require a forced expiratory manoeuvre and has been shown to be a sensitive method for the early diagnosis of peripheral airway disease even before clinical manifestations or spirometric abnormalities appear. In a prospective follow-up study of 59 patients conducted in Brazil, at 2 months and 5 months after the diagnosis of acute SARS-CoV-2 infection, the patients underwent spirometry and IOS. Spirometry was altered in 44.1% of cases at 2 months and in 33.9% of cases after 5 months, although without statistical significance ($P = 0.10$). Moreover, restrictive patterns were observed in 30.5% of cases at 2 months and 22% at 5 months, and obstructive patterns were observed in the same month in 13.6% and 11.9% of participants, respectively. On IOS, considering changes in the resistive and reactive parameters, an abnormal result was detected in 88.1% of patients at 2 months and in 71.2% of participants at 5 months ($P = 0.002$) (33).

Small airway disease is an essential finding in post-acute COVID-19 syndrome, according to another retrospective study in which 29 patients were included, 13 of whom had moderate to severe damage on chest CT, and 9 of them had changes on respiratory function tests. Seventy-five percent of patients who performed pulse oscillometry (IOS) had abnormal results. Among the patients with abnormal IOS results, 50% had abnormal alterations compatible with small airway disease (34).

Follow up

Considering the defining multisystemic impairment following COVID-19, follow-up of patients will require a multidisciplinary team, integrating pulmonology, pulmonary rehabilitation, cardiology, neurological, nephrological, psychiatric consultations, etc. depending on the clinical needs of COVID-19 survivors (35).

The most serious and potentially life-limiting pulmonary complications of COVID-19, such as pulmonary fibrosis and pulmonary vascular disease, should be identified expediently, with a robust follow-up procedure, and should be managed appropriately (36).

The multidisciplinary assessment comprises a complete physical examination, vital sign assessment, respiratory evaluation (dyspnoea assessment using the modified Medical Research Council (mMRC) scale, respiratory rate, peripheral oxygen saturation, lung ultrasound, pulmonary function

tests), cardiovascular assessment (electrocardiography, echocardiography), nutritional assessment (measurement of height and body weight, as well as of waist circumference as an estimate of adiposity, mini nutritional assessment screening tool), neurological examination to exclude neurological sequelae, cognitive tests and mental health assessment, including screening of insomnia, anxiety and post-traumatic stress disorder (35).

Patients who developed severe forms of COVID-19 and those who required transfer to an ICU (most frequently the elderly and individuals with comorbidities) are among the vulnerable patients who might need rigorous surveillance, at 4–6 weeks after discharge. This involves an accurate assessment of the degree of dyspnoea, the need for oxygen therapy at home, analysis of the coagulation status (taking into account the increased risk of pulmonary thromboembolism), symptoms or palliative care management where required, assessment and management of dysfunctional breathing and the active search for possible complications such as sarcopenia, cognitive impairment or post-traumatic stress disorder.

The next evaluation should be carried out 12 weeks after discharge when a clinical examination is recommended, followed by a chest X-ray and respiratory function tests. If the patient is asymptomatic and the radiological aspect is normal, the patient can be declared healed. In the case of persistence of symptoms or imaging changes, the following investigations are required: high-resolution thoracic computed tomography (HRCT) to evaluate possible interstitial fibrosis, thoracic CT angiography to rule out possible pulmonary thromboembolism, a 6-min walk test with the assessment of oxygen saturation, full pulmonary function testing, echocardiogram, microbiological examination of sputum to highlight possible bacterial or fungal co-infections (that can occur in case of an immunocompromised patient) and assessment of the need for referral to multidisciplinary rehabilitation services, with attention for respiratory and skeletal muscles and functional as well as mental restoration.

If there is evidence of clinically significant ILD such as organising pneumonia or pulmonary fibrosis or pulmonary hypertension (PH), patients should be considered for referral to regional specialist ILD/PH services.

Full pulmonary function testing carried out at 3 months after discharge should initially include spirometry and the determination of DLCO. If the evolution towards pulmonary fibrosis is suspected, body plethysmography should be performed, an exploration that allows the measurement of TLC, functional residual capacity (FRC) and residual volume (RV).

In patients who develop mild and moderate forms of COVID-19, a chest X-ray should be performed 12 weeks after discharge, and in the case of persistence of changes such as

‘ground-glass’ peripheral opacities (GGOs), it is necessary to continue imaging and respiratory function investigations, as previously mentioned.

At the point of discharge, all patients should be considered for early referral to rehabilitation services and for psychosocial support, where appropriate (2,36).

All this information will help physicians and researchers develop preventative and therapeutic strategies, emphasising the importance of following the evolution of patients with post-COVID-19 syndrome to appropriately manage any persistent or emerging long-term sequelae (35).

Perspectives and conclusions

Considering the increased number of patients with a history of COVID-19, lately, the emphasis is on the optimal follow-up of these cases, depending on the type of initial damage, the associated comorbidities or the therapeutic approaches required in the acute phase.

Currently, there is a multitude of scientific data, in a permanent dynamic, being necessary to deepen the study of lung function at a distance among patients with a history of COVID-19.

The impact of COVID-19 on pulmonary function is an indisputable reality that has posed major management problems for all categories of specialists, and the anticipation of possible functional respiratory sequelae, especially among vulnerable patients, is an essential point in the follow-up of these patients.

In conclusion, it is necessary to expand the current knowledge about COVID-19 by evaluating the progression of symptoms and changes in pulmonary function over 6–12 months after the acute viral episode.

Considering the situation faced by most specialists in the medical field and the need for clear information to help improve clinical practice, a careful and rigorous follow-up of these categories of patients, both in the post-acute phase and in the long term, becomes necessary to optimise the management of patients with COVID-19.

Funding

None.

Conflicts of interest

The authors declare no conflict of interest.

Institutional review board statement

Not applicable.

Informed consent statement

No informed consent was necessary.

References

1. Covid19.who.int. 2022. WHO Coronavirus (COVID-19) Dashboard. Available from: <https://covid19.who.int/>. [Accessed 14 December 2022].
2. George PM, Barratt SL, Condliffe R, Desai SR, Devaraj A, Forrest I, et al. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*. 2020;75(11): 1009–1016. doi:10.1136/thoraxjnl-2020-215314.
3. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270): 220–232. doi:10.1016/S0140-6736(20)32656-8.
4. Greenhalgh T, Knight M, A’Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ*. 2020;370: m3026. doi:10.1136/bmj.m3026.
5. Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine*. 2020;25: 100463. doi:10.1016/j.eclinm.2020.100463.
6. Dasgupta A, Kalhan A, Kalra S. Long term complications and rehabilitation of COVID-19 patients. *Journal of the Pakistan Medical Association*. 2020;70: S131–S135. doi:10.5455/JPMA.32.
7. Lehmann A, Gysan M, Bernitzky D, Bal C, Prosch H, Zehetmayer S, et al. Comparison of pulmonary function test, diffusion capacity, blood gas analysis and CT scan in patients with and without persistent respiratory symptoms following COVID-19. *BMC Pulmonary Medicine*. 2022;22: 196. doi:10.1186/s12890-022-01987-z.
8. 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. *Respiratory Research*. 2022;23(1): 233. doi:10.1186/s12931-022-02163-x.
9. You J, Zhang L, Ni-jia-Ti MY, Zhang J, Hu F, Chen L, et al. Anormal pulmonary function and residual CT abnormalities in rehabilitating COVID-19 patients after discharge. *Journal of Infection*. 2020;81(2): e150–e152. doi:10.1016/j.jinf.2020.06.003.

10. Blomberg B, Mohn KG, Brokstad KA, Zhou F, Linchausen DW, Hansen BA, et al. Long COVID in a prospective cohort of home-isolated patients. *Nature Medicine*. 2021;27(9): 1607–1613. doi:10.1038/s41591-021-01433-3.
11. Munblit D, Bobkova P, Spiridonova E, et al. Risk factors for long-term consequences of COVID-19 in hospitalised adults in Moscow using the ISARIC global follow-up protocol: StopCOVID cohort study. *Infectious Diseases (except HIV/AIDS)*. 2021. doi:10.1101/2021.02.17.21251895.
12. Salehi S, Reddy S, Gholamrezanezhad A. Long-term pulmonary consequences of coronavirus disease 2019 (COVID-19): what we know and what to expect. *Journal of Thoracic Imaging*. 2020;35(4): W87–W89. doi:10.1097/RTI.0000000000000534.
13. Zhu J, Ji P, Pang J, Zhong Z, Li H, He C, et al. Clinical characteristics of 3062 COVID-19 patients: a meta-analysis. *Journal of Medical Virology*. 2020;92(10): 1902–1914. doi:10.1002/jmv.25884.
14. Eksombatchai D, Wongsinin T, Phongnarudech T, Thammavaranucupt K, Amornputtisathaporn N, Sungkanuparph S. Pulmonary function and six-minute-walk test in patients after recovery from COVID-19: a prospective cohort study. *PLoS One*. 2021;16(9): e0257040. doi:10.1371/journal.pone.0257040.
15. 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. *The European Respiratory Journal*. 2020;55(6): 2001217. doi:10.1183/13993003.01217-2020.
16. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *American Journal of Respiratory and Critical Care Medicine*. 2012;185(4): 435–452. doi:10.1164/rccm.201111-2042ST.
17. Fresard I, Genecand L, Altarelli M, Gex G, Vremaroiu P, Vremaroiu-Coman A, et al. Dysfunctional breathing diagnosed by cardiopulmonary exercise testing in “long COVID” patients with persistent dyspnoea. *BMJ Open Respiratory Research*. 2022;9(1): e001126. doi:10.1136/bmjresp-2021-001126.
18. Skjorten I, Ankerstjerne OAW, Trebinjac D, Brønstad E, Rasch-Halvorsen O, Einvik G, et al. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation. *The European Respiratory Journal*. 2021;58(2): 2100996. doi:10.1183/13993003.00996-2021.
19. Cortés-Telles A, López-Romero S, Figueroa-Hurtado E, Pou-Aguilar YN, Wong AW, Milne KM, et al. Pulmonary function and functional capacity in COVID-19 survivors with persistent dyspnoea. *Respiratory Physiology and Neurobiology*. 2021;288: 103644. doi:10.1016/j.resp.2021.103644.
20. Bardakci MI, Ozturk EN, Ozkarafakili MA, Ozkurt H, Yanc U, Yildiz Sevgi D. Evaluation of long-term radiological findings, pulmonary functions, and health-related quality of life in survivors of severe COVID-19. *Journal of Medical Virology*. 2021;93(9): 5574–5581. doi:10.1002/jmv.27101.
21. Fumagalli A, Misuraca C, Bianchi A, Borsa N, Limonta S, Maggiolini S, et al. Long-term changes in pulmonary function among patients surviving to COVID-19 pneumonia. *Infection*. 2022;50(4): 1019–1022. doi:10.1007/s15010-021-01718-2.
22. Steinbeis F, Thibeault C, Doellinger F, Ring RM, Mittermaier M, Ruwwe-Glösenkamp C, et al. Severity of respiratory failure and computed chest tomography in acute COVID-19 correlates with pulmonary function and respiratory symptoms after infection with SARS-CoV-2: an observational longitudinal study over 12 months. *Respiratory Medicine*. 2022;191: 106709. doi:10.1016/j.rmed.2021.106709.
23. Tanni SE, Fabro AT, de Albuquerque A, Ferreira EVM, Verrastro CGY, Sawamura MVY, et al. Pulmonary fibrosis secondary to COVID-19: a narrative review. *Expert Review of Respiratory Medicine*. 2021;15(6): 791–803. doi:10.1080/17476348.2021.1916472.
24. Rumende CM, Susanto EC, Sitorus TP. The management of pulmonary fibrosis in COVID-19. *Acta Medica Indonesiana*. 2021;53(2): 233–241.
25. Safont B, Tarraso J, Rodriguez-Borja E, Fernández-Fabrellas E, Sancho-Chust JN, Molina V, et al. Lung function, radiological findings and biomarkers of fibrogenesis in a cohort of COVID-19 patients six months after hospital discharge. *Archivos de Bronconeumología*. 2022;58(2): 142–149. doi:10.1016/j.arbres.2021.08.014.
26. Wendisch D, Dietrich O, Mari T, von Stillfried S, Ibarra IL, Mittermaier M, et al. SARS-CoV-2 infection triggers profibrotic macrophage responses and lung fibrosis. *Cell*. 2021;184(26): 6243–6261.e27. doi:10.1016/j.cell.2021.11.033.
27. Lerum TV, Aaløkken TM, Brønstad E, Aarli B, Ik Dahl E, Lund KMA, et al. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. *The European Respiratory Journal*. 2021;57(4): 2003448. doi:10.1183/13993003.03448-2020.
28. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *The Lancet*. 2020;396(10247): 320–332. doi:10.1016/S0140-6736(20)31305-2.
29. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. *Zhonghua Bing Li Xue Za Zhi Chinese Journal of Pathology*. 2020;49(5): 411–417. doi:10.3760/cma.j.cn112151-20200312-00193.
30. Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, et al. Persistent post – COVID-19 interstitial lung disease. An observational study of corticosteroid treatment. *Annals of the American Thoracic Society*. 2021;18(5): 799–806. doi:10.1513/AnnalsATS.202008-1002OC.
31. Franquet T, Giménez A, Ketai L, Mazzini S, Rial A, Pomar V, et al. Air trapping in COVID-19 patients following hospital discharge: retrospective evaluation with paired inspiratory/expiratory

- thin-section CT. *European Radiology*. 2022;32(7): 4427–4436. doi:10.1007/s00330-022-08580-2.
32. Jia X, Han X, Cao Y, Fan Y, Yuan M, Li Y, et al. Quantitative inspiratory-expiratory chest CT findings in COVID-19 survivors at the 6-month follow-up. *Scientific Reports*. 2022;12(1): 7402. doi:10.1038/s41598-022-11237-1.
33. Lopes AJ, Litrento PF, Provenzano BC, Carneiro AS, Monnerat LB, da Cal MS, et al. Small airway dysfunction on impulse oscillometry and pathological signs on lung ultrasound are frequent in post-COVID-19 patients with persistent respiratory symptoms. *PLoS One*. 2021;16(11): e0260679. doi:10.1371/journal.pone.0260679.
34. Mogami R, Araújo Filho RC, Cobo Chantong CG, Santos de Almeida FC, Baptista Koifman AC, Jauregui GF, et al. The importance of radiological patterns and small airway disease in long-term follow-up of postacute COVID-19: a preliminary study. *Radiology Research and Practice*. 2022;2022: 7919033. doi:10.1155/2022/7919033.
35. Rovere Querini P, De Lorenzo R, Conte C, Brioni E, Lanzani C, Yacoub MR, et al. Post-COVID-19 follow-up clinic: depicting chronicity of a new disease. *Acta Bio-Medica: Atenei Parmensis*. 2020;91(9–S): 22–28. doi:10.23750/abm.v91i9-S.10146.
36. British Thoracic Society. British Thoracic Society guidance on respiratory follow up of patients with a clinico-radiological diagnosis of COVID-19 pneumonia. 2020. Available from: <https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/resp-follow-up-guidance-post-covid-pneumonia/> [Accessed 14 December 2022].