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Functional diagnostics of the respiratory system in patients with Long COVID

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Abstract. Given the considerable number of people with persistent respiratory symptoms more than 4 weeks after COVID-19, it is important to determine which examinations are most informative for assessing respiratory function, prognosis, and monitoring the effectiveness of treatment in such patients. The purpose of this study is to cover the functional diagnosis of the respiratory system in patients who survived Long COVID. Bibliosemantic and analytical research methods were applied. According to the world guidelines for patients with persistent respiratory symptoms after COVID-19, all of them should undergo respiratory system examinations: chest X-rays, spirometry, blood saturation measurements, lung diffusion capacity for carbon monoxide, walk tests, and others. The study confirmed that people who have had COVID-19, even after 1-6 months, show a decrease in diffusing capacity of the lung for carbon monoxide, which has a direct correlation with total lung capacity, the severity of clinical manifestations, and the results of rapid tests. Changes in spirometric parameters are observed much less frequently, mainly in patients hospitalised with severe pneumonia, which subsequently leads to post-cystic pulmonary fibrosis. Gradual improvement in functional respiratory tests occurs 3 months, 6 months, and 12 months after acute infection. The most informative tests for assessing respiratory function include the measurement of carbon monoxide diffusion capacity, total lung capacity, and blood gas composition. In conditions of limited access to the aforementioned diagnostic tests, and as a screening tool, quick tests such as the 3-minute/6-minute walk test (3MWT/6MWT) or the 1-minute sit-to-stand test (1-MSTST) can be utilised based on the patient's capabilities

Keywords: spirometry; pulmonary function tests; COVID; walk test

INTRODUCTION

The coronavirus disease (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) has become a real challenge for doctors around the world. Despite advances in treatment, thousands of people continue to experience illness, isolation, and mortality. It has become evident that even successful recovery from

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the acute phase of the disease does not guarantee individuals protection from delayed manifestations or complications. Reflecting the growing number of such patients, the World Health Organization (WHO) introduced a separate code, U09.9, in January 2021 to classify the post-COVID-19 condition. Such prolongation of clinical symptoms after COVID-19 requires new approaches to their monitoring and treatment, and innovative solutions from the medical community of the world.

The term "Long COVID" was initially used by Italian physician Elisa Perego (Lombardy, Italy) on social media to describe her own experience of battling the coronavirus, which had a fluctuating course with various and changing symptoms lasting for several months. Subsequently, it appeared in an article in the British Medical Journal (BMJ) by E. Mahase [1], noting that SARS-CoV-2 is a novel virus, leaving many questions unanswered for healthcare professionals and researchers, requiring studies that evaluate the long-term consequences of COVID-19. This term was used by other publications, and "Long COVID-19" became rooted in the medical and scientific communities. The United Kingdom National Health Service (NHS) [2] proposed the following definitions: acute COVID-19 – a condition where signs and symptoms of the disease last for four weeks; ongoing symptomatic COVID-19 describes symptoms lasting for 4-12 weeks; post-COVID-19 is used when signs and symptoms that develop during or after COVID-19 infection persist for more than 12 weeks and cannot be explained by an alternative diagnosis. Post-COVID-19 typically encompasses a range of symptoms that can vary and affect various body systems. Long COVID-19 is a term proposed to describe signs and symptoms that develop after acute COVID-19 and last for more than 4 weeks. Therefore, it includes both the ongoing symptomatic variants of COVID-19 (acute and persistent) and post-COVID-19 manifestations. There is a diversity and variability of clinical symptoms observed in a cyclical pattern of COVID-19. A considerable portion of patients did not have pre-existing health issues before contracting SARS-CoV-2. In some patients, persistent systemic manifestations persist for quite a long time, even after the fever and respiratory symptoms decrease. In others, after a full recovery, some symptoms return after a few days with greater intensity and duration. A number of patients report a pronounced cyclicity, with several days of improvement and deterioration [3-5].

In the pathogenesis of the viral disease, the sensitivity of viruses to the receptors of the host cells plays a crucial role, followed by their proliferation, and the variable expression of these receptors in different organs. W. Ni *et al.* [6] in their paper provide a rationale for one of the mechanisms explaining the absence of specific symptoms in COVID-19 due to the tropism of SARS-CoV-2 for angiotensin-converting enzyme 2 (ACE2) receptors present on the cell membranes of many human organs. This partially explains the wide spectrum of clinical symptoms and their development, independent of the route of infection, severity of the disease course, and variants of the acute phase outcome.

The purpose of the study was to identify the possibilities of functional diagnostics of the respiratory system in Long COVID based on the global experience by analysing available information and literature sources.

PREDICTED SYMPTOMS, CONSEQUENCES, AND PRIMARY DIAGNOSIS OF CORONAVIRUS DISEASE

The study by D.D. Lutchmansingh *et al.* [7] provides a basis for understanding possible complications and consequences following a COVID-19 infection. The researchers proposed a model (Fig. 1) of acute COVID-19 complications with predicted symptoms thereafter and ultimate multi-organ consequences that may arise as a result of direct viral damage through angiotensin-converting enzyme 2 (ACE2) receptors, hypoperfusion, systemic inflammation, toxic effects of treatment, or a multi-organ vascular component.

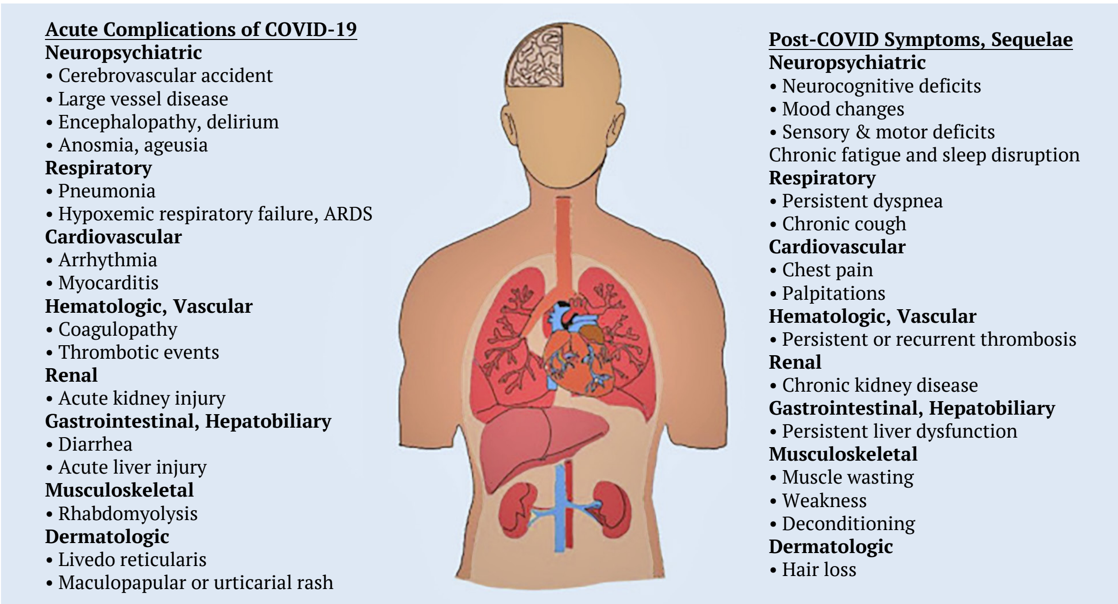

Figure 1. Model of acute pulmonary and extrapulmonary complications of coronavirus disease 2019 with predicted symptoms after COVID-19 and ultimate organ consequences
Source: [7]

Among the multifaceted long-term consequences of COVID-19, E.S. Izmailova & T.F. Reiss [8] outline three groups: pulmonary, neurological, and neuropsychiatric symptoms, including depression and cognitive dysfunction. The authors focus specifically on respiratory system changes, methods of their monitoring, and emphasise the need for further research dedicated to monitoring the condition of patients with prolonged respiratory manifestations both in hospital settings and at home.

According to a recent meta-analysis cited by D. Radovanovic & E. D'Angelo [9], 43% to 62% of recovered patients from acute COVID-19 have at least one residual symptom, with fatigue and dyspnea being the most prevalent. Numerous attempts to determine the cause of prolonged dyspnea and identify its possible associations with phenotype, patient age, and severity of the acute period are still incomplete and require a comprehensive approach to this complex condition.

K. Guziejko *et al.* [10] also provide similar observations: 24 weeks after recovery, 46% of patients report coughing, 23% – shortness of breath, and 13% – weakness. These symptoms occur not only after hospitalisation due to a severe onset of the disease but also after a period of home isolation with mild initial manifestations. Subsequently, many individuals who have had COVID-19 undergo routine examinations by general practitioners, infectious disease specialists, cardiologists, pulmonologists, and neurologists. However, the pronounced changes needed to explain all symptoms are not always detectable, and for such patients, the dominant diagnosis becomes "functional impairments".

As COVID-19 does not have strictly specific symptoms, according to global standards, the initial diagnostic workup begins with a complete blood count, blood biochemistry with a focus on urea, electrolytes, liver function tests, thyroid-stimulating hormone (TSH) levels, glycated hemoglobin (HbA1c), ferritin, vitamin D, and lipid profile [7, 11, 12] to exclude alternative diagnoses. Other examinations are prescribed according to the symptoms. For example, if a patient experiences dyspnea and chest pain, chest radiography, oxygen saturation determination, electrocardiography (ECG), echocardiography, and brain natriuretic peptide (NT-BNP) testing are included in the necessary examinations.

All individuals with persistent respiratory symptoms after COVID-19 should undergo respiratory system examinations that can visualise structural changes (chest X-ray, CT angiography of the pulmonary arteries, or high-resolution computed tomography) and assess its functional capacity: determining blood saturation, spirometry, body plethysmography, measuring lung diffusion capacity, and determining blood gas composition. It should be noted that a consensus has been reached on this recommendation [9, 11, 13].

The potential risk of SARS-CoV-2 infection considerably limited the use of respiratory diagnostic functional tests worldwide at the start of the pandemic. However, modern spirometry techniques, conducted according to American Thoracic Society/European Respiratory Society (ATS/ERS) standards and with adherence to all conditions for preventing cross-infection, allow for a qualitative assessment of respiratory function [14-16]. Their results are most valuable in the presence of airway obstruction [14, 17]. Therefore, this examination is considered the gold standard for diagnosing chronic obstructive pulmonary disease (COPD) according to the global initiative for chronic obstructive lung disease (GOLD) report 18, 19].

In the majority of patients with mild and moderate symptoms, forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and the FEV1/FVC ratio were within normal limits [11, 19]. It was found that changes in spirometry indicating obstructive or restrictive impairments were detected in 17% of cases, mainly in patients hospitalised with severe pneumonia. Subsequently, they were only observed in individuals with post-COVID lung fibrosis confirmed by X-ray. A similar trend was observed in other studies [20, 21].

More information about respiratory function can be obtained through body plethysmography. Residual lung volume, total lung capacity (TLC), and maximal voluntary ventilation are measured using body plethysmography. It also determines the maximum expiratory and inspiratory pressures, which allow for the assessment of the strength of respiratory muscles, which is crucial in the presence of hidden forms of respiratory insufficiency [19].

ASSESSMENT OF LUNG FUNCTION AFTER COVID-19

The effectiveness of gas exchange in the lungs can be judged by changes in carbon monoxide diffusing capacity (DLCO) and blood gas composition. According to many researchers, DLCO most often reflects respiratory system impairments in Long COVID. It has been confirmed that even 1 month after discharge from the hospital, individuals who have had COVID-19 commonly experience a decrease in DLCO, which is the most common lung function abnormality. The more severe the disease, the more frequent and significant the decrease in DLCO and TLC compared to non-severe cases [10, 11, 22]. A similar correlation was observed in patients over 60 years of age and those who received invasive ventilation, with a considerable portion of them having low DLCO even 4 months after discharge [23]. However, there are conflicting statements regarding the association between the decrease in DLCO and FEV1 – some studies show a correlation [24-26], while others do not find a clear dependence [11, 19].

Lung damage in COVID-19 is associated with diffuse destruction of alveolar epithelium, capillary damage and bleeding, formation of hyaline membrane, fibrotic proliferation of the alveolar septum, and lung consolidation. However, the changes observed during its prolonged course may indicate that impairment of membrane diffusion capacity is the dominant pathophysiological mechanism compared to a decrease in lung volume [27]. Its gradual regression contributes to the fact that most individuals who have recovered from COVID-19 demonstrate progressive improvement in functional respiratory test results at 3 months, 6 months, and 12 months after acute infection [28-30].

It should be noted that the most informative examination of respiratory function was for patients who, after acute COVID-19 affecting the respiratory system, have complaints such as prolonged coughing. Conversely, in individuals who only have shortness of breath, functional respiratory tests often do not reveal deviations from normal. Since shortness of breath is not necessarily associated with impaired pulmonary function caused by SARS-CoV-2, and may be a manifestation of concomitant pathology, patients require proper differential diagnosis [10].

RAPID TESTS TO ASSESS THE FUNCTIONAL ABILITY OF THE RESPIRATORY SYSTEM

In situations with limited access to the aforementioned investigations [13, 31], rapid tests such as the 3- or 6-minute walk test (3/6MWT) or the 1-minute sit-to-stand test (1MSTST) can be used to evaluate the functional capabilities of the respiratory system in Long COVID and other chronic conditions, depending on the patient's abilities [32, 33].

E.S. Izmailova & T.F. Reiss [8] propose including diagnostic methods in a comprehensive package of dynamic monitoring, both in the clinic and at home, for individuals with slow or incomplete recovery. The scheme of this comprehensive monitoring package is presented in Figure 2. According to the authors, remote monitoring is more convenient for patients and creates more complete data sets.Remote monitoring can help answer numerous questions about the nature of this condition and aid in assessing treatment effectiveness, thereby mitigating its consequences and reducing mortality. For example, computed tomography (CT) scans and DLCO assessments are performed in clinical settings, while other lung function parameters such as FVC and FEV1, pulse oximetry results, and walking tests can be obtained remotely.

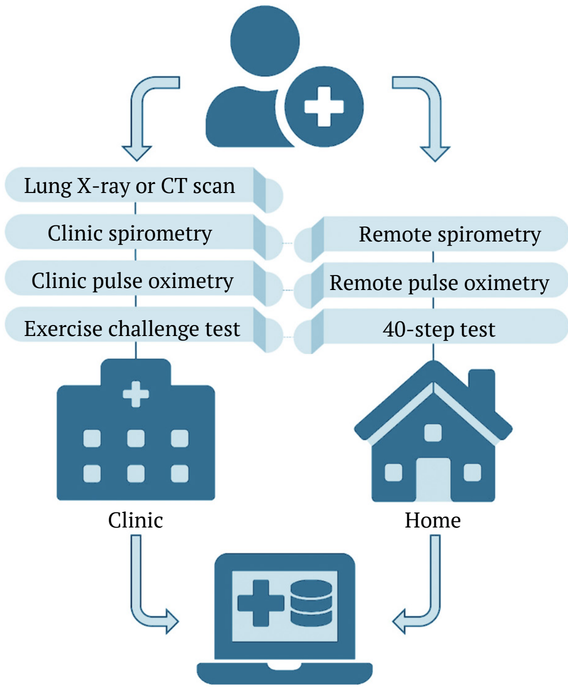

Figure 2. Examinations performed in the clinic and at home

Source: [8]

Tests such as the 3- or 6-minute walk test (3MWT or 6MWT) [20, 34, 35] play a crucial role in assessing the functional capacity of the respiratory system, determining physical exercise tolerance, evaluating prognosis, and treatment response in various respiratory conditions. In a medical facility, the patient is asked to walk as far as possible along the internal corridor in 3 or 6 minutes. If necessary, one can stop during the test. Before and after the test, measurements are taken of respiratory rate (RR), heart rate (HR), arterial oxygen saturation (SpO_2), blood pressure, shortness of breath, and subjective fatigue. The additional distance that the patient can cover compared to the previous trial is also recorded. During the test, SpO2 and HR are measured using a pulse oximeter.

In the conditions of deep desaturation development (reduced SpO_2 up to 80%), the test stops. If SpO_2 recovers to 85% during the 6MWT, the patient may be encouraged to continue walking. The test is also stopped if the patient experiences chest pain, severe shortness of breath, leg cramps, staggering, excessive sweating, or a change in skin colour to pale or ashen [36, 37]. Parameters within the test (pre- and post-test) are analysed and compared to previous results.

Proper conditions are required for the accurate execution of the 6-minute walk test (6MWT), such as a route length of 30 m or ideally longer [32]. Alternatively, the 1-minute sit-to-stand test (1-MSTST) can be used, where the patient performs the test with a chair of standard height (46 cm) without armrests placed near a wall. The person being assessed sits on the chair with a straight back, knees bent at a 90° angle, feet flat on the floor hip-width apart, and hands resting on the thighs without movement. The patient is asked to stand up (move to an upright position), and then sit back on the chair in the starting position at a speed that will be safe and comfortable. The use of hands for support should be avoided. As many repetitions as possible are performed within 1 minute, with rest allowed if needed. The position of the hands during the test (crossed on the chest, hanging by the sides, or resting on the thighs), the number of completed exercises, and the number of repetitions are recorded [37, 38]. The modified Borg scale (0-10) is used to assess breathlessness and fatigue immediately before and after the test [39, 40]. HR and peripheral oxygen saturation (SpO_2) are measured using a pulse oximeter before and after the test, along with the time taken for the parameters to return to baseline. A desaturation level of ⩾4% is considered clinically significant for this study.

Comparative analysis of the dynamics of changes during rapid tests with walking or squatting reveals a direct correlation between their results and spirometry and X-ray examinations [21, 39], pO values$_2$ and pCO_2 in venous blood [34], severity of clinical symptoms, SpO_2, and DLCO levels which may indicate that desaturation during exercise is associated with parenchymal and/or pulmonary vascular phenomena [36]. Considering this, physical exertion tests can be a reliable, valid, and sensitive alternative or complement in situations with limited access to instrumental investigations.

The post-COVID-19 condition is relatively new, and there is a lack of experience in choosing the best management strategy for it. The presence of persistent respiratory symptoms, which occur in almost half of these patients 1 month after COVID-19 and later, necessitates the search for optimal methods to diagnose respiratory dysfunction and expedite their implementation into daily practice.

CONCLUSIONS

The COVID-19 pandemic has undoubtedly become an unprecedented case in history, despite a fairly high awareness of the mechanisms of development of viral processes, experience in combating them, and the high-tech capabilities of modern medicine. The efforts of doctors and researchers were aimed at finding effective quarantine measures and innovative methods of treating acute diseases. Unlike previous viral epidemics, SARS-CoV-2 has the ability to prolong clinical manifestations, particularly in the respiratory system. In the vast majority of survivors, at least one symptom persists for over 3-6 months, requiring the exploration of new approaches in both treatment and diagnosis since timely and effective detection of changes is unquestionably crucial for considerably reducing the risk of complications.

The most informative investigation for assessing respiratory function is the measurement of DLCO. Decreased DLCO directly correlates with changes in total lung capacity and blood gas composition. However, these assessments can only be performed in a hospital setting. Therefore, in conditions of limited access to them, rapid tests can be used as outpatient monitoring to assess the prognosis and response to treatment: the 3-x/6-minute walking test (3mwt/6MWT) or the 1-minute sit-up test (1-MSTST).

The pronounced multiorgan involvement and nonspecific symptomatology in Long COVID necessitate the adaptation of analysis algorithms and the correlation of data obtained under different conditions, and the coordination of communication channels between patients and specialists from various fields, which may be crucial in effectively countering future epidemics.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Функціональна діагностика дихальної системи у пацієнтів при Long COVID

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Анотація. Враховуючи значну кількість осіб, що мають персистуючі респіраторні симптоми понад 4 тижні після перенесеного COVID-19, важливо визначити, які обстеження є найінформативнішими для оцінки респіраторної функції, прогнозу та контролю ефективності лікування у таких пацієнтів. Мета статті полягала у дослідженні функціональної діагностики дихальної системи у пацієнтів, які пережили Long COVID. Застосовано бібліосемантичний, аналітичний методи дослідження. Відповідно до світових рекомендацій щодо пацієнтів з персистуючими респіраторними симптомами після COVID-19, всі вони повинні пройти обстеження дихальної системи: рентгенографію органів грудної клітки, спірометрію, вимірювання сатурації крові, дифузійної здатності легень для монооксиду вуглецю, тести з ходьбою та інші. Дослідженням підтверджено, що в осіб, які перенесли COVID-19, навіть через 1-6 місяців виявляється зниження дифузної ємності легень для монооксиду вуглецю, що має прямий кореляційний зв'язок із загальною ємністю легень, важкістю клінічних проявів та результатами швидких тестів. Зміни спірометричних показників спостерігаються значно рідше, переважно у пацієнтів госпіталізованих з тяжкою пневмонією, яка згодом призводить до постковідного легеневого фіброзу. Поступове покращення показників функціональних дихальних тестів відбувається через 3 місяці, 6 місяців та 12 місяців після гострої інфекції. Найінформативнішими обстеженнями для оцінювання функції дихальної системи є визначення дифузійної здатності за монооксидом вуглецю, загальної ємкості легень та газового складу крові. В умовах обмеженого доступу до перерахованих обстежень та у якості скринінгового дослідження можна використати швидкі тести: тест з 3-х/6-хвилинною ходьбою (3MWT/6MWT) або 1-хвилинний тест «сісти-встати» (1-MSTST) відповідно до можливостей пацієнта

Ключові слова: спірометрія; функціональні легеневі тести; COVID; тест із ходьбою