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Position on the follow-up of patients after a bout of COVID-19 pneumonia

Mnenje za spremljanje bolnikov po preboleli covidni pljučnici

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Abstract

Pneumonia is the most common complication of SARS-CoV-2 infection. COVID-19 pneumonia is a serious illness and can lead to respiratory failure. Pulmonary infiltrates often resorb spontaneously; however, sometimes treatment with systemic glucocorticoids is required. Upon discharge from the hospital, treatment is usually not yet completed. The Slovenian Respiratory society made suggestions for the treatment and follow-up of patients with covid 19 pneumonia after discharge from hospital. We are aware that with new findings we will need to update these recommendations.

Izvleček

Pljučnica je najpogostejši vzrok za težji potek okužbe z virusom SARS-CoV-2 in s hospitalizacijo. Potek covidne pljučnice je lahko različen; infiltrati, vidni na rentgenski sliki, se lahko resorbirajo spontano, včasih pa je potrebno zdravljenje s sistemskimi glukokortikoidi. Ob odpustu iz bolnišnice zdravljenje običajno še ni končano, zato je Združenje pulmologov Slovenije v želji po enotnem obravnavanju bolnikov s covidno pljučnico izdelalo mnenje za obravnavo in sledenje bolnikov po odpustu iz bolnišnice. Zavedamo se, da ob novi bolezni ne gre za dokončno mnenje, saj bodo nova spoznanja o covidni pljučnici zanesljivo zahtevala obnavljanje mnenj.

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1 Introduction

Since the first cases of confirmed SARS-CoV-2 infection up to December 2020 there were more than 66 million cases worldwide, including more than 1.5 million deaths (1). In Slovenia, there were 131,700 cases of infection and 2,800 deaths (2,3). The infection can be asymptomatic, mild, or severe, which can result in the death of the patient. Studies show that 14% of those infected need hospitalization and 2% of those infected need treatment in an intensive care unit (4). The most common symptoms of SARS-CoV-2 virus infection are fever, cough, malaise with severe overall weakness, loss of smell and taste, and headaches. The target organ is the respiratory tract: the most severe form always affects the lungs. This is accompanied by respiratory failure, which can develop into ARDS. The main factors for a severe course of COVID-19 are age (especially over 55 (2)), diabetes, arterial hypertension, and obesity. Factors regarding the respiratory system include smoking and COPD, presenting risks for severe COVID-19 pneumonia (5). In immunocompromised people, a more difficult course is expected (6).

Based on the most recent findings, this article is an attempt to give a pulmonary perspective on monitoring patients with COVID-19 pneumonia.

2 Pathophysiology and pathology

Airway epithelial cells and alveolar epithelial type II cells express the angiotensin-converting enzyme 2 (ACE2), which is the SARS-CoV-2 point of entry into cells (7). Entering a cell requires the activity of a type 2 transmembrane serine protease on the same cell as ACE2. SARS-CoV-2 virus is an RNA virus that, after entering a cell, uses the cellular structures to replicate. When new virus particles are released from an infected cell, the cell dies. The loss of alveolar epithelial type II cells reduces the formation of surfactant, causing the alveoli to collapse. Regeneration and differentiation into alveolar epithelial type I cells are also interrupted, affecting the alveolar-capillary membrane and impaired gas exchange through it (8). The loss of alveolar epithelial type II cells is accompanied by a decline in ACE2 activity, which is crucial for the conversion of angiotensin II to angiotensin- (1–7). Altered balance of angiotensin II and angiotensin- (1-7) increases apoptosis, inflammation and fibrosis, and decreases alveolar fluid drainage (8). It is also associated with the development of microvascular thrombosis. Decreased ACE2 activity could be associated with increased bradykinin receptor-1 activation and the development of local angioedema (9). The SARS-CoV-2 virus also infects capillary endothelial cells in the lungs, causing additional damage to the alveolocapillary membrane (10). Due to the infection, various mediators are released, e.g. interleukin 6 and interleukin 8. Relatively mild interstitial infiltrations of T lymphocytes develop in lung tissue.

In those who died as a result of SARS-CoV-2 virus infection, acute diffuse alveolar damage develops in the lungs with intra-alveolar and interstitial oedema, fibrin exudation and the appearance of hyaline membranes (11,12). Alveolar epithelial cells are severely reactively altered. In the proliferative phase of alveolar damage, interstitial and intra-alveolar fibroplasia develop, which can lead to the development of fibrosis. Endothelial damage of the pulmonary vessel is manifested by microthrombosis (13). Autopsy samples from patients who died of COVID-19 pneumonia showed significantly more microthrombosis and thromboembolic changes than in patients who died from influenza pneumonia (14).

3 COVID-19 pneumonia

COVID-19 pneumonia is caused by SARS-CoV-2 virus infection and must be radiologically confirmed. It is clinically manifested by fever, cough, dyspnoea, chest tightness, and malaise (15). Extensive pneumonia can be the cause of hypoxemic respiratory failure. It can be in the clinical form of "silent hypoxemia", as some patients with severe hypoxemia and increased respiratory rate do not feel shortness of breath. The phenomenon of "silent hypoxemia" is explained by the formation of right-left shunts due to impaired hypoxic vasoconstriction and maintained preserved lung compliance. The ratio between minute ventilation and work of breathing is close to normal, so the patient does not feel dyspnoea despite hypoxemia (16,17).

Common laboratory findings in COVID-19 pneumonia are lymphopenia (up to 83% of patients), elevated inflammatory markers (such as CRP and interleukin 6), D-dimer, and lactate dehydrogenase (LDH) (10). Procalcitonin is elevated in a smaller proportion of patients and is associated with poorer prognosis (18).

In some patients, COVID-19 pneumonia progresses to ARDS, which is associated with poor prognosis (15).

After recovering from a severe form, pulmonary fibrosis may develop (19). There are cases of treating end-stage respiratory failure with lung transplantation described (20). There were also several such cases in Slovenia.

4 Imaging

An X-ray or CT of the lungs most commonly shows bilateral multilobar thickenings predominating in the peripheral, posterior, and basal segments of the lungs. The development of changes is similar to that of other causes of acute lung injury. In the early phase (0–4 days) ground-glass opacities predominate, consolidations are rare (visible mainly in the elderly). Dilated vessels in ground-glass opacities are visible at an early stage in more than half of the cases. As the disease progresses, the number and size of ground-glass opacities in the progressive phase (5-8 days) increase and usually thicken into consolidations or appear thickened in the inter- and intralobular septum (a pattern called crazy paving). Consolidations usually have a subpleural or peribronchovascular distribution characteristic of the radiological pattern of organizing pneumonia, which may also be associated with the histological proliferative phase of diffuse alveolar damage (DAD). The changes progress until about the tenth day after the onset of symptoms, when perilobular thickenings, bandlike opacities and a sign of reversed halo may also appear. The bronchi in consolidations are often tractionally dilated. The absorption phase is usually radiologically visible after day 14 and can last for a long time, even several weeks or months. The density of infiltrates gradually decreases, and the volume of the affected parts increases again, which may give the false impression of a greater extent of the disease. Traction bronchiectasis gradually disappears (21-25). A longer course is seen mainly in elderly patients with an initial greater extent of changes, in patients with associated diseases and in those treated in the intensive care; it also depends on the adequacy of the treatment. CT still shows thickening in a quarter of patients three months after inpatient treatment, predominantly as ground-glass opacities or subpleural parenchymal band, more common in patients treated in the intensive care unit (26-28).

Pulmonary emboli are common, especially in patients in intensive care units. Enlarged mediastinal lymph nodes, pleural or pericardial effusion, and cavitation or pneumothorax are unusual signs that may occur in the later stages of the disease (21,22).

Radiologically assessed extent of lung involvement is a predictor of the disease (29).

The sensitivity of the CT scan to show lung involvement in COVID-19 is more than 90% and is expected to be greater than the sensitivity of the radiograph. When using an X-ray, we must be especially careful at the beginning of the disease so as not to underestimate the extent of lung involvement. It is poorly sensitive in detecting lung involvement following a ground-glass opacity. Nevertheless, the radiograph is the first and most common imaging method for monitoring the course of the disease. CT is especially important for the detection of complications and associated diseases, and after suffering from pneumonia it is in place in patients with functional disorders or in the case of clinical suspicion of pulmonary embolism (30).

With clinical suspicion of COVID-19 pneumonia, chest CT exceeds the sensitivity of the polymerase chain reaction (PCR) test to SARS-Cov-2 virus in a nasal swab, but the CT image is not characteristic of COVID-19 pneumonia (31). If the CT scan result allows for the possibility of COVID-19 pneumonia, it is confirmed in the case of a negative throat swab by proving the presence of SARS-Cov-2 virus in bronchoalveolar lavage (BAL) or expectoration (32).

5 Treatment

Treatment for COVID-19 pneumonia includes supportive care, including respiratory support, and targeted treatment aimed at inhibiting virus replication or altering the patient's immune response (10,33).

Oxygenation is required by more than 75% of hospitalized patients (34). If sufficient oxygenation is not achieved, high-flow nasal oxygen systems or non-invasive ventilation can be used. In the most severe lung involvement, mechanical ventilation is required, in which we follow the principles of protective ventilation. In some patients, extracorporeal membrane oxygenation (ECMO) therapy may be chosen (either as a support until recovery or as a support until lung transplantation) (35).

Knowledge about the use of drugs to treat COVID-19 is rapidly expanding and changing. In February 2021, the European Respiratory Society (ERS) published recommendations recognizing systemic glucocorticoids, interleukin-6 (IL-6) inhibitors and anticoagulant preparations as effective drugs for treating COVID-19. Antiviral drugs developed for the treatment of other diseases have not been shown to be effective in clinical trials to date and are therefore not recommended in this document (36). The exception was only one randomized and placebo-controlled study in hospitalized patients with signs of lower respiratory involvement, in which remdesivir shortened the duration of the disease from 15 to 10 days (37), but was not confirmed in other studies with remdesivir (36). In Slovenia, remdesivir was still used in clinical practice at the time of writing this article. Some people also use plasma from patients who have had COVID-19, but the effectiveness of this approach has not yet been unequivocally confirmed in research (38). It is effective in a narrow group of patients receiving B cell-directed biologic therapy (anti CD20) and in patients who fail to produce specific antibodies to SARS-CoV-2 due to congenital defects or diseases of the immune system (39). There is no evidence of efficacy of hydroxychloroquine or azithromycin (10).

In the treatment of COVID-19, systemic glucocorticoids have been shown to be effective. Dexamethasone improved the survival of hospitalized patients who required oxygen or mechanical ventilation (39). The greatest effect was seen in patients who had symptoms for more than seven days or in patients who were mechanically ventilated. In these patients, an overactive immune response appears to play a greater role than the active viral replication. There are more and more published studies confirming the beneficial effect of systemic glucocorticoids on the course of pneumonia in the case of COVID-19 (40-42). Of the other anti-inflammatory drugs, according to some studies, interleukin-6 inhibitors (tocilizumab) are also potentially effective in hospitalized patients, reducing the proportion of patients who required mechanical ventilation or died of COVID-19 pneumonia (43,44).

All patients should be provided with adequate relief of dyspnoea and anxiety and with oxygenation. Patients who need it should be provided with appropriate rehabilitation or palliative care.

6 Currently established domestic practices

On the basis of the RECOVERY study (39), dexamethasone treatment was also introduced in our facilities. If acute respiratory failure requiring oxygen therapy occurs, patients with COVID-19 pneumonia are administered a daily dose of 6 mg of dexamethasone for a maximum of ten days or until the discontinuation of oxygen therapy, but no longer than ten days (45).

As a rule, methylprednisolone treatment is also introduced in patients in whom the infiltrates, visible on the chest radiograph, do not decrease and the need for oxygen remains the same or even higher. An assessment by the thoracic radiologist or a CT scan serves as additional help. In the case of a pattern of organizing pneumonia, treatment with methylprednisolone, 0.75 to 1.0 mg/kg body weight (reference), is initiated. The introduction of methylprednisolone and the method of reduction are usually done in consultation with a pulmonologist, as the duration of treatment has been modified. Treatment with glucocorticoids should last four to eight weeks and not for several months as in cryptogenic organizing pneumonia (46,47). All patients receiving systemic glucocorticoids for more than three weeks require substitution therapy and an adrenal function test after six months. Upon discharge, the patient should be provided with detailed instructions and a systemic glucocorticoid intake regimen. When long-term use of a systemic glucocorticoid is anticipated, caution should be taken to prevent pneumocystis infection (48).

If the pulmonologist decides that the patient still needs oxygen treatment at discharge, the application for temporary oxygen therapy at home should be submitted to the HIIS (Health Insurance Institute of Slovenia) regional unit, and the patient and relatives should be instructed on how to use it.

7 Monitoring patients with COVID-19 pneumonia

Given the radiological changes and with expanding clinical experience, it is becoming clear that the consequences detected in patients with clinically and radiologically confirmed COVID-19 pneumonia will manifest as interstitial lung involvement (49) and pulmonary hypertension. The rules of good clinical practice, applicable guidelines and the limited capacity of the healthcare system must be followed. The intensity of monitoring should be based on the severity of the pneumonia, the likelihood of late respiratory complications and the functional status at discharge.

A patient who recovers from pneumonia should be monitored by a pulmonologist after discharge from the hospital. He should be issued a referral with an appropriate urgency level of "very fast" and referred to a pulmonology clinic. The interval between discharge from hospital and follow-up visit should be determined by the discharge physician, taking into account the course of the COVID-19 pneumonia as well. The time to examination should be shorter for patients treated in the intensive care unit and for patients with mechanical ventilation, and those patients who have already been diagnosed with interstitial lung disease. In order to ensure equal treatment of patients with a comparably severe course of COVID-19 pneumonia, recommendations of approximate intervals are given further in this chapter.

The discharge documentation should also include the last chest X-ray and a CT scan of the chest before discharge (with the image placed on electronic media such as a CD, as not all pulmonary clinics have access to hospital image files). Where possible, the patient should obtain results of previous lung function tests before the follow-up examination (e.g. from a referral clinic or occupational medical examination) in order to determine deterioration of lung function compared to the condition before COVID-19.

The purpose of monitoring is to detect complications of COVID-19 pneumonia and their timely treatment:

- Early detection of lung damage after COVID-19 pneumonia (pulmonary fibrosis and pulmonary hypertension);
- Chest X-ray confirming complete absence of alterations;
- Patients with incidental pulmonary pathology identified with COVID-19 should be referred for appropriate treatment.

Unfortunately, we do not yet know the optimal time required to monitor and determine the late consequences. The advised treatment and check-up intervals are presented in Figures 1 and 2 (50). Patients with persistent or progressive respiratory symptoms such as dyspnoea, chest pain, or a cough may have early/acute COVID-19 complications (pulmonary hypertension, pulmonary embolism, interstitial lung disease, secondary infection) and should be treated appropriately in accordance with good clinical practice.

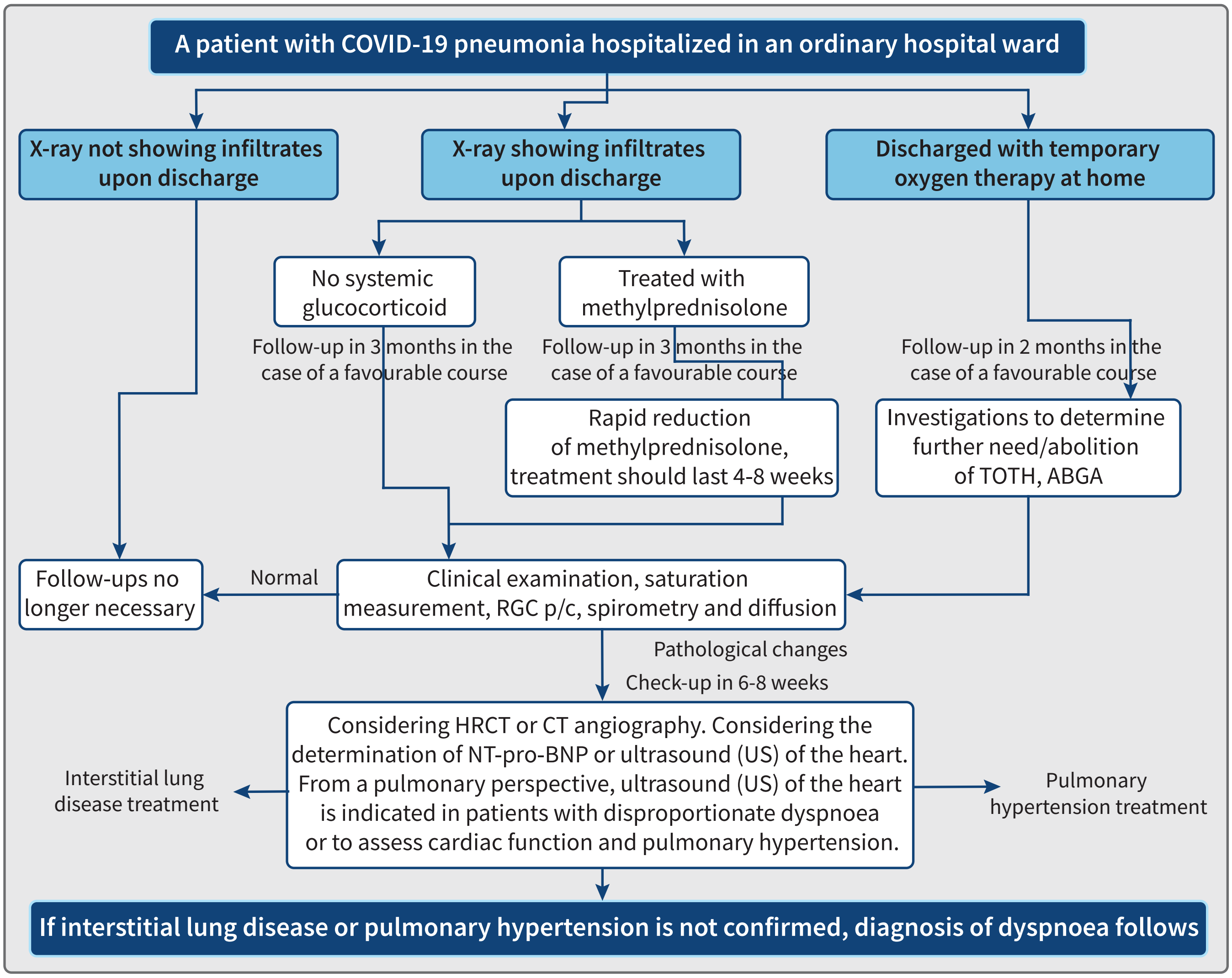

Figure 1: Algorithm 1.
Legend: TOTH – Temporary Oxygen Therapy at Home, ABGA – Arterial Blood Gas Analysis, US – Ultrasound, CT – Computed Tomography, HRCT – High Resolution Computed Tomography.
Image is from authors' own archive.

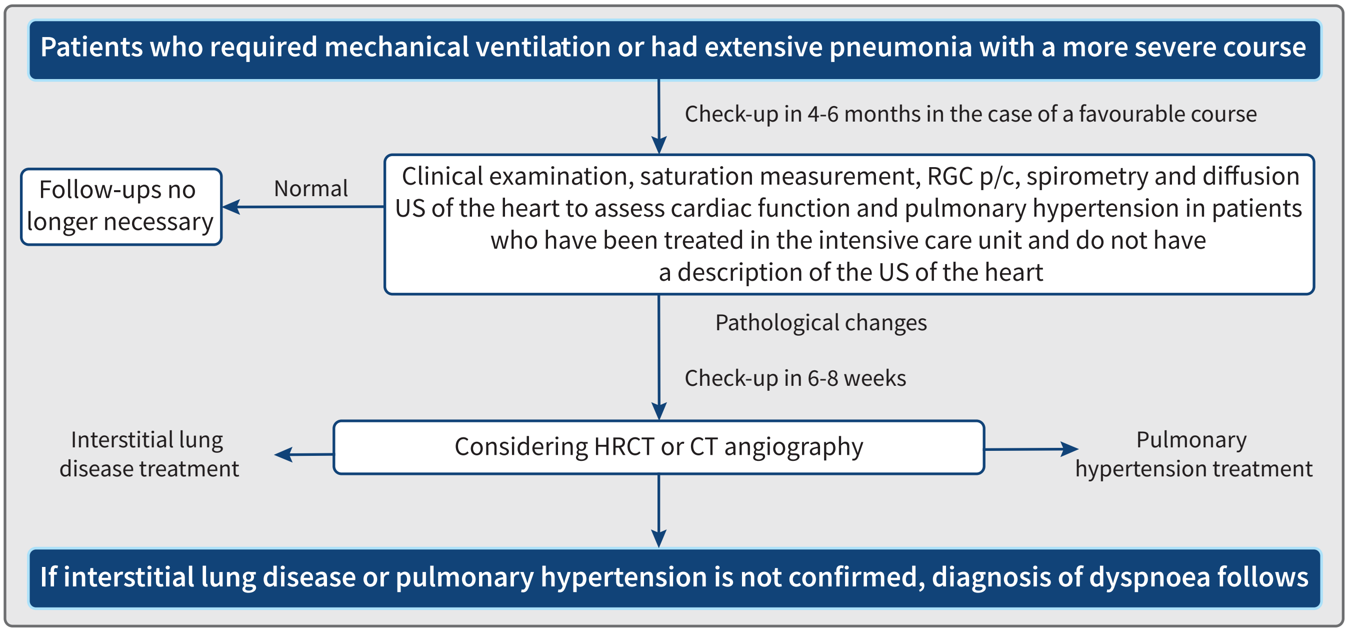

Figure 2: Algorithm 2. Summarized after George PM, et al., 2020 (50).
Legend: TOTH – Temporary Oxygen Therapy at Home, ABGA – Arterial Blood Gas Analysis, US – Ultrasound, CT – Computed Tomography, HRCT – High Resolution Computed Tomography.

8 Treatment and follow-up intervals of a patient group

8.1 Radiologically diagnosed pneumonia – treated at home

Outpatient check-up by a pulmonologist four to six weeks after confirmed infection.

8.2 Admitted to the hospital for pneumonia

8.2.1 Discharged from the ordinary ward and X-ray does not show infiltrates upon discharge

- If there is a complete regression of the infiltrates on the lung radiograph on discharge from the hospital, the patient does not need a follow-up by a pulmonologist unless he still has symptoms.

8.2.2 Discharged from the ordinary ward and X-ray shows infiltrates upon discharge

- First check-up by a pulmonologist in the case of a favourable course in three months, and earlier in the case of deterioration.
- Recommended examinations: clinical examination, measurement of oxygen saturation, chest X-ray, and if deemed necessary, spirometry with diffusion.
- With complete resorption and normal lung function at follow-up, no further examinations are required.
- In case of pathological changes – clinical problems, persistent infiltrates on the chest radiograph, impaired lung function – re-examination after six to eight weeks.
- In case of radiological deterioration or deterioration of lung function, undertake further diagnostic treatment to determine interstitial lung disease or pulmonary hypertension, and if deemed necessary, referral to hospital treatment.
- Considering the determination of NT-proBNP or ultrasound (US) of the heart. From a pulmonary perspective, an ultrasound examination of the heart is in place in patients with disproportionate dyspnoea or to assess cardiac function and pulmonary hypertension.

8.2.3 Discharged from the ordinary ward, X-ray does not show infiltrates, treated with methylprednisolone upon discharge

- First check-up by a pulmonologist in the case of a favourable course in three months.
- Methylprednisolone is reduced by 8-16 mg per week (more at first, then reduce to 8 mg per week), depending on the course of the disease.
- Methylprednisolone treatment should last four to eight weeks.
- The patient should be provided with detailed instructions and methylprednisolone dosing regimen.

After discontinuation of methylprednisolone, a rapid ACTH test is required due to the possibility of adrenal insufficiency.
- The rest of the treatment is the same as in point 8.2.2.

8.2.4 Patients discharged from the ordinary ward, receiving temporary oxygen therapy at home

- First check-up by a pulmonologist in the case of a favourable course in two months.
- Identifying the need to continue with temporary oxygen therapy at home (measurement of oxygen saturation, arterial blood gas analysis).
- The rest of the treatment is the same as in point 8.2.2.
- Due to the need for rehabilitation, patients who have had COVID-19 pneumonia and require temporary oxygen therapy upon discharge and who, according to the physician responsible for the discharge, are deemed to have adequate rehabilitation potential, are usually granted liquid oxygen.

8.2.5 Patients who required mechanical ventilation or who recovered from severe pneumonia with a severe course

- First check-up by a pulmonologist in the case of a favourable course in four to six months.
- Ultrasound examination of the heart to assess cardiac function and assessment of pulmonary hypertension in patients who were treated in the intensive care unit and have no recorded ultrasound examination of the heart.
- The rest of the treatment is the same as in point 8.2.2.

8.3 Lung function testing in patients after COVID-19

Depending on the pathology in the lungs, several structures are expected to be affected that affect lung function testing. In addition to lung parenchyma and vascular involvement, volume “restriction” in spirometry may be due to chest muscle involvement. Ventilation during physical activity can significantly improve chest mobility.

As almost all patients with COVID-19 can be found to have a functional deficit, it makes no sense to perform lung function tests at discharge. Even in patients who are recovering from the disease at home, we recommend that at least one month pass from the onset of symptoms or from a positive smear until testing lung function.

Spirometry and diffusion measurements are performed in all patients with respiratory symptoms. It is useful if the result can be compared with the result prior to COVID-19, if available. FVC and FEV1, which are at least 150 ml lower than previous measurements, may be due to infection.

No obstruction is expected in COVID-19; if measured, it is probably not due to COVID-19. COVID-19 also does not cause asthma (at least, the data does not show this so far), so a diagnosis in this direction is usually not necessary. It is not known whether COVID-19 increases FeNO in exhaled air.

A restrictive pattern (uniform reduction of FVC and FEV1 with a normal ratio) with FVC values around 80% of the reference is relatively common (up to 50%), and the diffusion capacity may be reduced. In such patients, it is very helpful to assess an X-ray of the lungs, as the restriction may be caused by the pleural sac or lung parenchymal disease.

When measuring DLCO, attention should be paid to both components – VA and KCO. The first correlates with volume reduction in spirometry and the second with pulmonary interstitial and/or vascular involvement. Since microvascular thrombosis is very common in more severe forms of COVID-19, a decrease in diffusion with low KCO and relatively normal VA will shift our attention in the direction of pulmonary embolisms. It is not known whether chronic thromboembolic lung damage may develop after COVID-19 unless, of course, pulmonary embolism has been demonstrated during the course of the disease (51-53).

8.4 Safety precautions during lung function testing

Investigations that form an aerosol are dangerous for infecting personnel and contaminating surfaces. It is recommended that the test not be performed until one month after the first symptoms of infection, but only if the patient shows no signs of acute infection. After this time, all investigations can be performed as part of functional respiratory treatment (54). However, hygiene measures are still needed as subjects can transmit the virus to their clothing and objects.

8.5 Physical performance tests in patients who recovered from COVID-19 in the pulmonary clinic

Physical performance tests in the pulmonary clinic are performed when hypoxemia is suspected during exercise. In this case, pulmonary embolism or significant heart damage, especially pulmonary hypertension, should be ruled out first. The standard test of a 6-minute walk with oxygen level monitoring is the gold standard in determining or confirming desaturation on exertion. A sit-to-stand test (STS) is simpler, but reliable enough to prove significant desaturation on exertion. Because the STS test is primarily a muscle strength test, desaturation can also occur due to increased pressure in the chest (55-57). The 6-minute walk test or STS should not be used routinely to determine physical performance in these patients, as the tests do not differentiate between pulmonary and extrapulmonary reasons for reduced physical activity. Ergospirometry is also included in the treatment of dyspnoea after COVID-19. We recommend this test be performed later or last in the course of diagnosing dyspnoea after COVID-19.

Patients with COVID-19 pneumonia are advised against physical activity, which increases the sensation of heavy breathing. While receiving systemic glucocorticoids, physical activity in which the heart rate rises above 140 beats/min is not recommended. In the first three months after recovering from pneumonia, we gradually increase the intensity of exercise by monitoring the symptoms and recovery time after the activity.

In patients with a more severe course, myopathy of a critically ill person and physical weakness, it is necessary to assess whether referral to rehabilitation at the University Rehabilitation Institute Soča or spa treatment is in place. When the regression of changes in the lungs is slow and persistent respiratory failure or hypoxemia with exercise persists, temporary oxygen therapy is initiated at home. At follow-ups, we assess whether such treatment is still necessary.

9 Conclusion

Pneumonia is the most common cause of severe SARS-CoV-2 virus infection and hospitalization. This can be mild, but can also be manifested by respiratory failure. Infiltrates vary in size. They may also appear differently on X-rays. They are often resorbed spontaneously, but sometimes treatment with systemic glucocorticoids is required. Upon discharge from hospital, treatment is usually not yet complete, so the Slovenian Respiratory Society, with a desire for the uniform treatment of patients with COVID-19 pneumonia, has prepared opinions for the treatment and follow-up of patients after discharge. We are aware that with this new disease the recommendations are not definitive, as new findings on COVID-19 pneumonia will certainly require the contents to be updated.

Conflict of interest

None declared.

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