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Long-Term Complications After Discharge of Patients With COVID-19: A Cross-sectional Study in Iran

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Abstract

Introduction: Many patients with COVID-19 complain about the remaining symptoms after being discharged from the hospital. Therefore, monitoring possible complications after contracting COVID-19 can play a significant role in the management of this disease. The purpose of this study was to assess long-term complications in patients with COVID-19.

Methods: Patients with COVID-19 who were referred to the hospital from June to November 2021 were examined in our cross-sectional study. Before the discharge of patients, the six-minute walk was performed and the patient's clinical information was recorded. Then, patients were recalled and analyzed 2 weeks and 1 month after discharge.

Results: Ninety-one patients participated in our study. After 2 weeks, fatigue with a prevalence of 62.6% was the most common clinical symptom residual in patients. In addition, 1 month after discharge, dyspnea (46.4%) and fatigue (35.7%), as well as muscle weakness and anxiety (28.6%), were the most common symptoms. The mean of oxygen saturation was 93.43 ± 3.71 two weeks after discharge and 94.79 ± 2.14 one month after discharge. The distance traveled at 6-minute walk test (6-MWT) was not significantly increased 1 month after discharge ($P=0.43$). However, the mean of forced expiratory volume in 1 second ($P=0.001$), forced vital capacity (FVC) average ($P=0.002$), and total lung capacity (TLC) ($P=05$) increased significantly after 1 month.

Conclusion: According to the results of this study, in some patients with COVID-19, symptoms such as dyspnea and fatigue remain until 1 month after discharge from the hospital. In such patients, chest computed tomography scans, pulmonary rehabilitation, and patient follow-up can help patients recover faster.

Keywords: COVID-19, Coronavirus infections, Complications, Pulmonary function test

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Introduction

A report on the spread of infectious particles causing pneumonia was first published in China at the end of 2019. After some time, the World Health Organization (WHO) named this infectious agent a novel 2019 coronavirus.[1] At that time, few people imagined that the wide spread of this infectious agent would cause an international emergency and the loss of countless lives. The passage of time and the acquisition of experience increased the knowledge of health and treatment systems about the nature of this infectious agent, clinical symptoms, and disease control methods. Investigations showed that the most common symptoms of this disease are cough, fever, fatigue, pneumonia, and shortness of breath. In some people, phlegm, headache, rhinorrhea, and diarrhea have been observed as well. However, the severity of the disease varies in different people.[2] In general, mild, moderate, severe, and critical levels have been considered for these

patients.[3]

Patients with mild symptoms of COVID-19 usually recover after a week. Nonetheless, in severe COVID-19 patients, extensive damage to the alveoli can lead to complications such as severe respiratory failure and death. In some cases, symptoms of COVID-19 will persist long after discharge. The WHO has stated that in critical cases, the symptoms of the disease can last for 6 weeks or even longer.[4] One of the most common problems caused by COVID-19 is acute respiratory distress syndrome (ARDS). ARDS can cause long-term disorders such as impaired consciousness and memory, dysfunction of the respiratory system, depression, anxiety, and muscle weakness in the patient and cause a decrease in the quality of life.[5] A review of past studies represents that during the outbreak of severe acute respiratory syndrome (SARS) in 2003, many patients had long-term symptoms such as persistent fatigue, myalgia, weakness, and depression after being discharged from the hospital.[6] Few studies have been published in the field of COVID-19 complications in Iran.[7-10] Considering the importance of examining the clinical condition of patients in the post-discharge period to ensure their full recovery, this study was conducted with the aim of investigating the long-term complications of COVID-19. Due to the publication of the preliminary results from a long-term follow-up, the study was introduced to be of cross-sectional type.

Materials and Methods

Patients whose COVID-19 infection was confirmed by chest computed tomography (CT) scan findings or reverse transcription polymerase chain reaction and who visited the COVID-19 clinic located in Masih Daneshvari hospital in Tehran, Iran from June to November 2021 were entered in the study. The samples were selected by total population sampling, and 91 patients were considered for investigation. The inclusion criteria included $SpO_2 \geq 90\%$ and symptoms of pneumonia such as fever, dyspnea, cough, and rapid breathing in moderate patients. Further, severe pneumonia and fever, cough, severe shortness of breath, rapid breathing, breaths/minute respiratory rate > 30, severe respiratory distress, and $SpO_2 < 90\%$ were checked in severe patients. On the other hand, patients who needed intubation and those with severe organ failure were excluded from the study. Before the participation of the patients in the study, a written consent form was given to each of them, and finally, patients who could attend the follow-up clinic underwent an examination.

Patients performed a six-minute walk test before being discharged from the hospital according to the current American Thoracic Society guidelines.[11] In addition to the necessary medication instructions, rehabilitation exercises and telerehabilitation instructions were taught to the patient with a brochure and under the close supervision of a physiotherapist.

Two weeks after discharge, the patients were called to the hospital for follow-ups. In all the participants, the airway function was examined using a flow spirometer according to the guidelines provided by the American Thoracic Society. The investigated pulmonary parameters included forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), total lung capacity (TLC), residual volume, FEV1-to-FVC ratio, and carbon monoxide diffusing capacity (DLCO). In addition, clinical manifestations, including dyspnea, cough, anxiety, fatigue, muscle pain, and weakness, were evaluated. The patients returned to the clinic and the mentioned examinations were repeated 2 weeks after the first follow-up (1 month after discharge). The flowchart of the patients participating in the follow-up is illustrated in Figure 1.

Statistical Analysis

All quantitative and qualitative variables were presented using a paired sample t-test as means and standard deviations, as well as numbers (percentages), respectively. Furthermore, the drop of SpO_2 in the 6-minute walk test (6-MWT) was analyzed with repeated measures analysis of variance (2×2) test. The obtained data were analyzed using SPSS 21 software with a significance level of 5%.

Results

In the present study, clinical manifestations of 91 patients with COVID-19 were followed 2 weeks after discharge and 84 patients after 1 month (Figure 1). The average age of the study participants was 56.42 ± 13.03, and 39 (42.9%) of them were males. The demographic information of the patients is presented in Table 1.

Examining the clinical symptoms of patients 2 weeks after discharge demonstrated that fatigue was the most frequent symptom, which was observed in 57 patients (62.6%). Muscle weakness [49 (53.8%)], dyspnea [43 (47.3%)], cough [26 (28.6%)], and anxiety [21 (23.1%)] were the most common remaining symptoms of the disease, respectively. Other clinical symptoms observed in patients 2 weeks after discharge included headache [14 (15.4%)], depression [13 (14.3%)], phlegm [7 (7.7%)], and dysphagia [1 (1.1%)].

The data obtained 1 month after discharge indicated that among the examined symptoms, dyspnea [39

Table 1. Demographic Characteristics of COVID-19 Patients Who Included in the Follow-up

Characteristics	Data (N = 91)
Age (y)	56.42 ± 13.03
Male	39 (42.9%)
Female	52 (57.1%)
Hospital stay	8.56 ± 4.21

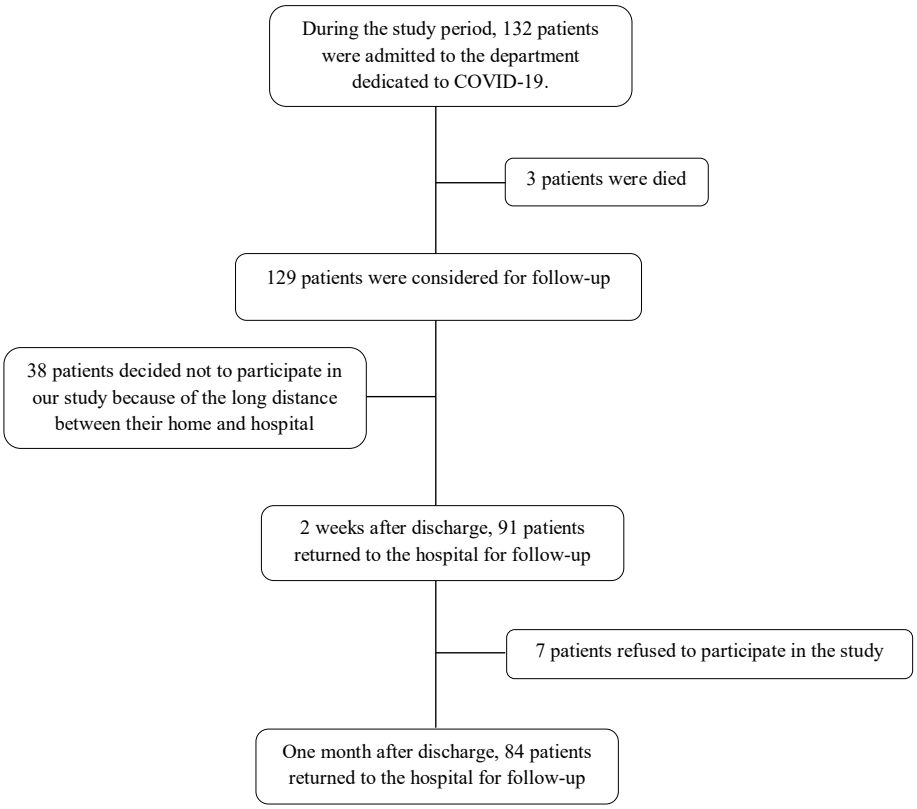

Figure 1. Flow Diagram of Patients Participating in the Study

(46.4%)] was more frequent. Based on the results, 30 patients (35.7%) had fatigue, and 24 patients (28.6%) had muscle weakness and anxiety. Other reported symptoms, in order of frequency, included depression [18 (21.4%)], headache [15 (17.9%)], cough and pain [12 (14.3%)], and phlegm [6 (7.1%)]. None of the patients had symptoms of dysphagia 1 month after discharge (Figure 2).

The comparison of changes in respiratory factors 2 weeks and 1 month after discharge is provided in Table 2. The results obtained from pulse oximetry revealed that the oxygen saturation percentage was 93.43 ± 3.71 two weeks after discharge and 94.79 ± 2.14 one month later. According to the results obtained from the six-minute walk test, the distance traveled in this test after 1 month (96.63 ± 391.79) did not increase significantly ($P = 0.43$) compared to 2 weeks after discharge (96 ± 364).

The examination of the changes in the respiratory factors of patients showed that the mean of FEV1 of the patients 2 weeks and 1 month after discharge was 90.81 ± 18.28 and 104.33 ± 12.88, respectively, indicating a significant increase in FEV1 ($P = 0.001$). Moreover, the average FVC after 2 weeks and 1 month was 84.90 ± 18.07 and 98.33 ± 9.95, respectively, and there was a significant increase ($P = 0.002$). The average TLC of the patients within 1 month after discharge from the hospital (81.72 ± 10.38) represented a significant increase ($P = 0.05$) compared to the first 2-week follow-up period (73.94 ± 14.77).

Discussion

The present study investigated the frequency of COVID-19 symptoms and the severity of changes in respiratory factors 2 weeks and 1 month after discharge. Studies demonstrated that some patients with COVID-19 recover completely, and in some patients, symptoms of COVID-19 remain for weeks or months after infection.[12,13] Therefore, the complete recovery of patients and the achievement of the best level of health and quality of life are the most important challenges. According to research published by King's College London, 5% of patients with COVID-19 have experienced long-term symptoms of COVID-19 at least once for a month or even longer.[13] The WHO has announced that in critical patients with COVID-19, it may take a few weeks to return to a healthy level before the infection. Getting back to normal can be a long process even for people who have recovered.

Patients with COVID-19 require hospitalization with various symptoms. This is despite the fact that within six weeks after discharge, the number of remaining symptoms decreases and only a few patients need to be re-hospitalized.[12] In our study, patients were evaluated between 2 weeks and 1 month after discharge, and prolonging the follow-up time can help obtain more accurate information.

The most common symptoms observed in patients 2 weeks after discharge were fatigue, muscle weakness, dyspnea, cough, and anxiety (23%-62%). After 1 month,

Table 2. Comparison of Respiratory Indices Between 2 Weeks and 1-month Follow-up

Variables		After 2 Weeks (n = 91)	After 1 Month (n = 84)	F-Value	*P* Value
SpO_2		93.43 ± 3.71	94.79 ± 2.14	-2.85	0.005
6MWT distance		364 ± 96	391.79 ± 96.63	-0.79	0.43
SpO_2 in 6MWT	Start of test	92.3 ± 2.71	93.29 ± 2.7	0.5	0.48
	End of test	88.38 ± 6.62	87.32 ± 7.52		
FEV1		90.81 ± 18.28	104.33 ± 12.88	-3.58	0.001
FVC		84.90 ± 18.07	98.33 ± 9.95	-3.37	0.002
FEV/FVC		88.13 ± 4.36	86.56 ± 5.19	1.35	0.18
DLCO		69.02 ± 16.54	73.38 ± 16.5	-.61	0.54
TLC		73.94 ± 14.77	81.72 ± 10.38	-2.01	0.05
PI max		78.71 ± 24.91	85 ± 37.36	-1.26	0.21
PE max		50.37 ± 17.59	50.25 ± 15.71	-1.1	0.28

Note. Pulmonary function data are presented as percentages of predicted values except FEV1/FVC, which is a percentage. SpO_2: Peripheral capillary oxygen saturation; 6MWT: Six-minute walking test; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; DLCO: Carbon monoxide diffusing capacity; TLC: Total lung capacity; PI max: Maximal inspiratory pressure; PE max: Maximal expiratory pressure.

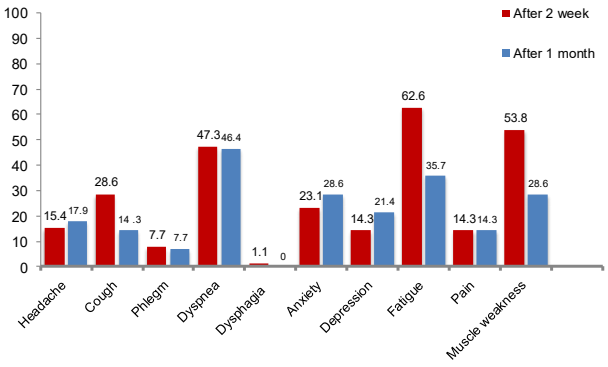

Figure 2. Comparison of Clinical Symptoms 2 Weeks and 1 Month After Discharge (Percentage)

dyspnea was the most observed symptom in patients (46.4%). After 1 month, dyspnea was the most detected symptom in patients (46.4%), followed by fatigue (35.7%) and muscle weakness (28.6%). In many viral diseases such as Epstein-Barr virus or SARS virus, fatigue is 1 of the common delayed symptoms.[14] Fatigue has also been reported in some patients 4 years after contracting SARS.[15] Previous studies reported that 53.1% of patients with COVID-19 suffer from fatigue. Therefore, it is highly important to pay attention to the behavioral and psychological symptoms of these patients. The results of our study showed that 2 other symptoms that can remain in patients with COVID-19 are dyspnea and muscle weakness. Since the body's main involvement with SARS-CoV-2 is related to the respiratory system, complete recovery of the lungs may require a long time.[16] Studies represented that after the recovery period of COVID-19, fatigue, muscle weakness, and breathing disorders are possible.[17,18] Many of the patients' delayed symptoms can be managed at home. Depression, cough, headache, cough, pain, and phlegm were the other remaining symptoms in patients in our 2 follow-up periods. Investigations revealed that some patients with SARS had psychological problems and stress up to 1 year after recovery. Hence, it takes more time to evaluate the symptoms of mental insufficiency in patients with COVID-19. On the other hand, the restrictions that the COVID-19 epidemic has imposed on societies can cause an increase in anxiety and mental disorders in patients.[19]

Examining the severity of changes in respiratory variables can play a significant role in evaluating the patient's recovery process. Based on the results obtained from pulse oximetry of the patients, SpO_2 increased significantly after 1 month. On the other hand, the results of the six-minute walk test 2 weeks after discharge demonstrated that the patient's SpO_2 decreased by 5.6% after the test. Likewise, after 1 month, the SpO_2 of patients who performed 6 MWT decreased by 6.39%.

These findings confirmed that the patient receives oxygen during the activity. After 1 month of discharge, the average distance traveled in 6MWT was increased compared to 2 weeks after discharge, but this was not statistically significant. Whyte et al obtained similar results in a three-month follow-up of patients. In their study, the average SpO_2 of the patients at the end of the 6MWT decreased in comparison to the beginning of the test.[20] Contrary to our results, Eksombatchai et al found that there was no difference in oxygen saturation of patients with COVID-19 before and after 6MWT.[21] According to the guidelines provided by ATS for 6MWT, age, and higher weight are factors influencing the results of this test,[22] justifying the difference in the obtained results.

From the beginning of the outbreak of COVID-19, lung dysfunction and parenchymal fibrosis were among the main concerns. One of the most important determining parameters in this field is lung diffusion capacity.[22] In our study, although the amount of DLCO increased after 1 month compared to 2 weeks after discharge, it was not significant. Zhao et al concluded that DLCO anomalies are observed in many recovered patients.[23] Another study examining the pulmonary function of patients about a month after discharge showed that the values of FEV1 and FVC were not significantly different at different levels of COVID-19, but the value of DLCO was significantly lower in severe patients.[24] It can be mentioned that the low DLCO is due to the fact that all patients examined in our study were suffering from severe COVID-19. Examining CT scans of patients can help obtain more accurate results. After the SARS outbreak in 2003, recoveries examined within 3 months of discharge demonstrated that fibrotic lung changes occurred more frequently in critically ill patients.[6] These data suggest that some of the recovered COVID-19 patients will have significantly

impaired lung function months after discharge. Similarly, the values of FEV1 and FVC were in the normal range 2 weeks after discharge (>80% predicted), but significant improvement was found in these variables after 1 month. The TLC of the patients was abnormal 2 weeks after discharge (<80%); however, it increased significantly after 1 month.

Various studies have been published in the field of the mechanism of lung damage after contracting COVID-19. However, the mechanisms involved in the prolonged severity of SARS-CoV-2 symptoms need further investigation.

In summary, our findings suggest that patients with COVID-19 should be carefully evaluated for pulmonary function and the possibility of pulmonary rehabilitation and its role in improving clinical conditions. Moreover, investigating biomarkers that may identify the potential progression of lung damage and comparing them at different levels of infection with COVID-19 could be effective in predicting the long-term complications of COVID-19.

Our study also had some limitations. We only published the results obtained from examining patients in 1 hospital over a limited period. The sample size is small to generalize the results, and multicenter studies with a larger sample size can help obtain more reliable results.

Conclusion

In general, people who have recovered from COVID-19 can still have symptoms such as fatigue, dyspnea, and muscle weakness a month after discharge. Additionally, despite the improvement of respiratory indices, their lung function is still affected by DLCO values. Therefore, continuing follow-ups, performing chest CT imaging (if needed), and checking pulmonary function and exercise tests for patients with severe degrees of the disease should be undertaken in this regard.

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Authors' Contribution

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Writing–original draft: Reyhaneh Zahiri.
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Competing Interests

There is no conflict of interests related to this article.

Ethical Approval

This study was approved as a research project with the code of IR.SBMU.NRITLD.REC.1400.013 by the Ethics Committee of Masih Daneshvari Hospital, Tehran, Iran.

References

1. Amirsavadkouhi A, Jahangirifard A, Shahrami R, et al. The role of hemoperfusion in COVID-19 infection: a case series. Arch Anesth Crit Care. 2021;7(3):189-194. doi:10.18502/aacc.v7i3.6912
2. Sadeghi S, Nasirian M, Keivany E, Nasri P, Mirenayat MS. The demographic, clinical, and medical manifestations of pulmonary thromboembolism development in COVID-19. Blood Res. 2021;56(4):293-300. doi:10.5045/br.2021.2021131
3. Fakharian A, Mirenayat MS, Ferdowsi F, et al. The efficacy of methylprednisolone in clinical manifestations, inflammatory biomarkers, and antioxidant changes in the COVID-19 patients. Arch Clin Infect Dis. 2022;17(4):e129799. doi:10.5812/archcid-129799
4. Li T, Wei C, Li W, Hongwei F, Shi J. Beijing Union Medical College Hospital on "pneumonia of novel coronavirus infection" diagnosis and treatment proposal (V2.0). Med J Peking Union Med Coll Hosp. 2020;15:9-29.
5. WHO. Coronavirus Disease (COVID-19) Pandemic. 2020. Available from: https://www.who.int/europe/emergencies/situations/covid-19. Accessed July 24, 2020.
6. World Health Organization (WHO). Diseases. Available from: https://www.who.int/emergencies/diseases/.
7. Saberian P, Pazooki B, Hasani-Sharamin P, et al. Persistent/late-onset complications of COVID-19 in general population: a cross-sectional study in Tehran, Iran. Int J Community Based Nurs Midwifery. 2022;10(3):234-245. doi:10.30476/ijcbnm.2022.93302.1917
8. Moradian ST, Parandeh A, Khalili R, Karimi L. Delayed symptoms in patients recovered from COVID-19. Iran J Public Health. 2020;49(11):2120-2127. doi:10.18502/ijph.v49i11.4729
9. Goërtz YMJ, Van Herck M, Delbressine JM, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res. 2020;6(4):00542-2020. doi:10.1183/23120541.00542-2020
10. Simani L, Ramezani M, Alavi Darazam I, et al. Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19. J Neurovirol. 2021;27(1):154-159. doi:10.1007/s13365-021-00949-1
11. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-117. doi:10.1164/ajrccm.166.1.at1102
12. Sepehrinezhad A, Shahbazi A, Sahab Negah S. COVID-19 virus may have neuroinvasive potential and cause neurological complications: a perspective review. J Neurovirol. 2020;26(3):324-329. doi:10.1007/s13365-020-00851-2
13. Zeng N, Zhao YM, Yan W, et al. A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic: call for research priority and action. Mol Psychiatry. 2023;28(1):423-433. doi:10.1038/s41380-022-01614-7

14. Islam MF, Cotler J, Jason LA. Post-viral fatigue and COVID-19: lessons from past epidemics. Fatigue. 2020;8(2):61-69. doi:10.1080/21641846.2020.1778227
15. Sironi M, Hasnain SE, Rosenthal B, et al. SARS-CoV-2 and COVID-19: a genetic, epidemiological, and evolutionary perspective. Infect Genet Evol. 2020;84:104384. doi:10.1016/j.meegid.2020.104384
16. Rodriguez B, Nansoz S, Cameron DR, Z'Graggen WJ. Is myopathy part of long-COVID? Clin Neurophysiol. 2021;132(6):1241-1242. doi:10.1016/j.clinph.2021.03.008
17. Buttery S, Philip KEJ, Williams P, et al. Patient symptoms and experience following COVID-19: results from a UK-wide survey. BMJ Open Respir Res. 2021;8(1):e001075. doi:10.1136/bmjresp-2021-001075
18. Pescaru CC, Marițescu A, Costin EO, et al. The effects of COVID-19 on skeletal muscles, muscle fatigue and rehabilitation programs outcomes. Medicina (Kaunas). 2022;58(9):1199. doi:10.3390/medicina58091199
19. Cowie H, Myers CA. The impact of the COVID-19 pandemic on the mental health and well-being of children and young people. Child Soc. 2021;35(1):62-74. doi:10.1111/chso.12430
20. Whyte MB, Barker R, Kelly PA, et al. Three-month follow-up of pulmonary embolism in patients with COVID-19. Thromb Res. 2021;201:113-115. doi:10.1016/j.thromres.2021.02.023
21. 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
22. Bazdyrev E, Rusina P, Panova M, Novikov F, Grishagin I, Nebolsin V. Lung fibrosis after COVID-19: treatment prospects. Pharmaceuticals (Basel). 2021;14(8):807. doi:10.3390/ph14080807
23. Zhao YM, Shang YM, Song WB, 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
24. Chan KS, Zheng JP, Mok YW, et al. SARS: prognosis, outcome and sequelae. Respirology. 2003;8(Suppl 1):S36-40. doi:10.1046/j.1440-1843.2003.00522.x