

Coronavirus Pandemic

Pulmonary functions and life quality assessment results two years after COVID-19 comparison with the sixth month results

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Abstract

Introduction: We aimed to investigate the effects of COVID-19 on patients 24 months after severe COVID-19 pneumonia.

Methodology: Fifty-four patients with severe COVID-19 pneumonia were evaluated on the 24th month after discharge from the hospital. Spirometry and short form of health-related quality of life scale (SF-36) were used. Chest computed tomography (chest-CT) was performed and the findings were grouped according to lung involvement.

Results: Forced expiratory volume in 1 second (FEV1) % values of 19 patients (35.18%) and forced vital capacity (FVC) % values of 23 patients (42.54%) were found lower than expected on the 24th month. Physical function, energy-vitality, social functionality and general health parameters were found lower than normal on the SF-36 scale. 27 (50.00%) patients had a chest-CT abnormality. There was a correlation between FEV1% and FVC% values and group 3: medium-lower lobe dominant, reticulation + traction, 10-50% surface area. Chest-CT of 6 patients was fully recovered. No correlation was found between chest-CT findings on the 24th month and BMI, length of hospitalization, white blood cell (WBC), lymphocyte, C-reactive protein (CRP), ferritin and D-dimer values at the time of hospitalization.

Conclusions: Functional and radiological abnormalities were detected in a significant number of patients on the 24th month. A systematic monitoring plan must be established to assess and properly manage the long-term problems that may arise.

Key words: COVID-19; pulmonary function; quality of life.

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Introduction

Coronavirus disease-19 (COVID-19) was defined as a new coronavirus related disease on 7th Jan 2020, following the reports of the initial cases in Wuhan, China in December 2019. It was determined to be a virus that had never infected humans before and due to the speed and severity of the spread of the virus, the state of global pandemic was declared on 11th March 2020 by the World Health Organization (WHO) [1]. Despite the different speeds of spread and different death rates in different countries, the virus caused one of the worst pandemics in the last hundred years. The clinical manifestations of COVID-19 ranges from asymptomatic/pauci-symptomatic to acute respiratory disease syndrome (ARDS) and to patients needing to be taken to intensive care units [2]. For this reason, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-

2) primarily affects the lungs, but it may also lead to a systemic involvement that causes sepsis and multiple-organ failure [3]. Some frequently used laboratory parameters play an important role in assessing the severity of the disease, foreseeing the intensive care need at an earlier stage and providing efficient treatment. A rise in rates of neutrophil/lymphocyte, C-reactive protein (CRP), troponin I, lactate dehydrogenase (LDH), ferritin, D-dimer and fall in the number of lymphocytes are observed and these are considered to be related to unfavorable prognosis [4]. According to the latest reports, chest computed tomography (CT) is an important method to diagnose COVID-19 related lung abnormalities at an early stage and is very useful for following the rapid damage in the lungs [5]. Radiologically, COVID-19 findings include multilobe involvement which develops with icy-glass

opacities on chest-CT and subsegmental consolidation. According to several studies, chest CT-scan abnormalities remained permanently in COVID-19 pneumonia survivors. In the case of the survivors, especially those whose inflammatory indicators were high, the probability of the development of fibrosis was strong and interstitial thickening, irregular interface, thick reticular pattern and parankimal band, which developed during the disease, were considered to be signs of pulmonary fibrosis [6].

The studies on the follow-up scans of COVID-19 survivors so far in the short span of the disease and the scans of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) survivors in the longer span of the diseases reveal that the abnormalities remain permanently [7]. The pulmonary interstitial fibrosis which develops due to COVID-19 causes disorders in the pulmonary functions of the patients and affect the life quality negatively in the long term. Our knowledge regarding the long term follow ups of these patients is still limited, even though the pandemic is in its second year. Early stage of the radiological changes of the survivors, abnormal pulmonary functions and lower quality of life have been recorded.

The aim of this study was to investigate the effects of COVID-19 on patients who have had severe COVID-19 pneumonia at the end of the twenty-fourth month after recovery. We investigated the potential long-term impacts of COVID-19 on pulmonary capacity and health-related quality of life. We compared the results at the end of the 24th month with our data from the end of the 6th month.

Methodology

Study design and participants

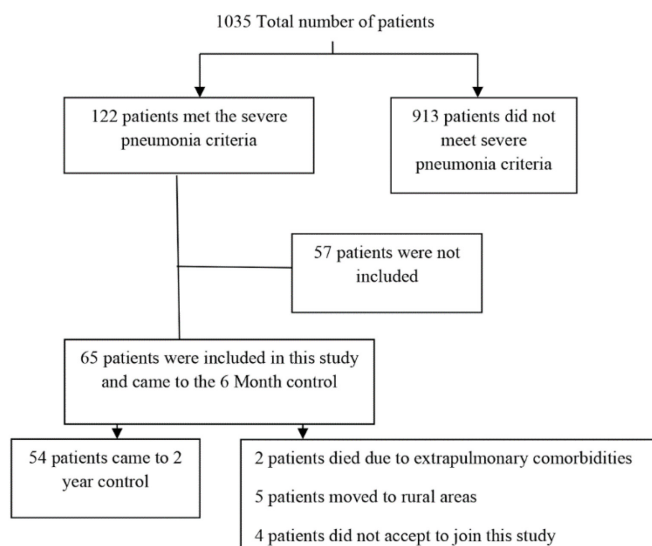
Patients who received inpatient treatment for severe COVID-19 in the hospital were called for outpatient clinic follow-ups at 3-month intervals. The patients who agreed to participate in the study at the end of 6 month follow-up were selected for the study. Pulmonary function test (spirometry), 6-minute walking test, and chest CT were performed. The participants were asked to fill out the SF-36 quality of life scale form. The data we obtained at the end of the 6th month has been published [8]. Spirometry and chest CT were performed at the end of the 24th month in our patients who continued their control and follow-up. At the end of the 24th month, the SF-36 quality of life scale form was filled out again. This study is a single-centered, prospective observational case study. Our study was approved by the ethics committee (22.02.2022/3409).

Patients who were over 18 years old and followed up between 11th March 2020 and 20th July 2020 in COVID-19 inpatient clinics of our hospital; patients with SARS-CoV-2 PCR (+) and/or SARS-CoV-2 IgM/G (+); patients clinically and radiologically compatible with COVID-19 diagnosis and patients whose cases could not be diagnosed as any other disease except for COVID-19 according to the T.C. Ministry of Health, Public Health COVID-19 Field Guide [9] were considered. Among these patients were those with severe pneumonia according to the Ministry's guide.

According to Ministry's guide, severe pneumonia findings include: patients who have symptoms such as fever, muscle/joint pains, cough, sore throat and nasal congestion, have tachypnea (≥ 30 /minute) or have SpO₂ level $< 90\%$ in room air; poor prognostic measurement in the blood tests taken at the time of admission (number of blood lymphocytes $< 800/\mu\text{L}$ or CRP > 40 mg/L or ferritin > 500 ng/mL or D-Dimer > 1000 ng/mL, etc.); and patients with bilateral diffuse pneumonia findings in pulmonary X-ray or CT.

Spirometry requires good physical function and patient compliance; so, among the patients with severe pneumonia criteria, we selected patients who were able to perform spirometry. Patients who have neurological diseases such as advanced dementia, Alzheimer's, cerebrovascular disease, etc., patients who had history of orthopedic or other surgical operations and patients over 90 years old were not included. Volunteer consent form was obtained from the patients who participated in the study. Patient participation scheme is shown in Figure 1.

Figure 1. Patient participation scheme.



Spirometry

The patients were tested with the pulmonary function test (spirometry). With this test, we aimed to evaluate respiratory functions. Spirometry was carried out by a spirometry technician wearing protective equipment to prevent contamination of our hospital's Pulmonary Function Testing Laboratory. Spirometry was carried out in accordance with the American Thoracic Society (ATS) - European Respiratory Society (ERS) guidelines using MIR Spirolab II (Rome, Italy) device [10-11]. The patients were informed about the maneuvers and 3 spirograms were performed. The best result that met the criteria of repeatability and acceptability was approved by the chest disease physician in charge of the Pulmonary Function Test Laboratory (this physician did not have prior information about the patient history and clinical parameters) and included in the study.

Short form 36-point questionnaire

With social progress and the transformation of medical care and service systems, interest in health-related quality of life is increasing. Health-related quality of life is defined as the subjective sensation of the multifaceted effect of a disease by patients [1]. The short form 36-point questionnaire (SF-36) is a popular tool for assessing health-related quality of life. In this study, we used the Turkish version of SF-36 to evaluate the change in health-related quality of life of our COVID-19 patients [13]. This survey included eight parameters: physical functioning, physical role difficulties, pain, general health, emotional role difficulties, energy-vitality, mental health and social functionality. The first four parameters were related to physical health and the others were related to mental health. Scores for each parameter varied between 0 and 100 and higher scores indicated better quality of life. Normal values for parameters were different from each other. Using this scale, we planned to assess health-related quality of life and objectively evaluated the physical and mental functionality of the patients at the end of the 24th month of recovery.

Radiographic assessment

The radiological lung findings of the patients were evaluated with lung chest-CT at the end of the 24th month. We aimed to evaluate the course of lung involvement and the effect of COVID-19 on the lung in the long term. CT scans were taken on the same day as the spirometry and SF-36.

At the end of the 24th month follow ups, 54 patients tested with non-enhanced chest-CT. The patients were

assigned to the protocol with 100 kilovolt (peak) (kV[p]) and 20 effective milliamper-second (eff mA-s) during single inspiratory breathhold. Axial images of two mm slice thickness were obtained using an image matrix of 512 × 512 pixels. We used a mediastinum window setting (width: 400 HU; level: 100 HU) and a lung window setting (width: 1,500 HU; level: -500 HU) for this analysis.

All physicians who participated in the study had consensus on collecting CT results in five groups by prioritizing tomography findings, interstitial changes and/or the percentage of distribution of fibrosis. This evaluation and grouping were also used in our analysis at the end of the 6th month [8]. All CT images were reviewed independently by two radiologists (HO, UY; 23 and 3 years of experience in thoracic radiology, respectively), and discrepancies were resolved by consensus. Readers were blinded to the participants' initial and subsequent clinical presentation but were allowed to review the CT scans obtained during the previous follow-up visits.

CT findings were grouped as shown below:

Group 1: Normal,

Group 2: Medium-lower lobe dominant, ≤ 10% surface area,

Group 3: Medium-lower lobe dominant, reticulation + traction, 10-50% surface area,

Group 4: All lobes, reticulation + traction, > 50% surface area,

Group 5: All lobes, diffuse reticulation + traction + honeycomb, > 50% surface area.

Analysis of data

Statistical analysis of the data was conducted in the SPSS Statics Version 17.0 program. The suitability of the variables to the normal distribution was examined by histogram graphs and Kolmogorov-Smirnov test. When presenting descriptive analyses, mean, standard deviation, median, minimum and maximum values were used. Variables that do not show normal distribution were evaluated among 2 groups and Mann Whitney U Test was used when evaluating between more than 2 groups. Kruskal Wallis Test was used. While the change in the measured values was examined with the Wilcoxon Test within the group, the change in the categorical variables was examined by the McNemar Test. $p < 0.05$ was considered statistically significant.

Results

Of the 54 patients who participated in the study, 40 (74.07%) were male and 14 (25.93%) were female. The

Table 1. Laboratory tests at the time of hospitalization and demographic data of patients.

Characteristics	Mean±SD	Median (Min-Max)
Age	56.19 ± 11.80	56.5 (32-83)
BMI	29.71 ± 4.27	29.23 (23.51-41.91)
Average hospitalization time	11.35 ± 5.59	11 (4-36)
WBC	6099.43 ± 2008.85	5850 (3380-13650)
Lymphocyte	1147.17 ± 532.38	1110 (450-3570)
CRP	70.67 ± 48.70	61 (1-201)
Ferritin	393.57 ± 351.84	349 (14-1983)
D-dimer	716.68 ± 494.25	588 (43-2380)

BMI: body mass index; WBC: white blood cell; C-RP: C-reactive protein.

average hospitalization time for the group was 11.35 days (min: 4 – max: 36 days). Demographic data of patients and laboratory tests at the time of hospitalization are shown in Table 1. 31 (57.41%) of our patients had additional diseases. 3 (9.68%) patients had asthma/COPD, 8 (25.81%) patients had heart diseases, 24 (77.42) patients had hypertension, 13 (41.94%) patients had internal metabolic diseases, and 2 (6.45%) patients had chronic renal failure. 5 (9.26%) patients smoked, 21 (38.89%) patients were ex-smokers and 28 (51.85%) patients were non-smokers. There were 7 (12.96%) patients admitted to the intensive care unit.

Spirometry

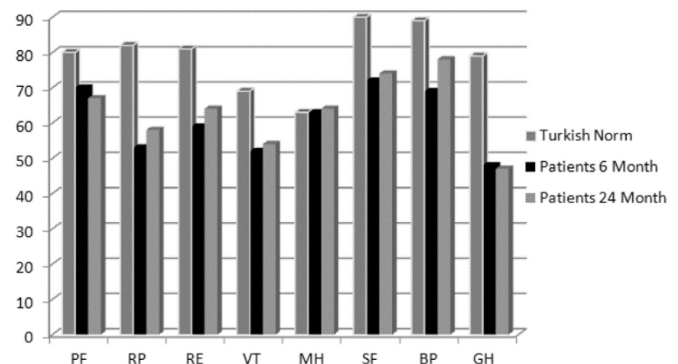
Spirometry was applied to 54 patients at the end of the 24th month controls. 19 of the patients (35.18%) were found to have low forced expiratory volume in 1 second (FEV1) % value, 23 of the patients (42.54%) had lower forced vital capacity (FVC) % values ($p < 0.05$). These values were compared with the results of the 6th month and no significant difference was detected. 3 of our patients were known to have a history of obstructive lung disease (COPD/asthma), but none of them had respiratory distress at the time of the tests and FEV1/FVC ratio measurements were $> 70\%$.

SF-36

SF-36 was applied to all 54 patients. This test could be separated into eight parameters. The parameter of physical function was lower than expected in the 50 patients (92.59%); energy-vitality parameter in 40 patients (74.07%), social functionality parameter in 47

patients (87.03%) and general health perception parameter in 52 patients (96.29%) were found to be lower than expected. Changes in these parameters were statistically significant ($p < 0.05$). When these values were compared with the 6th month data, improvement in bodily pain parameter was observed ($p < 0.05$) and there was no change in other parameters. Comparison of SF-36 scores of participants with those of the Turkish population is also shown in Figure 2.

Figure 2. Comparison of SF-26 scores of Turkish population and COVID-19 patients at the end of sixth month and at the end of twenty-fourth month.



The vertical axis represents mean (SD) SF-36 domain scores from 0 to 100. The horizontal axis shows SF-36 subparameters BP, pain; COVID-19, coronavirus disease 2019; GH, general health perception; MH, mental health; PF, physical function, RE, emotional role difficulties; RP, physical role difficulties; SF, social functionality; VT, energy vitality; Turkish Norm, valid values of the quality of life questionnaire for the Turkish people.

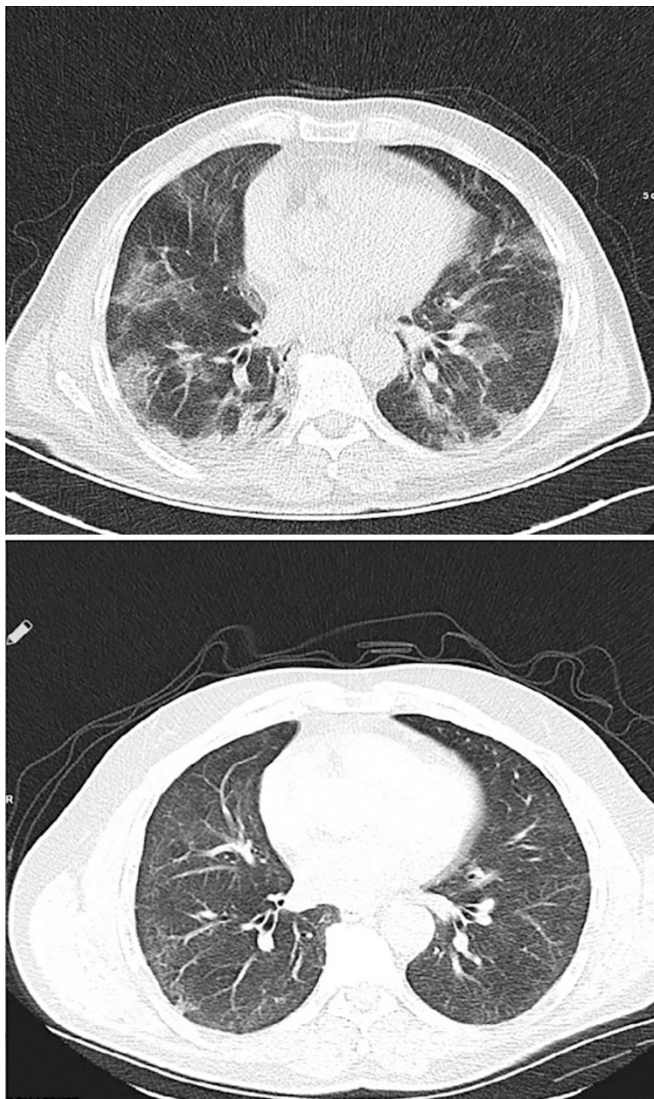
Table 2. Chest-CT distributions at the end of the twenty-fourth month and comparison with chest-CT at the end of the sixth month.

Chest-CT	6th month		24th month		P
	n	%	n	%	
Group 1: Normal	21	(38.89)	27	(50.00)	0.004
Group 2: Medium-lower lobe dominant, $\leq 10\%$ surface area	22	(40.74)	18	(33.33)	
Group 3: Medium-lower lobe dominant, reticulation + traction, 10%-50% surface area	8	(14.81)	8	(1.81)	
Group 4: All lobes, reticulation + traction, more than 50% surface area	3	(5.56)	1	(1.85)	
Group 5: Common in all lobes, reticulation + traction + honeycomb more than 50% surface area	0	(,00)	0	(,00)	

Chest CT

54 patients were evaluated with chest CT. While chest CT was normal in 27 patients (50.00%), another 27 patients (50.00%) had abnormal chest CT findings. CT changes were minimal in 18 of the 27 patients with abnormal CT findings. Group-3 included 8 patients with medium-lower lobe dominant, reticulation + traction, 10-50% surface area; group 4 included 1 patient with VCV all lobes, reticulation+traction, > 50% surface area. The chest CT findings at the end of the 24th month were compared with the chest CT at the end of the 6th month and were statistically significant ($p < 0.05$). A comparison of chest CT findings at the end of the 24th month and chest CT findings at the end of the 6th month is shown in Table 2. Figure 3 shows the

Figure 3. Chest CT image of our patient with Group 4: all lobes, reticulation + traction, > 50% surface area, during hospitalization and at the end of twenty-fourth month after discharge.



chest-CT image of group 4; all lobes, reticulation + traction, > 50% surface area; during hospitalization and at the end of 24th month after discharge.

Comparison of parameters

According to the chest CT examined at the 24th month follow ups of the patients, the cases with and without abnormalities were compared. FEV1% and FVC% values of patients who have abnormalities in chest CT, were significantly lower ($p < 0.05$). Patients with group-3, medium-lower lobe dominant, reticulation + traction 10-50% surface area findings, had low FVC% and FEV1% values at the end of 24th month ($p < 0.05$). There was no statistically significant difference between the groups in terms of other variables ($p > 0.05$).

According to the chest CT findings examined at the twenty-fourth month controls of the cases, when the mean distribution of SF-36 parameters was analyzed, there was no statistically significant difference between the groups ($p > 0.05$).

The correlation between chest CT findings at the end of twenty-fourth month and BMI, length of hospitalization, WBC, Lymphocyte, CRP, Ferritin and D-dimer values at the time of hospitalization was examined. No correlation was found between the values.

Discussion

The COVID-19 pandemic is in its second year and with the emergence of new cases every day, an increasing amount of data and findings on acute COVID-19 infection and its complications are available. In addition, the number of publications on COVID-19 is increasing every day. Although we do not know as yet the long-term effects of COVID-19, they are expected to be similar to those of SARS and MERS, which belong to the same coronavirus family [14]. In our previous study, we presented the pulmonary system results of 65 patients at the end of the 6th month of the disease. 54 of these patients resumed clinic follow-ups and we recorded and evaluated their symptoms at the end of the 24th month. In this study, we present a comparative analysis of the 24th and the 6th month observations.

An increasing number of studies point towards secondary changes varying in shape and intensity due to pulmonary involvement in chest CT of COVID-19 patients. The question as to how many of the patients will remain with fibrosis is still being studied, even though a partial or complete improvement in the monitored changes in chest CT is expected. Zhang *et*.

al. evaluated the condition of 40 patients for 8 months after their hospital release and detected abnormal CT in 12 patients [15]. They found a relation between long-term radiological abnormality, old age and the severity of the COVID-19 case. Luger *et al.* analyzed chest CT of 91 patients one year after their hospital release [16]. They observed CT abnormalities in 49 of the 91 (54%) patients; among them, 31 (34%) had subpleural reticulation, icy glass opacities or both, and 18 (20%) had large icy glass opacities, reticulations, bronchial dilatation, microkistal changes or a combination of these. They also spotted a relation between age > 60 years, severity of COVID-19, male gender and permanent CT abnormalities. Wu *et al.* followed the condition of 135 patients every 3 months for a year [17]. A part of the patients showed radiological improvement, but radiological abnormality resumed in 20 of the patients. Thus, the radiological abnormality and the severity of the COVID-19 case are found to be correlated. In our study, we found CT abnormality in 27 of our patients (50%). 18 of these patients (33.33) had minimal changes and were categorized as group 2 (middle-lower lobe dominant, reticulation surface area 10%). 8 of the patients (14.81%) had middle-lower lobe dominant, reticulation+traction 10-50% surface area abnormality. When CT results were compared to those taken at the end of the 6th month, an improvement was observed in CT findings and complete improvement was observed in 6 of the patients.

As COVID-19 primarily affects the lungs and respiratory system, studies on pulmonary functions of the COVID-19 survivors are increasing. Zhang *et al.* have recorded lower levels of FEV1% and FVC% in the tests 8 months after hospital release of survivors of severe COVID-19 [15]. Fumagalli *et al.* followed 13 patients who were hospitalized due to COVID-19 on the 6th week, 6th month and 12th month. The researchers detected a slight rise in the spirometric values, which were low at the beginning and at the end of the 6th month, and a considerable rise normalization of the same at the end of 12 months [18]. Yan *et al.* evaluated the conditions of 119 patients while Li *et al.* evaluated those of 230 patients one year after their hospital release and did not see any spirometric abnormality [19,20]. Iversen *et al.* evaluated 606 adults with pre-pandemic spirometer from 6 to 12 months. In the general population, the decrease in the pulmonary volume is considered to be small but measurable [21]. In our study, the patients were given a spirometer test at the end of the 24th month; 19 (35.18%) of the patients had FEV1%, 23 of the patients (42.54%) had low FVC% ($p < 0.05$). These results were compared to the results of

the tests done at the end of the 6th month and no significant change was recorded.

With the prolonged period of the pandemic and associated quarantines and risk of contamination running in the hospitals, the question of health-related quality of life has become very important both for the COVID-19 patients and for the patients with chronic illnesses. Video and telephone communications have proven to be satisfying means to follow COVID-19 patients, to perform follow-up consultations and even to provide tele-rehabilitation [22,23]. Combret *et al.* evaluated patients through telecovid method a year after their hospital release and found them to have weaker physical (30%), mental (27%) and functional exercise capacity (33%) [24]. Galan *et al.* found considerable deterioration (in comparison to general population) in all areas of SF-36 questionnaire 12 months after COVID-19 infection in comparison to the results of the general population [25]. The biggest gap was reported to be physical role (RP) difficulties and emotional role (RE) difficulties. Yet, an improvement was observed to develop in many areas of SF-36 with time. COVID-19 pneumonia causes a long-term deterioration in health-related quality of life (HRQoL) in comparison to general population. However, a trend of improvement, with time, was observed in many areas of SF-36. Siegerink *et al.* monitored the condition of 315 patients after their hospital release [26]. In their study, 182 patients completed the questionnaire in the 3rd month, 98 in the 6th month, and 131 in the 12th month. The total points in all areas in the 3rd month was 58, in the 12th month was 98 and in the control group it was 81. A significant rise was noted from the 3rd month to the 12th month and from the 6th month to the 12th month. In other words, although COVID-19 leads to a decrease in health-related quality of life and damages psychological health, a return to normal levels in a year was recorded. In our study, physical function was lower than expected in 50 (92.59%) patients, energy-vitality was lower than expected, in 40 (74.07%) patients, social function was lower than expected in 47 (87.03%) patients and general health perception was lower than expected in 52 patients. The changes in these parameters were statistically significant ($p < 0.05$). These figures did not differ much when compared to the results of tests at the end of the 6th month, except for an improvement in body pain ($p < 0.05$). In Table 2, a comparison of the SF-36 points between general Turkish population and COVID-19 patients is shown.

All of the patients included in our study were those admitted to and treated in the hospital with severe COVID-19 diagnosis. We wanted to see whether or not

it would be possible to predict at an early stage which of the patients were likely to develop CT abnormality. We compared the WBC, lymphocyte, C-RP, ferritin, D-dimer values and the BMI of the patients taken on the hospital admission day and hospital treatment duration of the patients with their CT taken on the 24th month. We did not find a co-relation between these parameters.

Limitations

This study has some limitations. First, pre-disease data of the patients included in the study were not available. Since the basal data results are unknown, the lower results detected may not be directly attributed to COVID-19. Previously undiagnosed pulmonary and other system diseases may affect our results. The other limitation is that this study could not cover all the severe COVID-19 pneumonia cases we followed. During to the continuing pandemic, some of the patients refused to come to health facilities due to the risk of transmission and isolation rules. A group of patients also had temporarily migrated to rural areas from Istanbul, the country's most crowded city.

Conclusions

Our study is the first to analyze 24-month follow up observations of severe COVID-19 patients. Our study showed that at the end of the 24th month, half of the patients (27/54) still had fibrotic changes in chest CT ranging from diffuse to less frequent involvement. Approximately 40% of our patients who survived severe COVID-19 infection had persistent dysfunction as observed by spirometry at the end of the 24th month. We noted deterioration in health-related quality of life parameters in most patients, especially in the perception of general health. Comprehensive evaluation and rehabilitation programs should be available for the management of the sequelae that occur. More research and follow-up are needed to understand the long-term sequelae of these patients.

Authors' contributions

Design of the study: Bardakci Mustafa Ilteris, Ozturk Esin Nagihan, and Yildiz Sevgi Dilek; data collection: Ozturk Esin Nagihan, Bardakci Mustafa Ilteris, and Ozkarafakılı Mufide Arzu; interpretation and analysis of the data: Ozturk Esin Nagihan, Bardakci Mustafa Ilteris, Ozkarafakılı Mufide Arzu, Ozkurt Huseyin, Yildiz Sevgi Dilek, and Yanç Ugur; all authors reviewed the results and approved the final version of the manuscript.

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