Long-term impairment of social-related quality of life in COVID-19 pneumonia survivors: a prospective longitudinal study

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Abstract

Long-term sequelae of COVID-19 can affect health-related quality of life (HRQOL). We examined the long-term impact of COVID-19 on HRQOL and elucidated factors associated with low HRQOL. Discharged COVID-19 patients were assessed at 3 and 6 months after disease onset. The patients completed a medical examination and SF-36 questionnaire at the two time points and underwent pulmonary function testing at 6 months. All had undergone computed tomography (CT) imaging upon hospital admission. Of the 74 included patients, 38% reported respiratory symptoms at 3 months and 26% at 6 months. The aggregated SF-36 scores declined in the role/social component summary (RCS), a category related to social activity. Patients with respiratory sequelae or impaired pulmonary function had lower RCS scores. There was a negative linear relation between the RCS score and the CT score, which reflected the extent of COVID-19 pneumonia (3 months, P = 0.0024; 6 months, P = 0.0464). A high CT score (≥ 10 points) predicted a low RCS score at 6 months (P = 0.026). This study highlights the long-term impairment of RCS and its associations with respiratory sequelae. The study also emphasizes the importance of radiological findings in predicting long-term HRQOL outcomes after COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global pandemic. As of May 15, 2023, more than 677 million people worldwide have been infected with SARS-CoV-2, with more than 6.9 million deaths [1] [accessed May 15, 2023]. Mortality rates have decreased owing to a combination of factors, including the widespread use of vaccines, treatment with antiviral drugs [2], and changes in viral strains [3]. However, long-term sequelae that occur in COVID-19 survivors have become a growing concern.

Post-acute sequelae of SARS-CoV-2 infection (PASC) is defined by the World Health Organization as the persistence of symptoms or new symptoms more than 30 days after SARS-CoV-2 infection [4]. Various symptoms of PASC, such as fatigue, dyspnea, anxiety/depression, palpitations, and hair loss [5], have been reported, and these symptoms can last more than 6 months in some patients [6]. Factors that may contribute to PASC include being female, a history of smoking, a high body mass index (defined as ≥ 30 kg/m^2), comorbidities, and intensive care unit admission in the acute phase [7]. In particular, patients with COVID-19 pneumonia have been reported to experience a long-term decline in respiratory function and fibrosis of the lungs [8]. These sequelae and respiratory function impairments can seriously impact a patient's quality of life (QOL), and thus need to be identified and addressed from both a medical and social perspective.

Measuring health-related quality of life (HRQOL) is useful for obtaining a comprehensive assessment of a patient's health status. Assessing HRQOL can help determine the burden of preventable disease, injuries, and disabilities and can provide valuable insight into the relationships between HRQOL and risk

factors [9]. The 36-item Short-Form Health Survey (SF-36) is a scientifically validated and reliable multidimensional scale that has been established as a questionnaire to measure HRQOL [10].

Previously reported studies that have assessed PASC at various time points after disease onset found a decrease in SF-36 scores [11 12 13 14 15 16 17 18]. However, the recovery process of HRQOL after COVID-19 is still not well understood. In addition, factors associated with prolonged impairment of HRQOL are also unclear.

This study aimed to systematically identify the trajectories of HRQOL and elucidate the predictors associated with low HRQOL in COVID-19 survivors.

Materials and Methods

1. Study Design and Participants

This was a multicenter prospective longitudinal cohort study that followed up hospitalized COVID-19 patients post discharge. The participants were previously hospitalized patients who visited an outpatient clinic 3 months after disease onset and gave consent for this study. The participants were recruited from 13 hospitals in Japan (1 university hospital and 12 general hospitals) from April 1, 2020 to December 31, 2021.

Patients over 20 years of age who were 1) diagnosed with COVID-19 based on SARS-CoV-2 PCR test results, 2) required hospitalization, and 3) were discharged alive were included in this study. Patients who 1) did not visit an outpatient clinic, 2) did not submit the SF-36 questionnaire, and 3) had missing data were excluded.

Written informed consent was obtained from all participants.

2. Procedures

The baseline characteristics and status during hospitalization (disease severity, treatment status, and chest computed tomography (CT) severity score on admission) of each patient were obtained from the patient's medical record. Patients were assessed at 3 and 6 months after COVID-19 onset. During the visits, the patients were interviewed about PASC. Based on patient's complaint, the symptoms were aggregated by dyspnea, cough, fatigue, numbness, joint pain, olfactory disorder, diarrhea and fever. Dyspnea, cough, or fatigue were defined as respiratory-related symptoms in this study. At both time points, each participant underwent a physical examination and filled out the SF-36 questionnaire. A pulmonary function test was administered at the 6-month time point.

3. Measures

3.1. SF-36 Questionnaire

The SF-36 questionnaire is a scale that consists of 36 questions measuring eight domains related to HRQOL. The eight component scores are physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). The eight domains are also aggregated into three summary measures: the physical component summary (PCS) score, mental component summary (MCS) score, and role/social component summary (RCS) score. In this study, the eight component scores and component summary scores were calculated as the deviation from the Japanese national standard of 50 points. A low score (less than 50 points) is indicative of a poor HRQOL.

3.2. Chest CT Evaluation

Patients underwent chest CT scans in the supine position and with breath-holding following inspiration. In our study, two pulmonologists with 11 years and 12 years of experience independently assessed the images. The pulmonologists were blinded to the clinical information and clinical course of the patients, except for the knowledge that these images were of patients with COVID-19. The pneumonia CT scores of the patients were recorded using the method described by Pan et al [19]. In this method, each of the five lung lobes is visually scored on a scale of 0 to 5 points according to the extent of lobar involvement (0: no involvement, 1: involvement of less than 5%, 2: 5–25% involvement, 3: 26–49% involvement, 4: 50–75% involvement, 5: involvement of more than 75%). In case of discrepancy between the two pulmonologists, the final scores were determined by consensus. Each patient's total CT score was calculated by adding each lobar score ranging from 0 to 25 points.

3.3. Pulmonary Function Tests

Spirometry was conducted to measure the forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV_1). The FEV_1/FVC ratio was then calculated. The pulmonary function test procedures were conducted in accordance with the American Thoracic Society and European Respiratory Society guidelines [2021]. The results are expressed as liters and percentages.

4. Data Analysis

In this descriptive analysis, continuous variables are expressed as the mean and standard deviation, and categorical variables are expressed as numbers and percentages. Student's t-test was used to compare the means of continuous variables, while simple linear regression analysis was used to compare continuous variables. Multiple linear regression analysis was performed to identify independent predictors associated with low HRQOL. The statistical analysis was conducted using EZR software version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [22], and GraphPad Prism version 9.4.1 (GraphPad Software Inc., La Jolla, CA, USA) was used for graphics visualization. Statistical significance was considered to be $P < 0.05$.

5. Ethics Declaration

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was also approved by the Medical Research Ethics Committee of Tokyo Medical and Dental University

(approval number: G2020-006) and by the Institutional Review Boards of the participating hospitals.

Results

From April 1, 2020, to December 31, 2021, 6,656 patients were hospitalized for COVID-19 in our facilities. Among the patients who visited a follow-up outpatient clinic 3 months after disease onset, 335 patients consented to participate in this study. Finally, 74 patients completed the physical examination and SF-36 questionnaire at the two time points and the pulmonary function test at the 6-month follow-up (Fig. 1). In this cohort, 46% were over 65 years old, 73% were male, and 65% had a history of smoking. 88% received medication during hospitalization-65% with systemic steroids and 72% with antiviral drugs. 80% received supplemental oxygen, and 19% were intubated. Additional baseline characteristics are described in Table 1.

Table 1

Patient characteristics (n = 74). Categorical variables are expressed as numbers and percentages. Abbreviation: BMI Body Mass Index, COPD Chronic Obstructive Pulmonary Disease, ECMO Extracorporeal Membrane Oxygenation.

Parameter	n = 74	Parameter	n = 74
Age group		Treatment received during hospital stay	65 (88%)
< 65 years	40 (54%)	Corticosteroids	48 (65%)
≥ 65 years	34 (46%)	Chloroquine	3 (4%)
Sex		Antiviral drugs	53 (72%)
Male	54 (73%)	Remdesivir	25 (34%)
Female	20 (27%)	Favipiravir	32 (43%)
BMI		Tocilizumab	5 (7%)
< 25 (kg/m^2)	40 (54%)	Macrolides	8 (11%)
≥ 25 (kg/m^2)	27 (36%)	Baricitinib	2 (3%)
Unknown	7 (10%)	Medical equipment	
Smoking history Yes	48 (65%)	Supplemental Oxygen	59 (80%)
No	26 (35%)	High-flow nasal cannula	2 (3%)
Comorbidity	54 (73%)	Intubation	14 (19%)
Hypertension	35 (47%)	ECMO	1 (1%)
Diabetes	18 (24%)	Data are expressed as No. (%).	
Cardiovascular disease	11 (15%)		
Cerebrovascular disease	6 (8%)		
Malignant tumor	3 (4%)		

Parameter	n = 74	Parameter	n = 74
Autoimmune disease	3 (4%)		
Interstitial lung disease	3 (4%)		
COPD	9 (12%)		
Bronchial asthma	7 (9%)		

At 3 months, 31 patients (42%) reported at least one symptom, the most common of which were dyspnea (22%), cough (12%), and fatigue (8%). At 6 months, there was an overall trend toward symptom improvement; however, 21 patients (28%) still experienced persistent symptoms. The most common residual symptoms were dyspnea (14%), cough (5%), and fatigue (9%) (Fig. 2).

The eight component scores and three component summary scores normalized by the Japanese national standard at each time point are shown in Table 2. At 3 months after disease onset, the average scores of five components (PF, RP, BP, SF, and RE) of the SF-36 were below the Japanese national standard (50 points). The average scores of PF and BP, which are the main components of PCS, were slightly below the national standard and had minimal change from 3 to 6 months. On the other hand, average scores of RP, SF, and RE, the main components of RCS, were the three lowest component scores among the eight components at 3 months. These three component scores showed recovery at 6 months. Reflecting on these results, RCS was the lowest of the three component summary scores at 3 months, but improvement of average scores was observed at 6 months follow-up.

Table 2
SF-36 scores normalized by the Japanese national standards at each time point. Scores are expressed as mean ± standard deviations (SD). Abbreviation: PF : Physical Function, RP : Role Physical, BP : Bodily Pain, GH : General Health, VT : Vitality, SF : Social Functioning, RE : Role Emotional, MH : Mental Health, PCS : Physical Component Summary, MCS : Mental Component Summary, RCS : Role/Social Component Summary

	3 months	6 months
SF-36 Scale	Mean score (± SD)	Mean score (± SD)
PF	46.6 ± 9.7	47.9 ± 8.1
RP	43.9 ± 13.1	46.7 ± 11.7
BP	49.8 ± 11.9	48.8 ± 11.1
GH	51.2 ± 7.6	51.9 ± 8.01
VT	54.3 ± 10.0	53.8 ± 10.1
SF	42.8 ± 14.3	47.6 ± 11.4
RE	45.0 ± 12.8	48.1 ± 11.3
MH	52.6 ± 9.1	53.9 ± 8.71
PCS	48.4 ± 11.0	47.5 ± 9.8
MCS	56.1 ± 8.5	55.5 ± 9.1
RCS	40.7 ± 13.9	45.7 ± 12.3

We further investigated the patient characteristics associated with a low RCS score at each time point. Patients with residual respiratory-related symptoms (dyspnea, cough or fatigue) tended to have a low RCS score at 3 months (P = 0.037). In addition, although the difference did not reach statistical significance, the RCS score tended to be lower in patients who had any symptoms (P = 0.090), respiratory-related symptoms (P = 0.088), or dyspnea symptoms (P = 0.086) at 6 months. Diarrhea and fever were not analyzed because no participants had these symptoms at either time point (Table 3). Several pulmonary function tests such as FVC, and FEV_1 measured at the 6-month follow-up were also significantly associated with the RCS score (Table 3).

Table 3
Association of PASC, pulmonary function tests and RCS score. Dyspnea, cough or fatigue were defined as respiratory symptoms. Abbreviation: PASC Post-acute sequelae of SARS-CoV-2 infection, FVC Forced vital capacity, FEV1 Forced expiratory volume in 1 second. "-" indicates no comparative patients. Significant values are in [bold].

	Role/Social Component Summary Score							
	3 months				6 months			
	coefficient	95% C.I.		*p*-value	coefficient	95% C.I.		*p*-value
PASC at each time points (yes/no)								
any symptoms	-4.76	-11.3	1.78	0.151	-5.52	-11.91	0.87	0.090
respiratory symptoms	-6.99	-13.54	-0.44	**0.037**	-5.74	-12.35	0.88	0.088
dyspnea	1.20	-6.76	9.14	0.766	-7.57	-16.23	1.10	0.086
cough	-6.86	-16.30	2.58	0.152	-2.94	-15.71	9.82	0.647
fatigue	-8.85	-20.67	2.96	0.140	-4.42	-14.25	5.40	0.372
numbness	-1.70	-16.17	12.78	0.816	2.50	-10.27	15.28	0.697
joint pain	-13.47	-33.41	6.48	0.182	2.88	-22.14	27.90	0.819
olfactory disorder	13.82	-6.11	33.75	0.171	-	-	-	-
Pulmonary Function Test at 6 months after onset								
FVC (L)	-	-	-	-	3.59	0.395	6.78	**0.028**
%FVC (%)	-	-	-	-	0.19	0.01	0.38	**0.045**
FEV_1 (L)	-	-	-	-	3.99	0.24	7.73	**0.037**
FEV_1/FVC (%)	-	-	-	-	-0.07	-0.31	0.17	0.554
Comparisons were determined by simple regression analysis.								

We used univariate analysis to examine whether the clinical history and disease course in the acute phase of illness may have influenced the RCS score. Age (over 65 years) was related to a low RCS score at both time points (3 months; P = 0.016, 6 months; P = 0.016). The use of a high-flow nasal cannula and a high CT score on admission (median value ≥ 10 points) were associated with a low RCS score at 3 months (P = 0.007) and 6 months (P = 0.014), respectively (Table 4). The association between CT score on admission and a low RCS score was also confirmed by the significant negative linear relationship

between the CT score and the RCS score at both time points, while no relation between the CT score and the PCS or MCS score was observed (Fig. 3a). Concerning the trajectory of the RCS score, the group with a high CT score showed poorer recovery (average of score change between 3 and 6 months: 3.4 points) than the group with a low CT score (average of score change between 3 and 6 months: 7.1 points) (Fig. 3b). Multiple regression analysis was conducted that included age (older than 65 years), sex (male), history of smoking, history of intubation, and CT score (median value ≥ 10 points). The results showed that older age (greater than 65 years) (P = 0.037) and a history of intubation (P = 0.042) were independent factors of a low RCS score at 3 months, and a high CT score (median value ≥ 10 points) (P = 0.026) was an independent factor of a low RCS score at 6 months (Table 5).

Table 4
Association of patient backgrounds, status during hospitalization and RCS score.Abbreviation: BMI Body Mass Index, ECMO Extracorporeal Membrane Oxygenation. Significant values are in [bold].

	Role/Social Component Summary Score							
	3 months				6 months			
	coefficient	95% C.I.		*p*-value	coefficient	95% C.I.		*p*-value
Background (yes/no)								
Age ≧ 65 (years old)	-7.74	-14.0	-1.45	**0.016**	-6.91	-12.5	-1.32	**0.016**
Sex, male	-4.61	-11.9	2.68	0.212	-0.32	-6.84	6.21	0.923
BMI ≧ 25 (kg/m^2)	2.0	-5.31	9.31	0.586	-3.25	-9.58	3.07	0.308
Smoking history	0.85	-6.01	7.71	0.806	-3.69	-9.70	2.33	0.226
Any comorbidities	-3.60	-3.59	-10.9	0.332	-6.23	-12.58	0.13	0.055
Status during hospitalization (yes/no)								
Treatment								
Corticosteroids	0.73	-6.13	7.59	0.833	-1.39	-7.46	4.67	0.648
Chloroquine	-9.21	-25.67	7.25	0.268	4.22	-10.4	18.84	0.567
Antiviral drugs	-0.07	-7.34	7.19	0.984	-0.88	-7.30	5.55	0.786
Tocilizumab	-5.13	-18.12	7.86	0.434	-5.06	-16.52	6.39	0.381
Macrolides	1.99	-8.55	12.52	0.708	7.34	-1.82	16.49	0.114
Baricitinib	11.72	-8.55	31.99	0.253	1.32	-16.71	19.36	0.884
Medical equipment								
Supplemental Oxygen	-7.80	-15.73	0.14	0.054	-5.76	-12.83	1.31	0.109
High-flow nasal cannula	-26.57	-45.78	-7.37	**0.007**	-6.74	-24.50	11.01	0.452
Intubation	-6.88	-15.08	1.33	0.099	1.34	-6.04	8.73	0.718
ECMO	-2.03	-30.39	26.33	0.887	2.90	-22.14	27.91	0.819

Role/Social Component Summary Score								
CT score (≥ 10 points) on admission	-4.08	-10.87	2.7	0.233	-7.76	-13.88	-1.65	**0.014**
Comparisons were determined by simple regression analysis.								

Table 5
Multivariate analysis results of factors predicting low RCS. Analyses were conducted using a multiple regression model. Objective variables were RCS score. The following dichotomized explanatory variables were entered into the model simultaneously; age (older than 65 years), sex (male), history of smoking, history of intubation and CT score (cut-off by median value, ≥ 10 points). Abbreviation: RCS Role/Social Component Summary. Significant values are in [bold].

	3 months				6 months			
	coefficient	95% C.I.		*p*-value	coefficient	95% C.I.		*p*-value
Age ≥ 65 (years old)	-7.60	-14.74	-0.46	**0.037**	-5.12	-11.75	1.49	0.127
Sex, male	-0.71	-8.77	7.35	0.861	1.07	-6.41	8.58	0.776
History of smoking	3.42	-3.93	10.78	0.356	-2.45	-9.27	4.38	0.476
History of intubation	-9.42	-18.51	-0.34	**0.042**	2.38	-6.05	10.81	0.574
CT score (≥ 10 points)	-1.09	-8.07	5.88	0.755	-7.39	-13.86	-0.92	**0.026**

Discussion

In this prospective cohort study, we observed a decline in HRQOL especially related to the RCS. RCS score decline was associated with respiratory-related symptoms and impaired pulmonary function. Although the average RCS score improved from 3 to 6 months after disease onset, the score had still not reached the Japanese national standard at the 6-month follow-up, indicating that recovery of the RCS score was insufficient at this time point. Furthermore, patients with a high CT score had a significantly lower RCS score at 6 months. These findings could be useful in predicting long-term low RCS scores.

Several cross-sectional studies focusing on HRQOL have found that HRQOL is often impaired in patients with PASC. These studies reported that the categories of RP, SF, and RE, which comprise the RCS score, were particularly low in PASC patients [14 15]. These trends were also validated in longitudinal studies. A cohort study following patients who suffered from COVID-19 pneumonia found marked declines in RP, SF,

and RE at the 3-month follow-up, but these were improved after 12 months of follow-up [23]. These trends in recovery are consistent with our study and might reflect the general course of recovery from PASC.

In this study, a low RCS score was significantly or nearly significantly associated (3 months; P = 0.037, 6 months; P = 0.088) with PASC-related respiratory symptoms at both time points. Decreased pulmonary function was observed in patients with lower RCS scores at the 6-month follow-up (FVC: P = 0.028, FEV_1: P = 0.037). Although our study design, which identified symptoms based on open-ended questions, may have led to some omissions about the symptoms, these trends suggest that the respiratory-related problems observed in PASC may influence social-related QOL.

The relation between respiratory symptoms in other chronic respiratory diseases and the components of the RCS score has been previously investigated. In patients with chronic obstructive pulmonary disease, several SF-36 component scores (including RP and SF) were significantly impaired in patients with a low baseline dyspnea index score [24]. In patients with interstitial pneumonia, the observed respiratory symptoms and severely impaired pulmonary function were associated with a decline in overall HRQOL, including in the categories related to social activities [25]. This commonly observed result in chronic respiratory diseases possibly reflects patients' decreased activity and interaction with others because of their symptoms. Moreover, patients with PASC may have avoided social interactions owing to concerns about being judged by others because of their prolonged respiratory symptoms.

In this study, older age and having a history of intubation were predictors of a low RCS at the 3-month follow-up, a finding that is consistent with previous reports of having a lower QOL after disease onset [26] [27]. We also found that a high CT score on admission was a predictor of a low RCS score at the 6-month follow-up, but no such association was found at the 3-month follow-up. This can be explained by the slower RCS score recovery in those with a higher CT score than in those with a lower CT score, which widened the score difference between the two groups at 6 months (Fig. 3b). These results suggest that the extent of COVID-19 pneumonia could be associated with the process of recovering from PASC. Although the details of the immunobiology associated with PASC are currently under investigation, aberrant innate immune stimulation during acute COVID-19 might be associated with PASC [28]. In particular, respiratory sequelae are thought to occur because of impairments in the airways owing to endothelial damage and the inflammatory reaction that occurs in the acute phase [29]. Patients with severe COVID-19 pneumonia are prone to respiratory sequelae and were shown to have prolonged impairment of the diffusing capacity of the lung for carbon monoxide 3–12 months after disease onset [30] [31]. Previous studies have shown that chest CT scan is an important tool for diagnosing COVID-19 [32] and can indicate disease severity and the short-term prognosis [33] [34]. The results of the present study suggest that patients with extensive COVID-19 pneumonia in the acute phase have a prolonged decline of HRQOL related to social activities. Thus, evaluating the extent of COVID-19 pneumonia by conducting a chest CT scan on admission could be helpful in considering the long-term medical and social support needs of COVID-19 survivors.

Limitations

This study had several limitations. First, a reduction in the number of participants available between recruitment and analysis occurred in exchange for higher data integrity; thus, there may have been selection bias. Participants were excluded because of inadequate responses to the SF-36 or missing either the 3-month or 6-month follow-up appointment. Second, there was no baseline SF-36 or pulmonary function data; therefore, comparisons with pre-COVID-19 onset were impossible. Third, as the study period ended on December 31, 2021, many of the patients were unvaccinated, which complicates comparisons with the sequelae of patients who were infected with more recent strains. Fourth, this study was designed to include only patients who had been hospitalized; therefore, the findings cannot be generalized to those with mild illness.

Conclusion

Our systematic assessment of HRQOL after COVID-19 revealed decreased SF-36 scores related to social activities and that this decrease was associated with chronic respiratory sequelae. Particular attention should be given to patients with extensive COVID-19 pneumonia observable on chest CT scans in the acute phase because this population may be more likely to experience a prolonged decline in HRQOL related to social activities.

Declarations

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Author contributions

Study concept and design: S.S., T.T., and Y.M. Data acquisition: K.T., M.K., Y.M., T.I., K.O., S.T., T.O., M.D., H.S., T.F., T.C., A.N., T.T., and Y.M. Data management: T.A., S.S., J.S., S.S., T.T., and Y.M. Statistical analysis: T.A., S.S., T.A., K.T., and T.T. Data interpretation: T.A., S.S., T.A., K.T., and T.T. Manuscript development: T.A., S.S., J.S., S.S., T.T., and Y.M. Study supervision: Y.M. All authors have read and agreed with the published version of the manuscript.

Data availability

The datasets used and analyzed in this study are available from the corresponding author upon reasonable request.

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Additional information

Competing interests The authors declare no competing interests.

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Figures

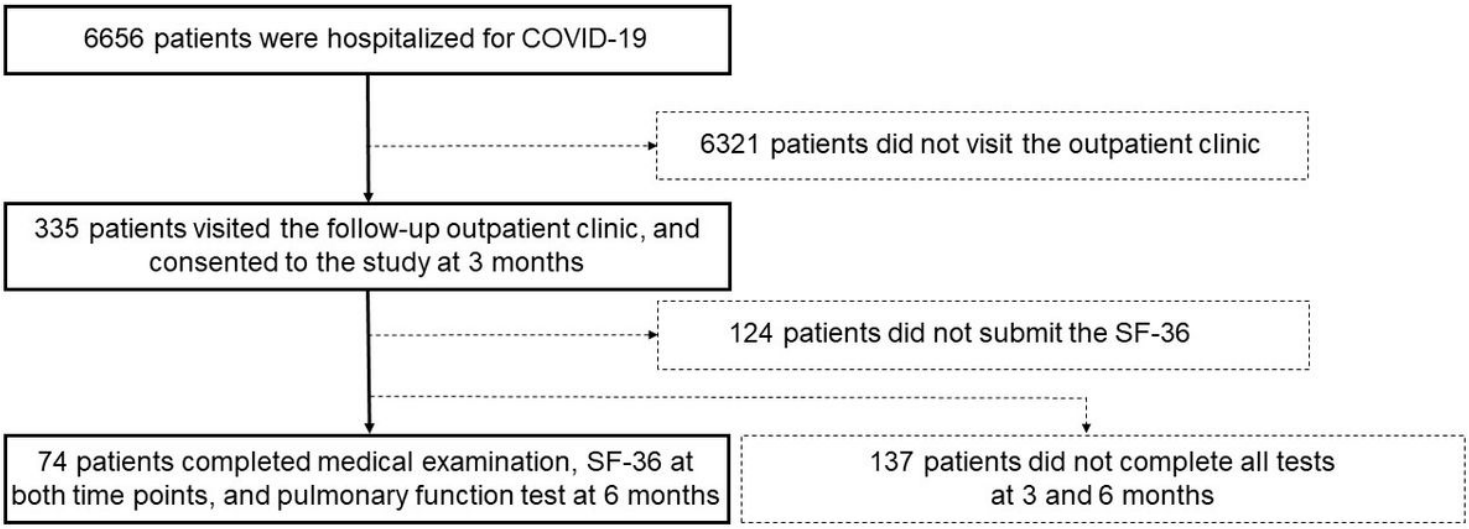

Figure 1

Flow chart of the study from April 1, 2020 to December 31, 2021. This study was conducted among 74 COVID-19 survivors who completed all tests at 3 and 6 months after disease onset.

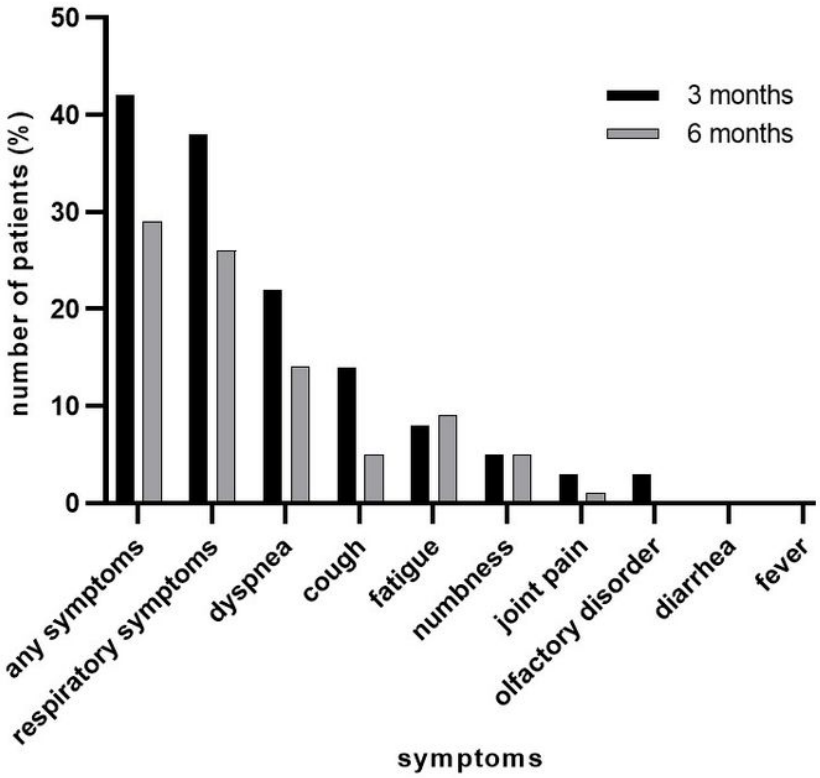

Figure 2

Symptoms observed at 3 and 6 months after COVID-19 onset.

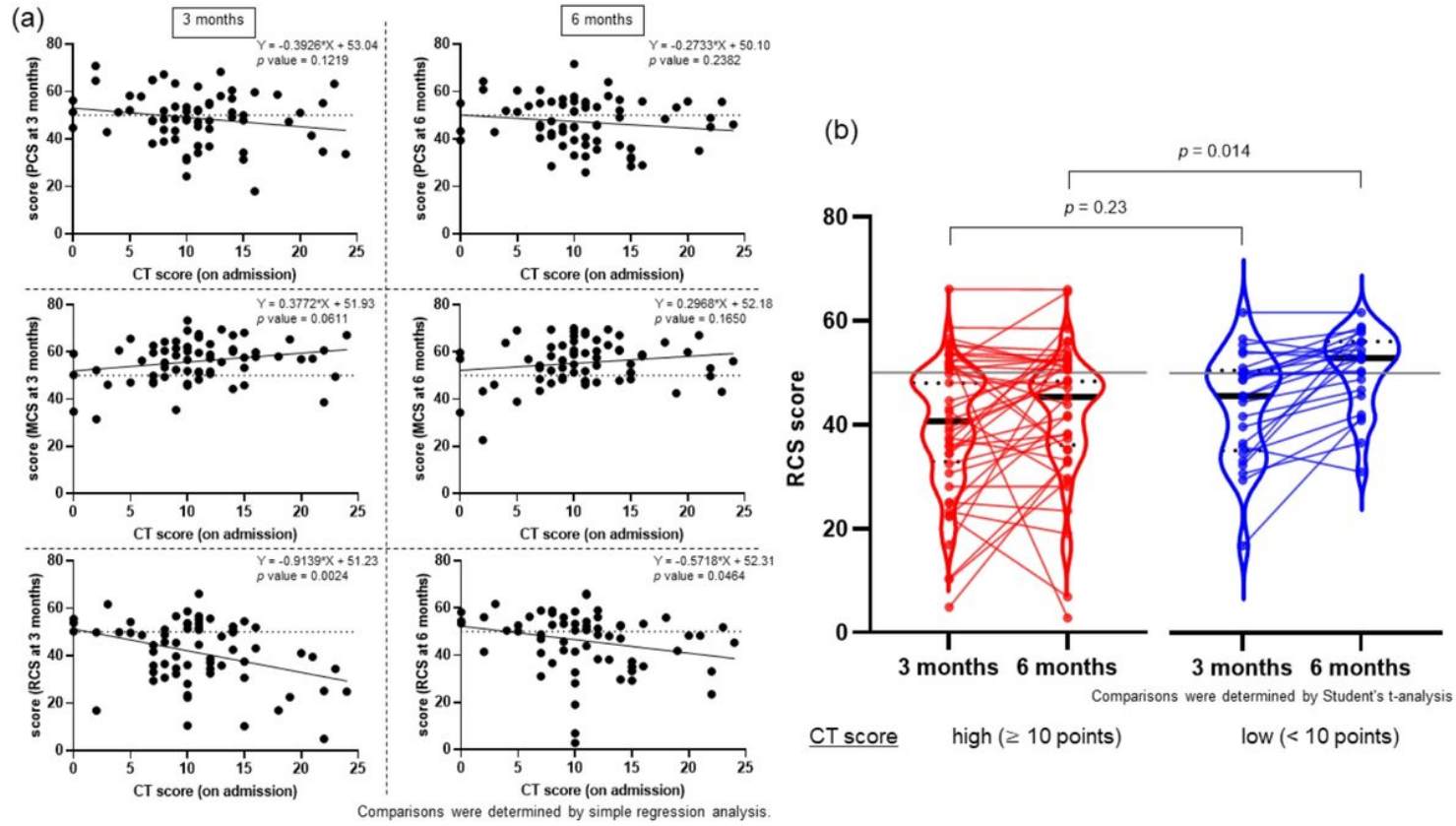

Figure 3

(a) Association between CT score and component summary score. (b) RCS score trajectories from 3 to 6 months of two groups based on CT score (cut-off = median value of 10 points). The gray bar shows the Japanese national standard (50 points).

Abbreviations: PCS, physical component summary; MCS, mental component summary; RCS, role/social component summary.