Research Article

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Future MICROBIOLOGY

Long-term effects of COVID-19 on lungs and the clinical relevance: a 6-month prospective cohort study

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Background: We aimed to explore the prevalence of prolonged symptoms, pulmonary impairments and residual disease on chest tomography (CT) in COVID-19 patients at 6 months after acute illness. **Methods:** In this prospective, single-center study, hospitalized patients with radiologically and laboratory-confirmed COVID-19 were included. **Results:** A high proportion of the 116 patients reported persistent symptoms (n = 54; 46.6%). On follow-up CT, 33 patients (28.4%) demonstrated residual disease. Multivariate analyses revealed that only neutrophil-to-lymphocyte ratio was an independent predictor for residual disease. **Conclusion:** Hospitalized patients with mild/moderate COVID-19 still had persistent symptoms and were prone to develop long-term pulmonary sequelae on chest CT. However, it did not have a significant effect on long-term pulmonary functions.

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Keywords: chest CT • COVID-19 • follow-up • pulmonary function • residual disease

COVID-19, caused by the coronavirus SARS-CoV-2, has resulted in serious complications and unexplored long-term consequences in some patients which are collectively known as 'long COVID' [1]. Long COVID has raised several concerns, as well as resulting in a significant healthcare burden. Some studies have shown that SARS-CoV-2 has a similar effect on the respiratory system to those of other coronaviruses and viral infectious agents, and patients with COVID-19 pneumonia may have functional problems in the pulmonary system and demonstrate residual radiological findings [1].

Although the clinical features and acute complications of COVID-19 are well known, its long-term effects after recovery from acute disease remain unclear. Therefore, studies on long-term effects of COVID-19, including chronic persistent symptoms or declined lung functions and impairments in lung capacity, are needed [2].

Imaging is suggested for patients with the presence of persistent symptoms or functional pulmonary impairment weeks after symptom onset [1,3]. Some studies have suggested that lung sequelae after recovery occur in certain patients [1,4], while others have not found any significant pulmonary sequelae [5].

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In this study we aimed to explore the prevalence of prolonged symptoms, pulmonary impairments and residual disease on chest computed tomography (CT) in COVID-19 patients after recovery from acute illness. In addition, we investigated the predictors for residual pulmonary disease.

Patients & methods

Patient population

In this prospective, single-center study, hospitalized patients with radiologically and laboratory-confirmed COVID-19 between 11 March 2020 and 11 April 2020, when the α variant of SARS-CoV-2 was dominant, were included. We excluded outpatients and asymptomatic patients. Because mechanical ventilation may cause additional sequelae in the lungs, patients with COVID-19 requiring mechanical ventilation during their hospital stay were also excluded. None of the patients were vaccinated against SARS-CoV-2. For laboratory confirmation, oropharyngeal or nasopharyngeal swab samples were obtained and tested by RT-PCR.

Patients with mild COVID-19 were defined as those with any signs and symptoms of COVID-19 including respiratory rate <30/min and peripheral capillary oxygen saturation >93%, but who did not have dyspnea. Patients with moderate COVID-19 were defined as those with any signs and symptoms of COVID-19 including dyspnea or peripheral capillary oxygen saturation >93% [6,7].

All patients with moderate or severe COVID-19 were hospitalized. Patients who had mild disease but who were older than 50 years or who had any of the following risk factors were also hospitalized according to the Republic of Turkey's Ministry of Health COVID-19 Guidelines during the first period of the COVID-19 pandemic [8]:

- Being older than 50 years;
- Having underlying diseases (cardiovascular disease, diabetes mellitus, hypertension, cancer, chronic lung diseases or other immunosuppressive conditions);
- Having severe pneumonia indicators (confusion or tachycardia >125 BPM);
- Having respiratory distress or tachypnea (>30/min) or hypotension <90/60 mmHg or SpO_2 <93% or bilateral diffused involvement on lung imaging;
- Having sepsis or septic shock;
- Having cardiomyopathies or arrhythmia;
- Having acute renal failure;
- Having poor prognostic indicators in blood analyses at admission (blood lymphocyte count <800/μl or serum C-reactive protein (CRP) >40 mg/l or ferritin >500 ng/ml or D-dimer >1000 ng/ml etc.).

Assessment during hospital stay

Demographic characteristics, clinical features, physical examination findings, laboratory parameters, radiological findings and short-term outcomes were retrospectively collected from medical records. However, the patients were prospectively followed up after discharge.

Assessment at follow-up

Eligible patients were invited by phone to provide a follow-up at 6 months after hospital discharge. Two phone reminders were performed for non-respondents.

Patients were followed-up at the COVID-19 outpatient clinics for 6 months after discharge. A standardized datasheet form with a questionnaire including questions relating to persistent symptoms, vital signs and St George's Respiratory Questionnaire (SGRQ) was filled out for each patient. Spirometry, peripheral capillary oxygen saturation (SpO_2) and low-dose CT scan were performed 6 months after discharge. All patients underwent CT, and 98 patients underwent SGRQ and spirometry. Blood samples were obtained for laboratory parameters and serum antibody measurement on all patients.

Symptom questionnaire

Symptoms at admission and newly occurring, persistent or worsening symptoms during the follow-up were assessed. Vital signs including body temperature, respiratory rate, SpO_2 and heart rate were recorded.

Laboratory examinations

Laboratory parameters including hemoglobin, hematocrit, leukocyte/neutrophil/lymphocyte/platelet counts, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), glucose, urea, creatinine, aspartate

aminotransferase, alanine aminotransferase (ALT), lactate dehydrogenase, CRP, procalcitonin, ferritin, troponin and D-dimer were examined at admission, discharge and 6 months after.

St George's Respiratory Questionnaire

Quality of life was assessed using the SGRQ, which is scaled from 0 (optimal health) to 100 (worst health). The SGRQ has three main subscales: the symptom subscale evaluates respiratory symptoms, the activity subscale evaluates the physical activity which causes or is limited by dyspnea, and the impact subscale evaluates social functioning and psychological disorders due to pulmonary problems [9,10].

Pulmonary function measurement

Spirometry was performed for all participants to measure the forced expiratory volume in 1 s (FEV_1), the forced vital capacity (FVC_{ex}) and the FEV_1-to-FVC_{ex} ratio.

Chest CT

Low-dose and thin-section chest CT scans were performed in all cases. Chest CT scans were reviewed by two radiologists who were unaware of the participants' clinical condition. For baseline chest CT evaluation at admission, pulmonary findings on chest CT scans were scored to estimate pulmonary involvement [11]. A complete resolution was defined as no residual finding on chest CT.

Serological tests

Serological tests were performed using the Siemens semiquantitative ADVIA Centaur® SARS-CoV-2 IgG kit (Siemens, USA). Detection of anti-SARS-CoV-2 IgG was confirmed by the presence of antibodies against the spike glycoprotein receptor-binding domain (S1 RBD). The method was a two-step fully automated sandwich immunoassay using chemiluminescence technology. The detection range of the kit was 0.50–150.00 index, where values $\geq$1 U/ml were considered positive and values <1 U/ml were considered negative. The unit recommended by the WHO was stated as 1 BAU/ml = 21.8 U/ml [12].

Outcome measures

The primary outcome was the presence of residual pulmonary abnormalities at 6-month follow-up. The secondary outcomes were persistent symptoms, laboratory parameters, lung function, SGRQ scores, anti-SARS-CoV-2 IgG seropositivity and antibody titers at the 6-month follow-up.

Statistical analysis

Continuous variables were described as median ± interquartile range (IQR), while categorical variables were described as numbers and percentages. χ-square and Fisher's exact tests were used to compare categorical variables. The closeness of the median and mean values of the normal distribution was evaluated according to the box plot analysis, the result of the Kolmogorov–Smirnov test and kurtosis–skewness values. While the independent sample *t*-test was used for variables with normal distribution, the Mann–Whitney *U* test was used for variables with non-normal distribution. Power analysis was done using the G*Power v. 3.1.9.6 (University of Kiel, Kiel, Germany) program. In this power analysis, the power was 80%, the α error was 0.05, and the effect size was 0.3; the required minimum sample size was 94. We performed univariate analysis and multivariate logistic regression analyses. For residual pulmonary sequelae, receiver operating characteristic (ROC) curves were obtained and area under the curve, optimal cutoff values, sensitivities and specificities were demonstrated. Odds ratio (OR) values with 95% CIs were calculated. SPSS v. 22.0 (IBM Corp., NY, USA) was used for statistical analyses. A p-value <0.05 was considered statistically significant.

Results

A total of 500 patients were called by phone. A total of 116 patients admitted to our outpatient clinic for follow-up examination 6 months after hospital discharge were included (Supplementary Figure 1). The median age was 52 (IQR: 42–61) years, and 58 patients (50%) were female. Baseline characteristics and well-recognized risk factors for severe COVID-19 hospitalization are described in Supplementary Table 1.

The most common symptoms on admission were weakness (n = 86; 74.1%), cough (n = 76; 65.5%), dyspnea (n = 73; 63%), myalgia (n = 67; 57.8%) and fever (n = 63; 54.3%). At follow-up examination 6 months after acute

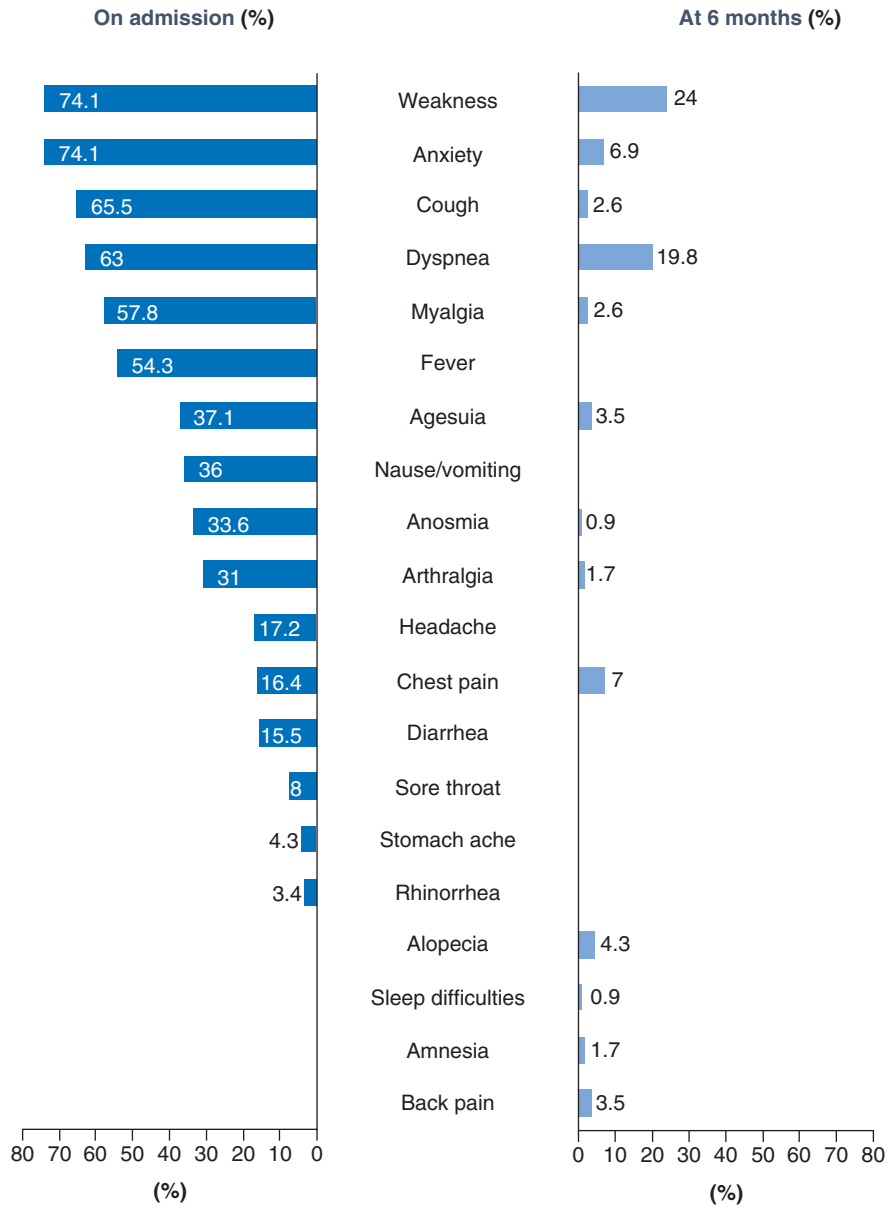


Figure 1. Clinical signs and symptoms of patients with COVID-19 pneumonia.

infection, only 62 patients (53.4%) were completely free of any COVID-19-related symptom, while 48 (41.4%) had one or two symptoms, and six patients (5.2%) had three or more. At 6 months after symptom onset, 33 patients (28.4%) had more than one symptom. A high proportion of the 116 patients reported persistent symptoms (n = 54; 46.6%), which included: weakness (n = 28; 24%), dyspnea (n = 23; 19.8%), anxiety (n = 8; 6.9%), chest pain (n = 8; 7%), alopecia (n = 5; 4.3%), ageusia (n = 4; 3.5%); back pain (n = 4; 3.5%), cough (n = 3; 2.6%), myalgia (n = 3; 2.6%), arthralgia (n = 2; 1.7%), amnesia (n = 2; 1.7%), anosmia (n = 1; 0.9%) and sleep difficulties (n = 1; 0.9%) (Figure 1).

Even though the median levels of leukocyte count, neutrophil count, platelet count, hemoglobin, hematocrit, aspartate aminotransferase, ALT and creatinine at hospital admission were in the normal range, the median levels of these parameters at 6 months were lower than the normal range. At hospital admission, median values of D-dimer (510 mg/l; IQR: 320–840), lactate dehydrogenase (254 UI/l; IQR: 216–318), CRP (23.5 mg/dl; IQR: 11–56) and ferritin (132 ng/l; IQR: 75–232) were higher than the upper limits (Table 1).

Table 1. Vital signs and laboratory parameters of patients with COVID-19 pneumonia.

Vital parameters, median (IQR)	Admission, n (%)	Discharge, n (%)	6 months, n (%)	p-value
SpO_2 (%)	95 (94–97)	96 (95–97)	97 (96–98)	<0.001‡
Body temperature (°C)	36.6 (36.2–37)	36.4 (36.2–36.6)	36.2 (36–36.5)	<0.001‡
Respiratory (rate/min)	23 (20–24)	20 (19–21)	18 (16–20)	<0.001‡
Heart (rate/min)	84 (76–96)	79 (75–88)	80 (73–87)	<0.001‡
Laboratory parameters, median (IQR)				
Leukocyte (count/mm^3)	5580 (4500–7300)	6150 (4890–8030)	6595 (5800–7685)	<0.001‡
Neutrophil (count/mm^3)	3195 (2610–4855)	3700 (2800–5380)	3845 (3135–4550)	0.03†
Lymphocyte (count/mm^3)	1415 (1120–1975)	1710 (1410–2260)	2040 (1605–2685)	<0.001‡
Platelet (count/mm^3)	205 (161–249)	305 (226–391)	245 (212–285)	<0.001‡
Neutrophil-to-lymphocyte ratio	2.37 (1.58–3.54)	2.09 (1.56–3.27)	1.82 (1.35–2.49)	<0.001‡
Platelet-to-lymphocyte ratio	0.14 (0.11–0.19)	0.18 (0.13–0.23)	0.12 (0.09–0.16)	<0.001‡
Hemoglobin (g/dl)	13.2 (12.1–14.3)	12.3 (11.4–13.5)	14 (12.3–15.1)	<0.001‡
Hematocrit (g/dl)	38.7 (36–41.2)	36.5 (33.8–39.2)	41.2 (37.6–45)	<0.001‡
Urea (mmol/l)	27 (21–37)	27 (19–34.4)	30 (24–35)	0.232
Creatinine (mg/dl)	0.82 (0.7–0.1)	0.71 (0.59–0.9)	0.8 (0.69–0.94)	0.032†
AST (UI/l)	32 (24–45)	36 (26–55)	20 (15–23)	<0.001‡
ALT (UI/l)	25 (16–46)	44 (25–83)	19 (15–27)	<0.001‡
LDH (UI/l)	254 (216–318)	246 (206–309)	191 (175–209)	<0.001‡
Ferritin (ng/l)	132 (75–232)	101 (59–191)	50 (23–98)	<0.001‡
CRP (mg/l)	23.5 (11–56)	7.9 (2.8–21)	2.1 (1.35–5)	<0.001‡
Troponin (ng/l)	4.3 (3–9)	2.4 (2.1–5.4)	–	–
Procalcitonin (ng/ml)	0.05 (0.03–0.1)	0.04 (0.02–0.05)	–	–
D-dimer (mg/l)	0.51 (0.32–0.84)	0.64 (0.35–1.19)	0.33 (0.25–0.5)	<0.001‡

†$p < 0.05$.
‡$p < 0.001$.
AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein; IQR: Interquartile range; LDH: Lactate dehydrogenase.

On admission, 110 patients (94.74%) had bilateral opacities and six (5.26%) had unilateral opacities on initial CT. On follow-up CT, 22 patients (19.47%) had bilateral opacities and 11 (9.73%) had unilateral opacities. The most common radiological finding on chest CT at hospital admission was ground-glass opacity (n = 107; 93.9%), followed by consolidation (n = 23; 20.18%), atelectasis (n = 11; 9.65%) and air bronchogram (n = 8; 7.02%). On follow-up CT, 83 patients (71.6%) demonstrated complete resolution of pulmonary parenchymal lesions and 33 (28.4%) demonstrated residual disease. The most common radiological findings in patients with residual disease were fibrosis (n = 16; 14.54%), atelectasis (n = 15; 13.4%), ground-glass opacity (n = 7; 6.25%), pulmonary nodules and mediastinal lymphadenopathy (n = 5; 4.42%) (Table 2). One-third of the 83 patients (n = 37; 33.3%) with complete resolution had at least one symptom, including 15 patients (40.5%) with mild dyspnea and seven (18.9%) with mild chest pain. Just over one-half (n = 18; 54.5%) of the 33 patients with residual disease had at least one symptom, including eight patients (34.8%) with mild dyspnea and one (12.5%) with mild chest pain.

In follow-up examination 6 months after acute infection, serum IgG was positive in 114 patients (98.3%) and RT-PCR was positive in two patients (1.7%). The patients with positive SARS-CoV-2 PCR tests before the pulmonary function test at 6 months did not have any symptoms. No patients were vaccinated against or reinfected with SARS-CoV-2 during the 6-month follow-up period. The anti-SARS-CoV-2 IgG median was 8.31 U/ml (IQR 3.65–16.9). On average, spirometry revealed no impairments (FVC_{ex}: 101% of predicted [IQR: 91–110]; FEV_1: 101% of predicted [IQR: 91–115]; FEV_1/FVC: 103% [IQR: 98–108]). The SGRQ test showed that median score for activity was 12.2 (IQR: 12.1–12.6), for symptom score was 16.1 (IQR: 15.1–21.7) and for impact score was 14.5 (IQR: 12.7–15.9). Total score was 14.1 (IQR: 13.7–15.9), in the normal range.

Factors associated with residual pulmonary disease on chest CT at 6 months were age (p = 0.042), needing supplemental oxygen (p = 0.023), neutrophil count (p = 0.034), NLR (p = 0.008), PLR (p = 0.08), CRP (p = 0.016) and procalcitonin (p = 0.04) among admission parameters; leukocyte count (p = 0.044) and ALT

Table 2. Chest computed tomography findings and SARS-CoV-2 test results of patients with COVID-19 pneumonia on admission and at 6-month follow-up.

Chest CT findings	Admission	6 months
Unilateral, n (%)	6 (5.26)	11 (9.73)
Bilateral, n (%)	110 (94.74)	22 (19.47)
Pleural fluid, n (%)	3 (2.63)	3 (2.65)
Ground-glass opacity, n (%)	107 (93.9)	7 (6.25)
Consolidation, n (%)	23 (20.18)	0 (0)
Air bronchogram, n (%)	8 (7.02)	0 (0)
Interlobular septal thickening, n (%)	10 (8.77)	2 (1.77)
Pulmonary nodules, n (%)	6 (5.31)	5 (4.42)
Mediastinal lymphadenopathy, n (%)	2 (1.75)	5 (4.42)
Atelectasis, n (%)	11 (9.65)	15 (13.4)
Fibrosis, n (%)	4 (3.51)	16 (14.54)
CT involvement according to severity scores		
Mild, n (%)	21 (18.1)	–
Moderate, n (%)	95 (81.9)	–
Severe, n (%)	0 (0)	–
Virological diagnostic results		
SARS-CoV-2 RNA positive, n (%)	111 (97.4)	2 (1.7)
SARS-CoV-2 IgG positive, n (%)	–	114 (98.3)
SARS-CoV-2 IgG: (quant.), median ± IQR	–	8.31 (3.65–16.9)

Five pulmonary lobes were visually scored on a scale of 0–5: 0, no involvement; 1, <5% involvement; 2, 5–25% involvement; 3, 26–50% involvement; 4, 51–75% involvement; 5, 76–100% involvement.
CT: Computed tomography; IQR: Interquartile range.

Table 3. Factors associated with residual pulmonary disease on chest computed tomography.

Parameters	Residual pulmonary disease: presence	Residual pulmonary disease: absence	p-value
At admission			
Age (years), median (IQR)	53 (48–66)	51 (41–59)	0.042†
Needing supplemental oxygen, n (%)	41 (63)	24 (36.9)	0.023†
Neutrophil count/mm^3, median (IQR)	3940 (2790–5410)	3120 (2520–4080)	0.034†
Neutrophil-to-lymphocyte ratio, median (IQR)	2.97 (1.94–4.71)	2.26 (1.5–3.25)	0.008‡
Platelet-to-lymphocyte ratio, median (IQR)	0.17 (0.13–0.24)	0.13 (0.11–0.18)	0.008‡
C-reactive protein (mg/dl), median (IQR)	38.7 (18–64)	19 (9.8–48.8)	0.016†
Procalcitonin (ng/ml), median (IQR)	0.08 (0.03–0.11)	0.04 (0.02–0.1)	0.040†
At discharge			
Leukocyte count/mm^3, median (IQR)	7065 (5685–9040)	5980 (4750–7870)	0.044†
ALT (UI/l), median (IQR)	47 (30–84)	27 (18–76)	0.018†
At 3 months			
Leukocyte count/mm^3, median (IQR)	7300 (5789–8210)	6320 (5289–7423)	0.039†
Creatinine (mg/dl), median (IQR)	0.84 (0.69–1.02)	0.71 (0.63–0.89)	0.032†
At 6 months			
FEV_1 (% of predicted), median (IQR)	95 (88–104)	104 (93–112)	0.041†
ALT (UI/l), median (IQR)	17 (14–20)	19 (16–28)	0.028†

†$p < 0.05$.
‡$p < 0.01$.
ALT: Alanine aminotransferase; FEV_1: forced expiratory volume in 1 s; IQR: Interquartile range.

(p = 0.018) among discharge parameters; and cough (p = 0.006), FEV_1 (p = 0.041) and ALT (p = 0.028) among the 6-month follow-up parameters (Table 3).

Table 4. Univariate and multivariate analyses for residual pulmonary disease on chest computed tomography at 6 months.

Logistic regression	Univariate			Multivariate		
	OR	CI	p-value	OR	CI	p-value
Age (years)	1.041	1.006–1.077	0.021†	1.035	0.999–1.072	0.058
Neutrophil-to-lymphocyte ratio	1.379	1.122–1.944	0.002‡	1.346	1.093–1.658	0.005
Platelet-to-lymphocyte ratio	3287.9	8.590–8540.4	0.008‡	–	–	–
C-reactive protein (mg/dl)	1.008	1.001–1.015	0.050	–	–	–
Needing supplemental oxygen therapy	2.732	1.135–6.577	0.025†	–	–	–

†$p < 0.05$.
‡$p < 0.01$.
OR: Odds ratio.

Univariate analysis demonstrated that potential predictors for residual disease were: patients who had a need for supplemental oxygen therapy (OR: 2.732; 95% CI: 1.135–6.577; p = 0.037), age >65 years (OR: 1.041; 95% CI: 1.006–1.077; p = 0.021), CRP (OR: 1.008; 95% CI: 1.001–1.015; p = 0.050), NLR (OR: 1.379; 95% CI: 1.122–1.944; p = 0.002) and PLR (OR: 3287.9; 95% CI: 8.590–8540.4; p = 0.008). However, multivariate analyses revealed that only NLR was an independent predictor for residual disease at the time of follow-up chest CT (Table 4). However, although residual disease was more frequent in patients with higher CT involvement (p = 0.041), CT grade was not associated with residual disease in univariate analysis (p = 0.221). We did not detect any patients with long COVID.

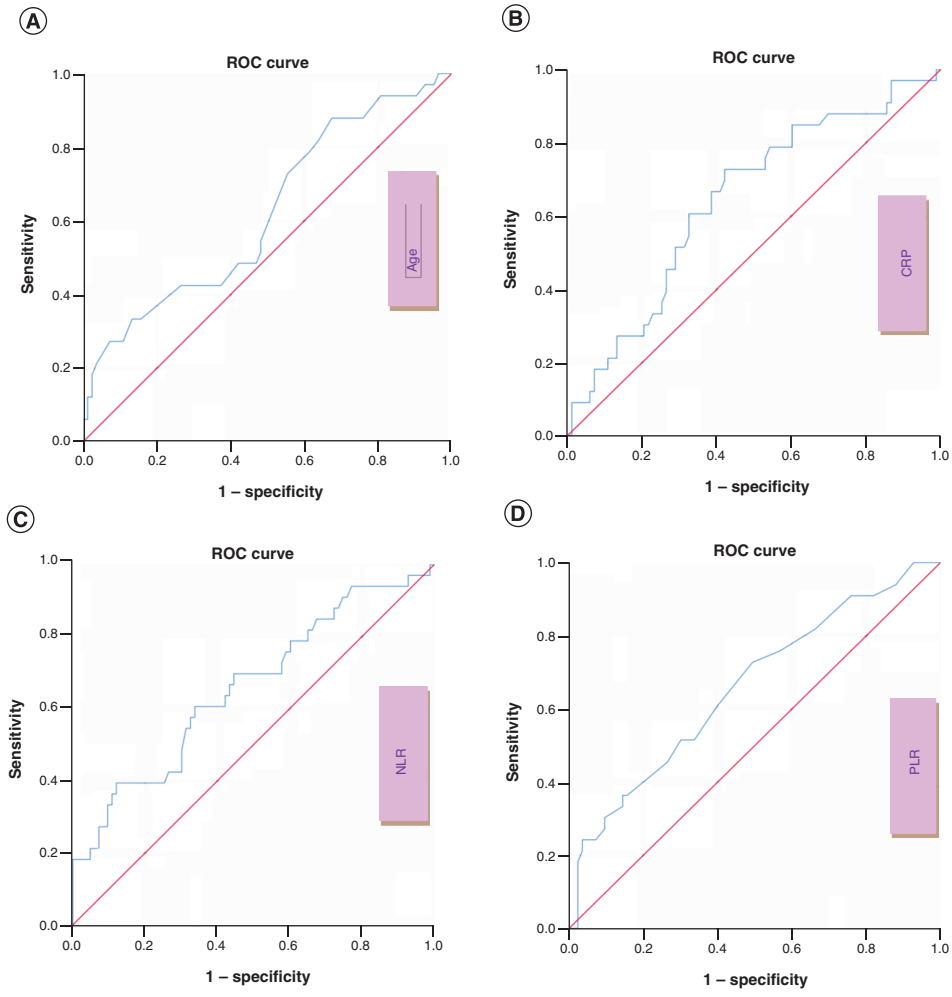
ROC curve analyses for the best cutoff age, CRP, NLR and PLR at admission using residual disease on chest CTs are shown in Figure 2. Given that vital signs and symptoms at admission were not significant in the univariate analysis, we did not perform a ROC curve for other parameters. We performed a ROC curve for the parameters that were significant in the univariate analysis.

Discussion

At 6 months, nearly all patients (n = 112; 96.6%) had positive serum antibody levels. Although two patients tested positive by RT-PCR for SARS-CoV-2 at 6 months, both of them were asymptomatic. For most patients (n = 98; 89.2%), spirometry results were within normal limits at 6 months. Similar to the studies of Zheng *et al.*, Hui *et al.* and Xie *et al.* [13–15], most patients in our study had normal lung function at 6 months after discharge. Despite normal pulmonary function, some patients had persistent pulmonary symptoms such as dyspnea and cough at 6 months. The SGRQ total and domain scores indicated normal quality of life at 6 months. In contrast, Ong *et al.* reported that SGRQ scores confirmed a decreased normal quality of life related to pulmonary symptoms [16].

Recovery time from acute illness with COVID-19 is between 2 and 6 weeks in most cases [17]. Chronic persistent or prolonged symptoms including myalgia, fatigue, cough and dyspnea are frequent among patients recovering from COVID-19. In addition, post-intensive-care syndrome symptoms such as psychological and cognitive disorders have been increasingly reported [18–20]. Prolonged symptoms can follow mild or severe illness and include: fatigue (13–87%), dyspnea (10–71%), chest pain or tightness (12–44%) and cough (17–34%) [19–20]. Several observational series describe persistent symptoms in patients following acute COVID-19, with one-third or more experiencing more than one symptom [21–23]. In our study, 28.4% of patients (n = 33) had more than one symptom. We found that 48 patients (41.4%) had one or two COVID-19-related symptoms at 6 months after symptom onset, with six (5.2%) patients having three or more symptoms. The prevalence of persistent symptoms was high (n = 54; 46.6%). In the study of Huang *et al.*, at 6 months 74% of patients had one or more prolonged symptoms. They reported that the most frequent prolonged symptoms were muscle weakness and/or fatigue (n = 1038; 63%), sleep difficulties (n = 437; 26%) and anxiety or depression (n = 367; 23%) [2]. A comparison of the present study's findings of chronic persistent symptoms with other study results is summarized in Table 5 [21–23].

In the present study, patients with pulmonary symptoms did not have low rates of oxygen saturation. In addition, these patients did not have any significant ventilatory problems in the pulmonary function tests. In our cohort, although radiological pulmonary opacities at admission and residual imaging at 6 months were more frequent on chest CT, spirometry revealed that there was no significant limitation on pulmonary function at the 6-month follow-up. Some autopsy studies have reported that patients with COVID-19 had no relevant organized interstitial



Parameters	p-value	AUC	95% CI	Cutoff	Sensitivity (%)	Specificity (%)
Age (years)	0.042	0.621	0.507–0.736	48.5	72.7	44.6
CRP (mg/dl)	0.016	0.643	0.533–0.753	22.95	72.7	57.8
NLR	0.008	0.658	0.545–0.772	2.755	60.6	66.3
PLR	0.008	0.658	0.547–0.769	0.135	72.7	50.6

Figure 2. Receiver operating characteristic curve and performance value for the best cutoffs. (A) For age at admission using residual disease on chest CT. **(B)** For C-reactive protein at admission using residual disease on chest CT. **(C)** For neutrophil-to-lymphocyte ratio at admission using residual disease on chest CT. **(D)** For platelet-to-lymphocyte ratio at admission using residual disease on chest CT.
CRP: C-reactive protein; CT: Computed tomography; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio.

fibrosis or other fibrotic changes [24,25]. Long-term pulmonary abnormalities are not frequent after recovery from mild/moderate COVID-19 alone [26].

Huang *et al.* showed that COVID-19 patients had decreased short-term pulmonary functions at 1 month after discharge [27]. However, in their cohort, there were patients with severe or critical COVID-19 who were supported by mechanical ventilation, which may result in additional sequelae.

Table 5. Comparison of the present study and other study results of chronic persistent symptoms.

Results	Tuncer *et al.* (present study)	Munblit *et al.*	Sonnweber *et al.*	Pérez-González *et al.*
Ref.	–	[21]	[22]	[23]
Sample size (n) Female, n (%)	116 58 (50)	2649 1351 (51.1)	145 63 (43.4)	248 100 (40.3)
Age (years)	52 (42–61)	56 (46–66)	57.3 ± 14.3	54 ± 12
Study design	Single-center Prospective	Multicenter Prospective	Multicenter Prospective	Single-center Prospective
Severity of illness	Mild–moderate	Mild–moderate	40 (27.6%) patients severe, 73 (50.3%) patients mild–moderate	Severe
Need for mechanical ventilation	No patients	68 (2.6%)	32 (22.1%)	29 (10.2%)
Follow-up mean duration	6 months	218 days	6 months	6 months
Chronic persistent symptoms	54 (46.6%) Weakness (n = 28; 24%), dyspnea (n = 23; 19.8%), anxiety (n = 8; 6.9%), chest pain (n = 8; 7%), alopecia (n = 5; 4.3%), ageusia (n = 4; 3.5%), back pain (n = 4; 3.5%), cough (n = 3; 2.6%), myalgia (n = 3; 2.6%), arthralgia (n = 2; 1.7%), amnesia (n = 2; 1.7%), anosmia (n = 1; 0.9%), sleep difficulties (n = 1; 0.9%)	247 (47.1%) Fatigue (21.2%), shortness of breath (14.5%) and forgetfulness (9.1%) the most common symptoms; chronic fatigue (25%) and respiratory (17.2%) the most common symptom categories	71 (49%) Impaired physical performance (34.7%), sleep disorders (27.1%) and exertional dyspnea (22.8%) as leading manifestations	119 (48.0%) Extrathoracic symptoms (39.1%), chest symptoms (27%), dyspnea (20.6%) and fatigue (16.1%)
Risk factors for persistent disease		Female sex	–	Chronic obstructive pulmonary diseases, female sex and tobacco consumption

In this study we found that the median titer of serum IgG at 6 months was 8.31 (IQR: 3.65–16.9). Similarly, Wajnberg *et al.* reported a significant decline in SARS-CoV-2 IgG titers in patients who recovered from COVID-19 at 5 months [28]. The decline in the antibody titers observed in our study and other studies has raised concerns about COVID-19 reinfection. The increased reinfection risk should therefore be considered in patients with symptoms compatible with COVID-19 [29,30].

In this long-term follow-up study, patients with residual findings on chest CT had fibrosis, atelectasis and ground-glass opacities, which together constituted the majority of abnormalities. We identified patients at risk for developing residual pulmonary disease and could determine its predictors. In univariate analysis, residual pulmonary parenchymal disease at 6 months was associated with the need for supplemental oxygen therapy, age (>65 years old), and increased NLR and PLR. Multivariate analyses revealed that the NLR was an independent predictor for residual disease.

We found that the extent of the pulmonary involvement at hospital admission may give a suggestion but cannot certainly predict the pulmonary findings in a long-term follow-up. However, Wang *et al.* and Francone *et al.* showed that extensive pulmonary involvement may predict the potential to progress to fibrosis and that these patients can benefit from follow-up CTs [6,31]. In the study of Caruso *et al.*, patients with residual disease at the 6-month follow-up CT received supplemental oxygen therapy, and their length of hospital stay was higher than those without. They reported a high prevalence of residual disease at 6 months (n = 85; 72.0%). However, in their cohort, the mean age was higher and they included a high number of mechanically ventilated patients (n = 34; 28.8%) [32]. Other studies have also shown that critically ill older adults are more likely to have residual findings [33–34]. Comparison of the present study and other study results related to residual pulmonary disease on chest CT are summarized in Table 6 [5,32,33,35,36].

While several laboratory tests have been used for predicting poor outcomes, only a few laboratory parameters have been studied for predicting long-term pulmonary sequelae in COVID-19 [37–40]. Patients with residual disease at 6 months had significantly higher NLR, PLR and CRP on admission.

In our study, patients with abnormal CT findings were mostly older adults, inconsistent with the study of Zhao *et al.* [34]. In the study of Han *et al.*, the multivariable analysis identified age, heart rate at admission, duration of

Table 6. Comparison of the present study and other study results of residual pulmonary disease on chest computed tomography.

Results	Tuncer *et al.* (present study)	Rogliani *et al.*	Tabatabaei *et al.*	Han *et al.*	Caruso *et al.*	McGroder *et al.*
Ref.	–	[5]	[33]	[35]	[32]	[36]
Sample size (n) Female, n (%)	116 58 (50)	27 7 (26)	52 20 (38)	114 34 (30)	118 62 (52.5)	76 31 (39)
Age (years)	52 (42–61)	60.79 (57.11–64.46)	50.17 ± 13.1	54 ± 12	65 ± 12	54 ± 13.7
Study design	Single-center prospective	Single-center prospective	Single-center retrospective	Single-center prospective	Single-center prospective	Single-center prospective
Severity of illness	Mild–moderate	Mild–moderate	10 (19.23%) patients severe, 42 (80.77%) patients mild–moderate	Severe	Moderate–severe	32 (42%) patients severe, 44 (57.9%) patients mild–moderate
Need for mechanical ventilation	No patients	No patients	11 (57.2%)	No patients	87 (74%)	32 (42%)
Follow-up mean duration	6 months	1 month	3 months	6 months	6 months	4 months
Residual pulmonary sequelae	33 (28.4%)	In none of the follow-up HRCTs were significant extension of fibrotic abnormalities (including reticular opacities, traction bronchiectasis and honeycombing) detected	22 (42.3%)	71 (62%)	85 (72%)	32 (42.1%) Underwent mechanical ventilation: 23 (72%) Did not undergo mechanical ventilation: 9 (20%)
Radiological pattern in the patients with residual disease	Fibrosis (16/33; 48.5%), Atelectasis (15/33; 45.5%) Ground-glass opacity (7/33; 21.2%) Pulmonary nodules and mediastinal lymphadenopathy (5/33; 15.2%)	–	Ground-glass opacity (12/22; 54.5%) Mixed ground-glass opacity and subpleural parenchymal bands (7/22; 31.8%) Pure subpleural parenchymal bands (3/22; 13.7%)	Fibrotic-like changes (40/114; 35%) Ground-glass opacity or interstitial thickening (31/114; 27%)	Fibrosis-like opacity (85/118; 72%) Ground-glass opacity (49/118; 42%)	Ground-glass opacity (43%) Reticulation (39%) Traction bronchiectasis (38%)

HRCT: High-resolution computed tomography.

hospital stay, acute respiratory distress syndrome, need for noninvasive mechanical ventilation and total CT score at initial CT as independent predictors for fibrotic-like changes in the lung at 6 months [35].

In our study, 28.4% of the patients with COVID-19 had more than one symptom 6 months after symptom onset. In another Turkish study conducted by Vural *et al.*, the prevalence of long-term pulmonary sequelae with a median follow-up of 112 days after symptom onset was 35% in 84 surviving patients with moderate and severe COVID-19 pneumonia [41]. They demonstrated that independent risk factors for pulmonary sequelae changes were prolonged length of hospital stay (≥22 days) and an increased baseline CT score (≥15 points). In our study, on follow-up CT, 33 patients (28.4%) demonstrated residual disease; need for supplemental oxygen therapy, older age, increased NLR and increased PLR were associated with residual pulmonary parenchymal disease. However, only the NLR was found to an independent predictor for residual disease in multivariate analysis. Lerum *et al.* reported that among 108 patients from the NOR-SOLIDARITY study, which is a multicenter randomized clinical trial, nearly 40% of patients had pulmonary sequelae [42]. In that study, high levels of SARS-CoV-2 viral load and MMP-9, poor antibody response, need for intensive care unit admission and increased respiratory support were associated with poorer pulmonary outcomes at a 3-month follow-up period. In another follow-up study evaluating persistent symptoms, pulmonary functions and radiological features at 8 weeks and 4 months, smoking (past or current), pre-existing diabetes mellitus and length of hospital stay were associated with persistent symptoms among 177 ward patients. The authors revealed that fibrosis-like changes at an average of 18 weeks post-discharge were more common among patients in the intensive care unit than in those discharged from the ward (32 vs 9%) [43]. In another follow-up study, the researchers reported that ground-glass opacities on chest CT scans were seen frequently

(89%) at 3 months after hospital discharge in patients requiring intensive care. Fibrosis-like changes were seen in 67% (n = 31) of the patients. Nearly 25% of the survivors had new emphysematous destruction, new cavitation, or deterioration of pre-existing emphysema [44].

It is noteworthy to mention that although the quality of life at the 6-month follow-up was not negatively affected in our cohort, which was consistent with our cohort of patients with mild-to-moderate COVID-19, physicians should be aware of the importance of follow-up visits, especially in patients with severe COVID-19 pneumonia. Thus, to reduce long-term poor pulmonary outcomes, possible treatment options and different therapeutic strategies should be considered [45]. In addition, an increased number of studies demonstrating the importance of COVID-19 vaccination in reducing long COVID symptoms have been published [46,47]. Therefore, it must be highlighted that the most effective strategy for reducing the incidence and severity of long-term effects of COVID-19 such as persistent symptoms and pulmonary sequelae is to prevent severe COVID-19 pneumonia.

This study had some strengths. First, the strength of this follow-up study lies in its prospective design. Second, we excluded patients with COVID-19 requiring mechanical ventilation during their hospital stay in order to understand the impact of COVID-19 on residual sequelae. Third, we could evaluate different variables such as demographic and clinical characteristics, laboratory parameters, spirometry, radiological examinations and SGRQ scores.

However, the study also had several limitations. First, this study had a relatively small sample size. Second, a high percentage of patients refused to undergo follow-up; this may cause selection bias. Third, we did not include patients with mild symptoms who did not require hospitalization. Fourth, we could not evaluate patients who died within 6 months after discharge. Finally, the baseline data of pulmonary function were unknown. Because of this, we did not compare the prevalence of pulmonary dysfunction in patients prior to the development of COVID-19. Therefore, not all findings associated with pulmonary sequelae on chest CT can be directly attributed to COVID-19. However, the prevalence of chronic pulmonary disease in our cohort was low.

Conclusion

Hospitalized patients with mild/moderate COVID-19 still had persistent symptoms and were prone to develop long-term pulmonary sequelae on chest CT. However, it did not have a significant effect on long-term pulmonary function. Clinicians should consider older age, the need for supplemental oxygen therapy and increased levels of CRP, NLR and PLR as potential predictors for residual disease. However, the decision to perform follow-up chest CT should be taken on a patient-by-patient basis.

Summary points

- Hospitalized patients with mild/moderate COVID-19 still had persistent symptoms and were prone to develop long-term pulmonary sequelae on chest computed tomography.
- Long-term pulmonary sequelae on chest computed tomography did not have a significant effect on long-term pulmonary functions. Spirometry revealed no impairments in pulmonary functions, and St George's Respiratory Questionnaire test scores showed no impairments in quality of life.
- The most common radiological findings in patients with residual disease were fibrosis, followed by atelectasis, ground-glass opacity, pulmonary nodules and mediastinal lymphadenopathy.
- Eighteen of the 33 patients with residual disease had at least one symptom, including eight patients with mild dyspnea and one patient with mild chest pain.
- Univariate analysis revealed that predictors for pulmonary parenchymal disease were: needing supplemental oxygen therapy, age >65 years, and increased C-reactive protein, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio.
- Multivariate analyses revealed that only the neutrophil-to-lymphocyte ratio was an independent predictor for residual disease.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fmb-2022-0121

Author contributions

G Tuncer, S Simsek-Yavuz, F Pehlivanoglu, R Turkay, G Sengoz and E Canel-Karakus contributed to the study conception and design, acquisition/analysis/interpretation of data, drafting and critical review of the article. O Bayramlar, S Surme, G Tuncer and C Belge contributed to study conception and design, statistical analysis/interpretation of data, critical revision and supervision. All authors have contributed to and approved the final manuscript.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Shaw B, Daskareh M, Gholamrezanezhad A. The lingering manifestations of COVID-19 during and after convalescence: update on long-term pulmonary consequences of coronavirus disease 2019 (COVID-19). *Radiol. Med.* 126(1), 40–46 (2021).
2. Huang C, Huang L, Wang Y *et al.* 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 397(10270), 220–232 (2021).

• **At 6 months after acute infection, COVID-19 survivors were mainly troubled with fatigue or muscle weakness, sleep difficulties and anxiety or depression. Patients who were more severely ill during their hospital stay had abnormal chest imaging manifestations.**

3. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus disease 2019 (COVID-19) imaging reporting and data system (COVID-RADS) and common lexicon: a proposal based on the imaging data of 37 studies. *Eur. Radiol.* 30(9), 4930–4942 (2020).
4. Daher A, Balfanz P, Cornelissen C *et al.* Follow up of patients with severe coronavirus disease 2019 (COVID-19): pulmonary and extrapulmonary disease sequelae. *Respir. Med.* 174, 106197 (2020).
5. Rogliani P, Calzetta L, Coppola A *et al.* Are there pulmonary sequelae in patients recovering from COVID-19? *Respir. Res.* 21(1), 286 (2020).

• **Provides preliminary evidence that hospitalized patients with mild-to-moderate forms of COVID-19 are not at risk of developing pulmonary fibrosis.**

6. Francone M, Iafrate F, Masci GM *et al.* Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. *Eur. Radiol.* 30(12), 6808–6817 (2020).
7. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 323(13), 1239–1242 (2020).
8. Republic of Turkey Ministry of Health. Study of scientific board, COVID-19 (SARS-CoV-2 infection) Guide (2020). https://hsgm.saglik.gov.tr/depo/birimler/goc_sagligi/covid19/rehber/COVID-19_Rehberi20200414_eng_v4_002_14.05.2020.pdf

• **Guideline based on WHO recommendations which provides information about SARS-CoV-2 infection, its transmission routes, case definitions, diagnostic methods, the strategies and applications in case of COVID-19 case or contact.**

9. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am. Rev. Respir. Dis.* 145(6), 1321–1327 (1992).
10. Polatlı M, Yorgancıoğlu A, Aydemir Ö *et al.* Validity and reliability of Turkish version of St. George's respiratory questionnaire. *Tuberk. Toraks* 61(2), 81–87 (2013).
11. Chang YC, Yu CJ, Chang SC *et al.* Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. *Radiology* 236(3), 1067–1075 (2005).
12. Irsara C, Egger AE, Prokop W *et al.* Clinical validation of the Siemens quantitative SARS-CoV-2 spike IgG assay (sCOVG) reveals improved sensitivity and a good correlation with virus neutralization titers. *Clin Chem Lab Med.* 59(8), 1453–1462 (2021).

13. Zheng ZG, Chen RC, Wu H *et al.* Changes in pulmonary function in severe acute respiratory syndrome patients during convalescent period. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 17(6), 329–331 (2005).

14. Hui DS, Joynt GM, Wong KT *et al.* Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax* 60(5), 401–409 (2005).

15. Xie L, Liu Y, Fan B *et al.* Dynamic changes of serum SARS-coronavirus IgG, pulmonary function and radiography in patients recovering from SARS after hospital discharge. *Respir. Res.* 6(1), 5 (2005).

16. Ong KC, Ng AW, Lee LS *et al.* 1-year pulmonary function and health status in survivors of severe acute respiratory syndrome. *Chest* 128(3), 1393–1400 (2005).

17. World Health Organization. Post COVID-19 condition (Long COVID) (20 January 2022). www.who.int/srilanka/news/detail/16-10-2021-post-covid-19-condition

18. Xiong Q, Xu M, Li J *et al.* Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin. Microbiol. Infect.* 27(1), 89–95 (2021).

- **Clinical sequelae during early COVID-19 convalescence were common; some of these sequelae might be related to gender, age and clinical characteristics during hospitalization.**

19. 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.* 6(4), 00542-2020 (2020).

20. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 324(6), 603–605 (2020).

21. Munblit D, Bobkova P, Spiridonova E *et al.* Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID-19. *Clin. Exp. Allergy* 51(9), 1107–1120 (2021).

- **Almost one-half of patients reported persistent symptoms 6–8 months after discharge. Fatigue and respiratory symptoms were most common, and female sex was associated with persistent symptoms.**

22. Sonnweber T, Tymoszuk P, Sahanic S *et al.* Investigating phenotypes of pulmonary COVID-19 recovery: a longitudinal observational prospective multicenter trial. *Elife* 11, e72500 (2022).

23. Pérez-González A, Araújo-Ameijeiras A, Fernández-Villar A, Crespo M, Poveda E, Cohort COVID-19 of the Galicia Sur Health Research Institute. Long COVID in hospitalized and non-hospitalized patients in a large cohort in Northwest Spain, a prospective cohort study. *Sci. Rep.* 12(1), 3369 (2022).

- **The most prevalent symptoms were: extra-thoracic symptoms (39.1%), chest symptoms (27%), dyspnea (20.6%) and fatigue (16.1%). These symptoms were more common in hospitalized patients (52.3 vs 38.2%) and in women (59.0 vs 40.5%).**

24. Tian S, Xiong Y, Liu H *et al.* Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod. Pathol.* 33(6), 1007–1014 (2020).

25. Ware LB. Autopsy in ARDS: insights into natural history. *Lancet Respir. Med.* 1(5), 352–354 (2013).

26. Blanco JR, Cobos-Ceballos MJ, Navarro F *et al.* Pulmonary long-term consequences of COVID-19 infections after hospital discharge. *Clin. Microbiol. Infect.* 27(6), 892–896 (2021).

27. Huang Y, Tan C, Wu J *et al.* Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir. Res.* 21(1), 163 (2020).

28. Wajnberg A, Amanat F, Firpo A *et al.* Robust neutralizing antibodies to SARS-CoV-2 infection persist for months. *Science* 370(6521), 1227–1230 (2020).

29. Doke P, Gothankar JS, Doke PP *et al.* Time dependent decline of neutralizing antibody titers in COVID-19 patients from Pune, India and evidence of reinfection. *Microbes Infect.* 24(4), 104979 (2022).

30. Fakhroo A, Al Khatib HA, Al Thani AA, Yassine HM. Reinfections in COVID-19 patients: impact of virus genetic variability and host immunity. *Vaccines (Basel)* 9(10), 1168 (2021).

31. Wang Y, Dong C, Hu Y *et al.* Temporal changes of CT findings in 90 patients with COVID-19 pneumonia: a longitudinal study. *Radiology* 296(2), E55–e64 (2020).

32. Caruso D, Guido G, Zerunian M *et al.* Post-acute sequelae of COVID-19 pneumonia: six-month chest CT follow-up. *Radiology* 301(2), E396–e405 (2021).

33. Tabatabaei SMH, Rajebi H, Moghaddas F, Ghasemiadl M, Talari H. Chest CT in COVID-19 pneumonia: what are the findings in mid-term follow-up? *Emerg. Radiol.* 27(6), 711–719 (2020).

- **Extensive lung involvement on initial CT scan, intensive care unit admission, long duration of hospitalization, presence of underlying medical conditions, high initial white blood cell count and development of leukocytosis during the course of disease are associated with more prevalence of chronic lung sequelae of COVID-19.**

34. 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* 25, 100463 (2020).

35. Han X, Fan Y, Alwalid O *et al.* Six-month follow-up chest CT findings after severe COVID-19 pneumonia. *Radiology* 299(1), E177–e186 (2021).

36. Mcgroder CF, Zhang D, Choudhury MA *et al.* Pulmonary fibrosis 4 months after COVID-19 is associated with severity of illness and blood leucocyte telomere length. *Thorax* 76(12), 1242–1245 (2021).
37. Wynants L, Van Calster B, Collins GS *et al.* Prediction models for diagnosis and prognosis of COVID-19: systematic review and critical appraisal. *BMJ* 369, m1328 (2020).
38. Guan WJ, Liang WH, Zhao Y *et al.* Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur. Respir. J.* 55(5), 2000547 (2020).
39. Franquet T. Imaging of pulmonary viral pneumonia. *Radiology* 260(1), 18–39 (2011).
40. Shang Y, Liu T, Wei Y *et al.* Scoring systems for predicting mortality for severe patients with COVID-19. *EClinicalMedicine* 24, 100426 (2020).
41. Vural A, Kahraman AN. Pulmonary fibrotic-like changes on follow-up chest CT exam in patients recovering from COVID-19 pneumonia. *Tuberk. Toraks* 69(4), 492–498 (2021).
42. Lerum TV, Maltzahn NN, Aukrust P *et al.* Persistent pulmonary pathology after COVID-19 is associated with high viral load, weak antibody response, and high levels of matrix metalloproteinase-9. *Sci. Rep.* 11(1), 23205 (2021).
43. Robey RC, Kemp K, Hayton P *et al.* Pulmonary sequelae at 4 months after COVID-19 infection: a single-centre experience of a COVID follow-up service. *Adv. Ther.* 38(8), 4505–4519 (2021).
44. van Gassel RJJ, Bels JLM, Raafs A *et al.* High prevalence of pulmonary sequelae at 3 months after hospital discharge in mechanically ventilated survivors of COVID-19. *Am. J. Respir. Crit. Care Med.* 203(3), 371–374 (2021).
45. Ruggiero V, Aquino RP, Del Gaudio P, Campiglia P, Russo P. Post-COVID syndrome: the research progress in the treatment of pulmonary sequelae after COVID-19 infection. *Pharmaceutics* 14(6), 1135 (2022).
46. Azzolini E, Levi R, Sarti R *et al.* Association between BNT162b2 vaccination and long COVID after infections not requiring hospitalization in health care workers. *JAMA* 328(7), 676–678 (2022).
47. Antonelli M, Penfold RS, Merino J *et al.* Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect. Dis.* 22(1), 43–55 (2022).