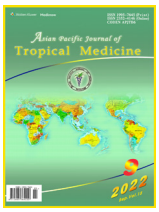
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Original Article

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/1995-7645.354422

Impact Factor: 3.041

The predictors of long-COVID in the cohort of Turkish Thoracic Society-TURCOVID multicenter registry: One year follow-up results

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How to cite this article: Argun Baris S, Baydar Toprak O, Duru Cetinkaya P, Fakili F, Kokturk N, Kul S, et al. The predictors of long-COVID in the cohort of Turkish Thoracic Society-TURCOVID multicenter registry: One year follow-up resultsAsian Pac J Trop Med 2022; 15(9): 400-409.

Article history: Received 20 July 2022 Revision 1 September 2022
Accepted 25 September 2022 Available online 30 September 2022

[Downloaded free from http://www.apjtm.org on Thursday, March 9, 2023, IP: 88.255.99.29]

ABSTRACT

Objective: To evaluate long-term effects of COVID-19, and to determine the risk factors in long-COVID in a cohort of the Turkish Thoracic Society (TTS)-TURCOVID multicenter registry.

Methods: Thirteen centers participated with 831 patients; 504 patients were enrolled after exclusions. The study was designed in three-steps: (1) Phone questionnaire; (2) retrospective evaluation of the medical records; (3) face-to-face visit.

Results: In the first step, 93.5% of the patients were hospitalized; 61.7% had a history of pneumonia at the time of diagnosis. A total of 27.1% reported clinical symptoms at the end of the first year. Dyspnea (17.00%), fatigue (6.30%), and weakness (5.00%) were the most prevalent long-term symptoms. The incidence of long-term symptoms was increased by 2.91 fold (95% *CI* 1.04-8.13, *P*=0.041) in the presence of chronic obstructive pulmonary disease and by 1.84 fold (95% *CI* 1.10-3.10, *P*=0.021) in the presence of pneumonia at initial diagnosis, 3.92 fold (95% *CI* 2.29-6.72, *P*=0.001) of dyspnea and 1.69 fold (95% *CI* 1.02-2.80, *P*=0.040) fatigue persists in the early-post-treatment period and 2.88 fold (95% *CI* 1.52-5.46, *P*=0.001) in the presence of emergency service admission in the post COVID period. In step 2, retrospective analysis of 231 patients revealed that 1.4% of the chest X-rays had not significantly improved at the end of the first year, while computed tomography (CT) scan detected fibrosis in 3.4%. In step 3, 138 (27.4%) patients admitted to face-to-face visit at the end of first year; at least one symptom persisted in 49.27% patients. The most common symptoms were dyspnea (27.60%), psychiatric symptoms (18.10%), and fatigue (17.40%). Thorax CT revealed fibrosis in 2.4% patients.

Conclusions: COVID-19 symptoms can last for extended lengths of time, and severity of the disease as well as the presence of comorbidities might contribute to increased risk. Long-term clinical issues should be regularly evaluated after COVID-19.

KEYWORDS: Long COVID-19; Dyspnea; Fatigue; Comorbidity

Significance

SARS-CoV-2 affects several organs and systems and it is still uncertain how severe, what kind of symptoms are persistent in the post-acute period, and what other factors are involved. This study demonstrates that COVID-19 symptoms can remain for a very long period, and the severity of the condition as well as the existence of comorbid conditions may increase risk. After COVID-19, ongoing clinical concerns should be frequently assessed.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first described in December 2019, caused the most famous disease in the world called COVID-19 with a wide clinical spectrum ranging from asymptomatic illness to respiratory failure and death[1]. As of 23 August 2022, nearly 602 million COVID-19 cases have been reported worldwide; of these cases, 576 million recovered and over 6 million people deceased[2].

Although most of the patients recovered, it was reported that some of these patients continued to have symptoms in both early and late post-infection periods[3]. Definitions such as post-acute sequelae of COVID-19, post-acute COVID syndrome (PACS), and long COVID have been used to clinically describe these patients who cannot return to their baseline health status after SARS-CoV-2 infection and whose symptoms persist[4].

The incidence of symptoms in the early period (<12 weeks) after COVID-19 infection ranges from 37% to 68%[2,5–8]. This rate is 39.5%-61.7% for the long term (1 year)[6,7,9–12]. Although only a fraction of patients recovering from acute infection will experience persistent symptoms, the potential public health implications of long COVID can be predicted to be much greater given the increasing global burden of COVID-19[4]. It is an unavoidable fact that long COVID cases will increase in parallel of the continuation of the pandemic with addition of many new cases every day. These patients with persistent symptoms are the invisible part of the iceberg. Since it is not possible to follow all patients after infection, it is important to identify COVID-19 population at risk for long COVID, which will become an increasing burden for the whole world.

The aim of this study is to evaluate the prolonged symptoms of the patients in the post-COVID period of 1 year in Turkish Thoracic Society (TTS)-TURCOVID-19 multicenter study cohort and to determine the factors that predict the presence of long-term symptoms.

2. Subjects and methods

2.1. Study design, population and site distribution

Targeted study population, multicenter TTS-TURCOVID-19 registry cohort, included 1 500 patients aged over 18 years, who were followed up and treated in the first wave of the COVID-19 pandemic (between 11 March and 18 July 2020)[13]. Thirteen of the 26 centers (11 university hospitals, 2 large tertiary hospitals, and 1 private hospitals) agreed to participate in the study with 831 patients.

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2.2. Inclusion criteria

The research covered all patients over 18 years who were a part of the first investigation and who could be reached by phone and accepted to participate. The case definition of the first investigation was based on the World Health Organization (WHO) COVID-19 case definition sheet. Accordingly, a proven case was defined as the presence of a positive nucleic acid amplification test or a positive rapid antigen detection test together with clinical and radiographic findings that were strongly suggestive of COVID-19 and highly probable cases presented with similar clinical and radiographic findings but could not be confirmed with an RT-PCR test.

The patients in the study population were contacted by telephone, informed about the study at the end of the 1 year-follow-up period. Patients who could not be reached (despite at least 3 times call at three different times), who did not accept to participate in the study and who deceased (death information was reported by patients' relatives in the phone call) were excluded from the study. Of 831 patients, 230 (27.7%) could not be reached; 28 (3.4%) did not agree to participate in the study; and 69 (8.3%) were deceased. After all, 504 (60.6%) patients were enrolled.

2.3. Ethical approval

This study was approved by the Institutional Review Board (IRB) of Cukurova University Faculty of Medicine (356/22.05.2021). The study was supported by the Turkish Thoracic Society (TTS). Patients were called and informed about the study *via* telephone.

2.4. Study protocol and selection/description of participants

This study, which evaluates the long-term effects of COVID-19, consisted of three steps including (1) telephone questionnaire (Supplementary questionnaire); (2) retrospective evaluation of the medical records and (3) face-to-face visit with participants who were accepted to admit to hospitals (Figure 1).

This stepwise study protocol contributed to assessing both the early post-acute and long-term effects of COVID-19 in patients. In the first step, both early and long-term symptoms of the patients were questioned by the telephone questionnaire. The second step included the retrospective examination of the medical records of the patients who stated that they were admitted to outpatient clinics for control. The third was a prospective step and included the results of face-to-face evaluation of long-term symptoms.

2.4.1. Step 1: telephone questionnaire

The patients were called by phone in the first year of their diagnosis. After obtaining verbal consent from the volunteers, a questionnaire including 13 sets of questions was applied to evaluate the symptoms for the early and long-term periods after the disease. Symptoms of each body system were questioned one by one in a structured evaluation form based on the NICE post-COVID guideline[14].

2.4.2. Step 2: retrospective evaluation of the medical records

Medical records (clinical and radiological) of the patients who were interviewed by phone who declared that they applied for a control visit in the outpatient clinic were evaluated retrospectively based on paid visit periods as first month/2-3 months/3-6 months/6-9 months/9-12 months. Chest X-ray and thoracic computerized tomography (CT) were coded according to the British Society of Thoracic Imaging (BSTI)[15].

2.4.3. Step 3: face-to-face visit

Individuals were invited to face-to-face follow-up visits via phone in Step-1. Symptom questionnaire that was administered in Step-1, the modified British Medical Research Council (mMRC) dyspnea scale, physical examination, routine laboratory tests (hemogram,

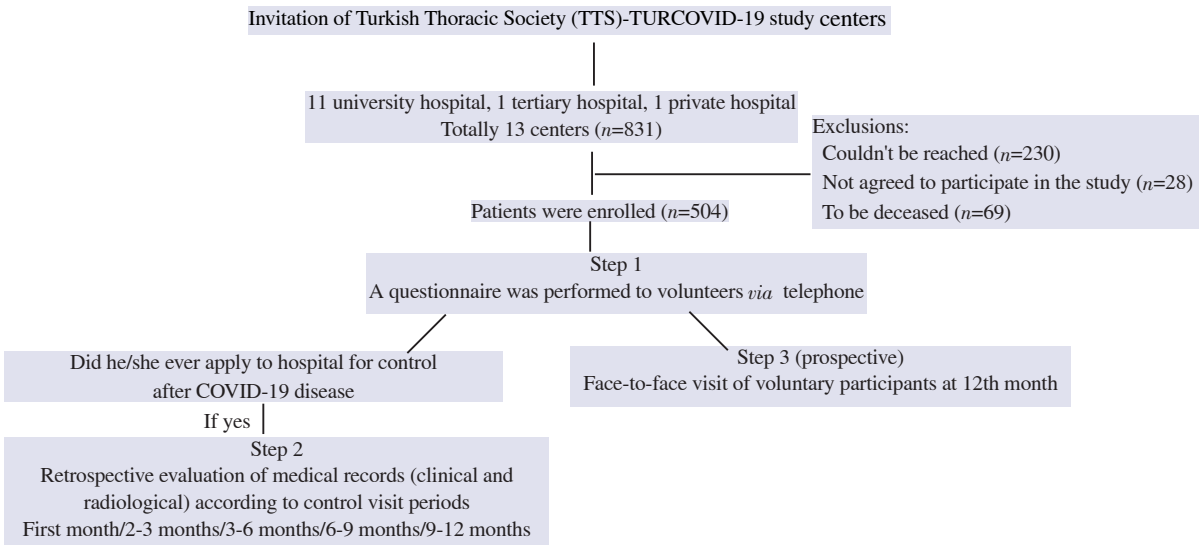


Figure 1. Study protocol and flow chart.

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biochemistry), ferritin, *D*-dimer, C-reactive protein (CRP) and pulmonary function test when required were performed. According to the physician's decision, chest X-ray or thoracic CT were performed.

2.5. Recordings and coding

To evaluate parameters that predict long-term symptoms, data including the initial symptoms in acute infection, clinical spectrum of the disease [asymptomatic, acute respiratory disease, pneumonia, severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome, sepsis, septic shock, and macrophage activation syndrome], comorbidities, basal laboratory parameters and length of stay in hospital were recorded from the index cohort data[13].

2.6. Definitions

Acute COVID-19: signs and symptoms of COVID-19 for up to 4 weeks. Ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4 weeks up to 12 weeks. Post-COVID-19 syndrome: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. Long COVID: in addition to the clinical case definitions, the term 'long COVID' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)[14].

2.7. Statistical analysis

The statistical analysis was performed by IBM SPSS for Windows version 25. The normality of the numerical variables was evaluated by the Shapiro-Wilk test. The Mann-Whitney *U* test was performed to compare patients with long term symptoms and without ones for nonnormal numerical variables. Univariate and binary logistic regression analyses were performed to estimate crude and adjusted odds ratios (a*OR*s) and 95% confidence intervals (*CI*s). In the multivariate analysis, variables were selected based on significance in the univariate analysis. Variance inflation factor (VIF) values were calculated to evaluate multicollinearity. A *P* value <0.05 was considered statistically significant.

3. Results

3.1. Results of telephone questionnaire

Among the 504 patients, there were 225 females (44.6%) and 279 (55.4%) males. The mean age was (48.9±16.6) years. Among all cases, 471 (93.5%) were hospitalized, 311 (61.7%) had a history of pneumonia at initial diagnosis. A total of 221 (43.8%) patients had at least one comorbidity. Twenty-two (4.4%) patients had a history of having COVID-19 for the second time. Fifty-seven patients (11.3%) admitted to the emergency room after discharge. Re-hospitalization was performed in 9 (1.8%) patients. The most common reasons for admission to the emergency department were dyspnea (*n*=19, 33.3%) and chest pain (*n*=11, 19.3%).

In the on-going symptomatic COVID-19 period (4-12 weeks), 57.9% of the participants had at least one on-going symptom. The most common ongoing symptoms were fatigue (32.8%), dyspnea (21.0%) and cough (20.8%) (Table 1).

Table 1. Demographic and clinical characteristics of the patients.

Characteristics	*n* (%)
Sex	
Male	279 (55.4)
Female	225 (44.6)
Hospitalization during COVID-19 infection	
No	33 (6.5)
Yes	471 (93.5)
Comorbidity (at least one comorbidity)	221 (43.8)
Hypertension	131 (26.0)
Asthma	39 (7.7)
Diabetes mellitus	85 (16.9)
Atherosclerosis	42 (8.3)
COPD	24 (4.8)
Bronchiectasis	3 (0.6)
Congestive heart failure	23 (4.6)
Chronic renal failure	15 (3.0)
Cerebrovascular disease	11 (2.2)
Interstitial lung diseases	6 (1.2)
Malignity	14 (2.8)
Rheumatological disease	6 (1.2)
Initial clinical spectrum of the COVID-19 infection	
Asymptomatic	50 (9.9)
Acute lower respiratory disease	88 (17.5)
Pneumonia	311 (61.7)
Severe pneumonia	69 (13.7)
ARDS	3 (0.6)
Multiple organ dysfunction syndrome	4 (0.8)
Sepsis	20 (4.0)
Septic shock	1 (0.2)
Macrophage activation syndrome	16 (3.2)
Admission to the emergency room after discharge	57 (11.3)
History of having COVID-19 for the second time	22 (4.4)
Re-hospitalization	9 (1.8)
On-going symptomatic COVID-19 period (4-12 weeks)	292 (57.9)

COPD: chronic obstructive pulmonary disease.

At the first year of follow-up, 120 (27.1%) of 442 patients who answered the current symptom question by phone still had complaints. The most common symptoms in the long term were dyspnea (17.00%), fatigue (6.30%) and weakness (5.00%). The distribution of the symptoms was shown in Figure 2.

Data comparing the patients according to presence of long-term symptoms revealed that there was no significant difference with respect to sex (*P*=0.300). However, the mean age was found to be higher in patients with long-term symptoms (52.2±15.5) years *vs.* (48.3±16.5) years (*P*=0.027). The univariate analysis showed that the following characteristics were associated with the presence of the symptoms in the long term: hospitalization (*P*<0.001), presence of pneumonia at initial diagnosis (*P*=0.010), presence of comorbidity

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(*P*=0.002) [especially atherosclerosis, chronic obstructive pulmonary disease (COPD) and bronchiectasis], and history of admission to the emergency department in the post-COVID period (*P*<0.001) (Table 2).

Table 2. Univariate analysis of risk factors for long-term symptoms.

Varaible	Long term symptom		*P*
	Yes, *n* (%), *n*=121	No, *n* (%), *n*=321	
Age, year, mean ±SD	52.2 ± 15.5	48.3 ± 16.5	0.027*
Sex			
Male	62 (51.2)	182 (56.7)	0.300
Hospitalization during COVID-19 infection			
Yes	121 (100.0)	289 (90.0)	<0.001*
Comorbidity			
Presence of any comorbidity			
Yes	68 (56.2)	127 (39.6)	0.002*
Hypertension			
Yes	40 (33.1)	79 (24.6)	0.070
Asthma			
Yes	12 (9.9)	22 (6.9)	0.280
Diabetes mellitus			
Yes	27 (22.3)	50 (15.6)	0.090
Atherosclerosis			
Yes	16 (13.2)	23 (7.2)	0.045*
COPD			
Yes	13 (10.7)	11 (3.4)	0.002*
Bronchiectasis			
Yes	2 (1.7)	0 (0.0)	0.020*
Congestive heart failure			
Yes	9 (7.4)	14 (4.4)	0.190
Chronic renal failure			
Yes	2 (1.7)	11 (3.4)	0.330
Cerebrovascular disease			
Yes	5 (4.1)	5 (1.6)	0.110
Interstitial lung diseases			
Yes	2 (1.7)	1 (0.3)	0.130
Malignity			
Yes	3 (2.5)	8 (2.5)	0.990
Rheumatological disease			
Yes	1 (0.8)	5 (1.6)	0.550
Initial clinical spectrum of the COVID-19 infection			
Asymptomatic			
Yes	8 (6.6)	38 (11.8)	0.110
Acute lower respiratory disease			
Yes	14 (11.6)	53 (16.5)	0.190
Pneumonia			
Yes	88 (72.7)	191 (59.5)	0.010*
Severe pneumonia			
Yes	18 (14.9)	46 (14.3)	0.880
Acute respiratory distress syndrome			
Yes	1 (0.8)	2 (0.6)	0.820
Multiple organ dysfunction syndrome			
Yes	1 (0.8)	3 (0.9)	0.920
Sepsis			
Yes	6 (5.0)	12 (3.7)	0.560
Septic shock			
Yes	0 (0.0)	1 (0.3)	0.280
Macrophage activation syndrome			
Yes	5 (4.1)	10 (3.1)	0.590
Admission to the emergency room in the post-COVID period			
Yes	26 (21.7)	28 (8.7)	<0.001*

COPD: chronic obstructive pulmonary disease.

Multivariate logistic regression analysis for presence of symptoms in long term follow-up is as follows: A multivariate model was tested in 442 patients, including clinical parameters, disease spectrum and comorbidities. The incidence of long-term symptoms was increased 2.91 fold (95% *CI* 1.04-8.13, *P*=0.041) in the presence of COPD, 1.84 fold (95% *CI* 1.10-3.10, *P*=0.021) in the presence of pneumonia at initial diagnosis, 3.92 fold (95% *CI* 2.29-6.72, *P*=0.001) of dyspnea and 1.69 fold (95% *CI* 1.02-2.80, *P*=0.040) fatigue persists in the early-post-treatment period and 2.88 fold (95% *CI* 1.52-5.46, *P*=0.001) in the presence of emergency service admission in the post COVID period (Table 3).

Initial laboratory parameters at the time of diagnosis of patients stratified according to the presence of long-term symptoms did not differ between the groups except for higher platelet count (*P*=0.003) and lower direct bilirubin values (*P*=0.030) in patients with long-term symptoms.

3.2. Results of Step–2

Among study population, 231 (45.8%) had at least one follow-up visit during one year. The distribution of symptoms during the follow-up revealed that fatigue, dyspnea, and cough were the most prominent symptoms in the early post-infection period, and the symptoms regressed as the time progress. Dyspnea was the most common symptom at the end of the first year (Figure 3).

There was also an improvement in radiological findings including chest X-ray and thorax CT during the follow-up depending on the retrospective analysis. According to the BSTI radiology scoring system, 1.4% of the chest radiographs did not significantly improve or unchanged at the end of the first year, while fibrosis was observed in 3.4% of the chest CTs (Figure 4 and 5).

3.3. Results of Step–3

A total of 138 (27.4%) patients admitted to hospital for face-to-face visit at the end of the first year. The mean age of these patients was (44.64±15.19) years. Totally, 75 (54.3%) of the cases were male and 63 (45.7%) were female. Twenty-seven (19.6%) has been infected with SARS-CoV-2 for the second time.

At the end of the first year, at least one symptom still persisted in 49.27% (*n*=68) of the cases. The most common symptoms were dyspnea (27.60%), psychiatric symptoms (18.10%), fatigue (17.40%), chest pain (17.40%) and brain fog (10.90%). The detailed persistent symptoms are shown in Figure 2.

Chest radiographs of 83.3% (*n*=115) of the cases were observed to be fully recovered. Thorax computed tomography was required in 41 cases, and findings consistent with fibrosis in one of these cases (2.4%); complications or findings of non-COVID disease were observed in 5 (12.2%) cases (Figure 6).

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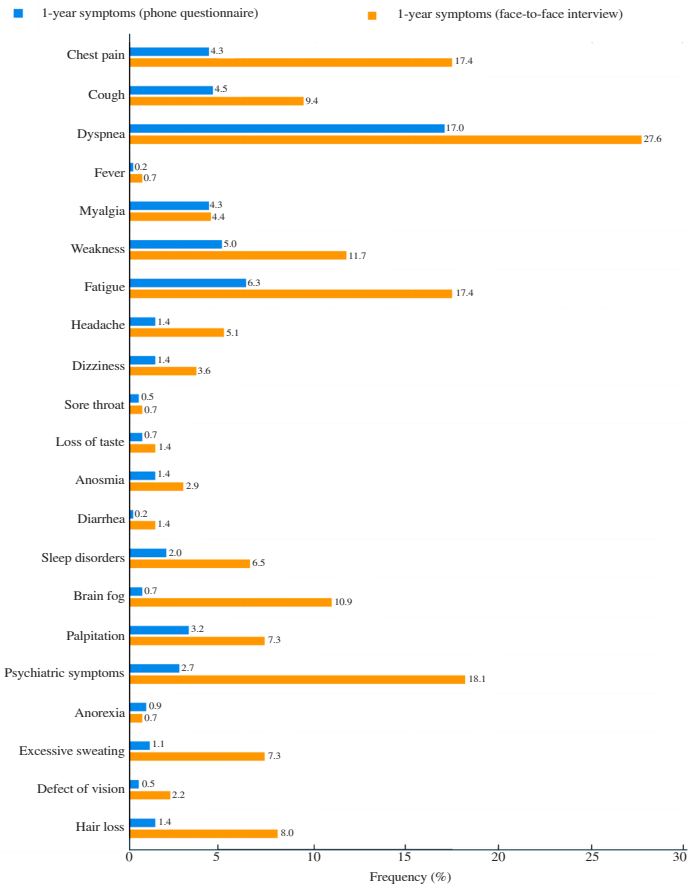


Figure 2. Symptoms in 1-year with phone questionnaire and 1-year at face-to-face interview.

Table 3. Multivariate analysis of risk factors for long-term symptoms.

Variable	Long-term symptoms (+) (*n*=121)	Long-term symptoms (-) (*n*=321)	*OR* (95% *CI*)	*P*
Age, mean±SD	52.07 ± 15.43	48.33 ± 16.56	1.00 (0.98-1.02)	0.812
Sex (male/female)	62/59	182/139	1.45 (0.90-2.35)	0.128
Atherosclerosis [*n* (%)]	16 (13.2)	23 (7.2)	0.99 (0.41-2.37)	0.983
COPD [*n* (%)]	13 (10.7)	11 (3.4)	2.91 (1.04-8.13)	0.041*
Hypertension [*n* (%)]	40 (33.1)	79 (24.6)	1.02 (0.55-1.87)	0.956
Diabetes mellitus [*n* (%)]	27 (22.3)	50 (15.6)	1.21 (0.64-2.30)	0.560
Pneumonia as an initial presentation [*n* (%)]	88 (72.7)	191 (59.5)	1.84 (1.10-3.10)	0.021*
Cough in the early post-COVID period [*n* (%)]	36 (29.8)	60 (18.7)	1.12 (0.64-1.95)	0.695
Dyspnea in the early post-COVID period [*n* (%)]	51 (42.1)	49 (15.3)	3.92 (2.29-6.72)	0.001*
Fatigue in the early post-COVID period [*n* (%)]	49 (40.5)	69 (21.5)	1.69 (1.02-2.80)	0.040*
Emergency service admission in the post-COVID period [*n* (%)]	26 (21.5)	28 (8.7)	2.88 (1.52-5.46)	0.001*

*Significant at the 0.05 level; *OR*: odds ratio. *CI*: confidence interval. COPD: chronic obstructive pulmonary disease.

4. Discussion

The severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) are well known coronaviruses with possible long-term consequences. However, in the case of the recent COVID-19 pandemic, the existing research focused on hospitalized patients with short follow-ups, leaving the long-term consequences unexplored. The main finding of this study was that nearly one fourth of the study population assessed by phone calls retrospectively, and nearly half of the patients who admitted to hospital had persistent symptoms at the end of the first year. The independent predictors of long-term symptoms were the presence of comorbidity especially COPD, pneumonia at the time of initial diagnosis, prolongation of symptoms after treatment, and emergency admission in the post-COVID period. Pulmonary fibrosis in thoracic CT was present in 3.4% of the retrospectively assessed group and 2.4% of the patients that admitted to the hospital for face-to-face interview at the end of the first year.

In our study, the highlighted data was that nearly one fourth of the study population stated long-COVID at the end of the first year on phone questionnaire and at least one symptom still persisted in 49.27% of the cases on face-to-face visit. This might be because more symptomatic individuals prefer to confess to face-to-face visits, or because patients can more easily convey their problems in person. The most common symptoms in the long term were dyspnea (17.00%), fatigue (6.30%) and weakness (5.00%) on

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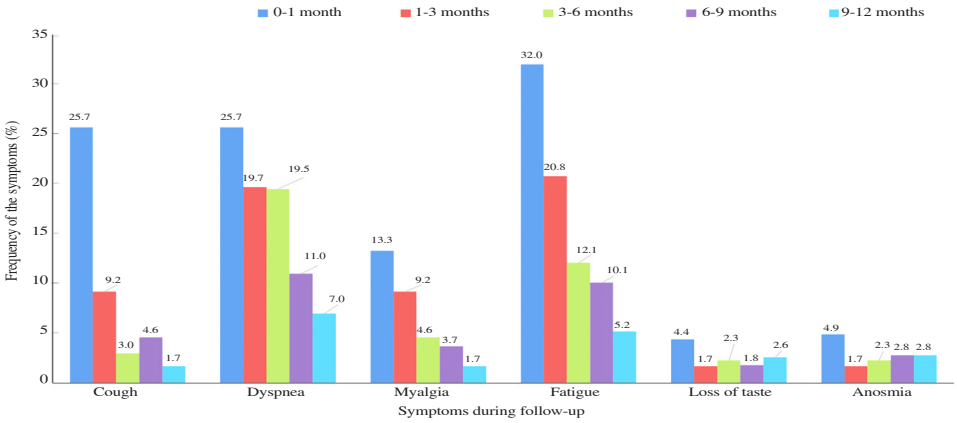


Figure 3. Distribution of the symptoms by time during follow-up (the results of retrospective Step 2).

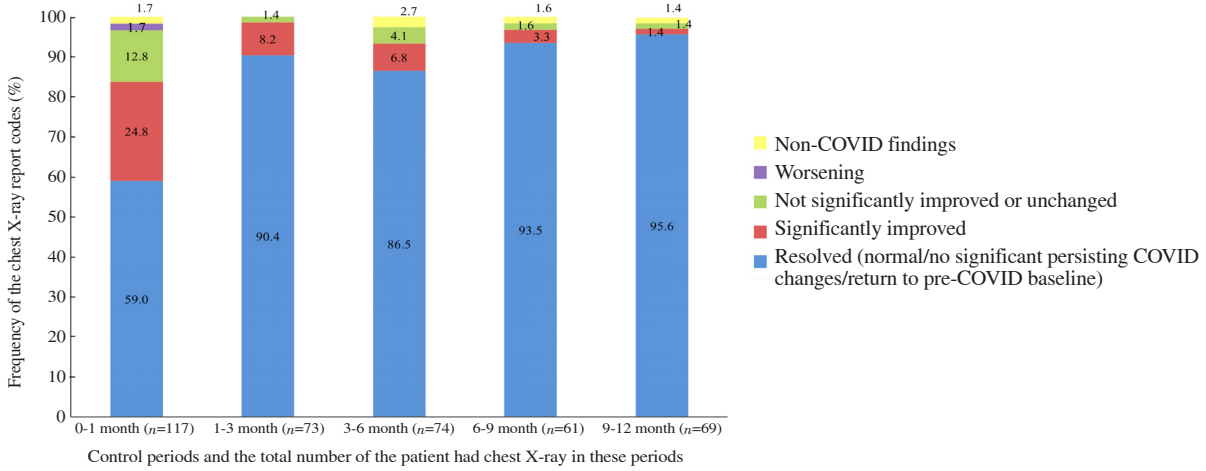


Figure 4. British Society of Thoracic Imaging, post-COVID-19 chest X-ray report codes according to control periods[15].

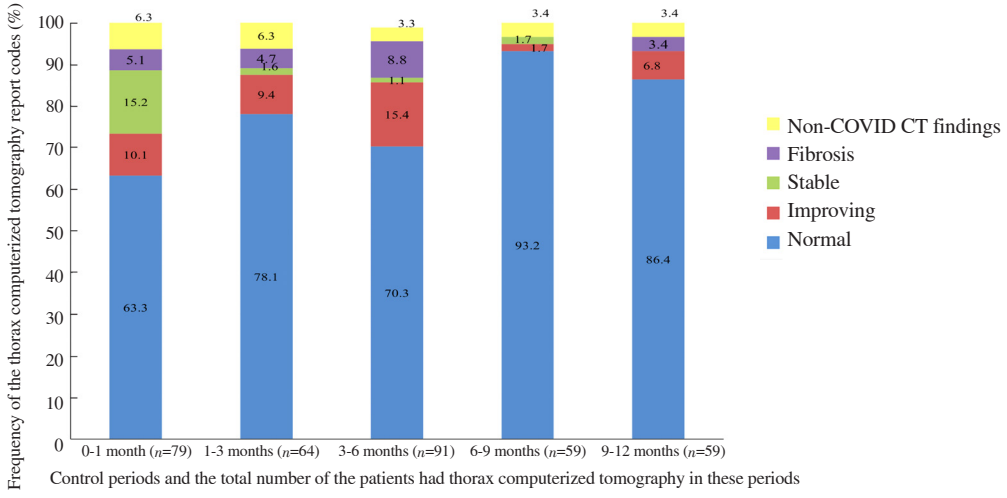


Figure 5. British Society of Thoracic Imaging, post-COVID-19 computerized tomography (CT) report codes according to control periods[15].

phone questionnaire and dyspnea (27.60%), psychiatric symptoms (18.10%), fatigue (17.40%), chest pain (17.40%), weakness (11.70%), and brain fog (10.90%) on face-to-face interview in our study. A study represented that the most common respiratory symptoms in survivors of COVID-19 were fatigue, dyspnea, chest discomfort, and cough, which were found in 52%, 37%, 16%, and 14% of patients, respectively, between 3 weeks and 3 months following discharge[3]. A study revealed that 13.3% of participants reported symptoms lasting ≥28 days, 4.5% for ≥8 weeks, and 2.3% reported symptoms for ≥12 weeks[16]. In a similar study with 60 days mean follow-up period, only 12.6% of the participants were free of symptoms while fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%) were the most common symptoms[17]. In a meta-analysis that included studies with a follow-up period between 14 and 118 days range, the most common manifestations were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%) and dyspnea (24%)[18]. Garrigues *et al.* found that fatigue (55%), dyspnea (42%), loss of memory (34%), concentration disorders (28%) and sleep disorders (30.8%) were the most prevalent post-COVID symptoms 3 months after

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hospital discharge[19]. More recently, it is observed that 59% of hospitalized and 37% of non-hospitalized patients exhibited post-COVID symptoms 3 months after the infection[5]. In a study conducted between May-July 2020, 56.3% patients experienced unresolved symptoms after a month of discharge and 28.8% of the cohort had not returned to their pre-COVID baseline state after a median 4 months of follow-up[4]. A cohort study conducted between January and May 2020 with a 186 days of mean follow-up period revealed that fatigue muscle weakness (63%) and sleep difficulties (26%) and anxiety or depression (23%) were the most common dysregularities[20]. In a multi-center study from Spain, dealing with the patients from the first wave of pandemic, participants were assessed a mean of seven months after hospital discharge showed that only 18.6% were completely free of any post-COVID symptom and the most frequent symptoms were fatigue (60.8%), hair loss (26.3%), and dyspnea (23.5%)[21]. At the end of one-year follow-up of the same group, the prevalences of cough, chest pain, dyspnea, and fatigue were 2.5%, 6.5%, 23.3%, and 61.2%, respectively[10]. The reported disparity in long-COVID symptom prevalence could be explained by the different methodologies used, with active inquiry implying a larger prevalence than passive inquiry. The frequency of symptoms continues to diminish when the time of post-COVID follow-up is extended, as is typically noted in literature. Considering the approximate one-year follow-up time in our study, our findings were compatible with the literature. Patients who were assessed face-to-face had greater symptoms and abnormal radiologic features in our study. As a result, face-to-face examination should be advised whenever feasible, especially for those with risk factors.

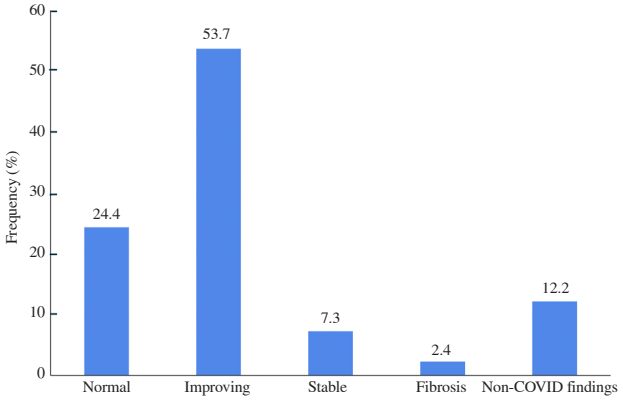


Figure 6. Computerized tomography (CT) findings in 1-year (on face-to face interview).

The prevalence of comorbidity, particularly COPD, pneumonia at the time of diagnosis, persistence of symptoms following therapy, and emergency admission in the post-COVID interval were all independent predictors of long-term symptoms; and the patients with prolonged COVID symptoms had higher platelet counts and lower direct bilirubin levels at admission were at higher risk of long-COVID symptoms in our study. In a retrospective study performed with the participation of approximately five thousand patients reflecting a follow-up of 3-12 months, 62.3% of the patients stated that they still had symptoms. In this group, women were significantly more likely than men to have long-term COVID syndrome (*OR*=1.268). Long COVID syndrome was also substantially linked with the presence of respiratory symptoms at admission (*OR*=1.425) and inversely linked with a shorter hospital stay (*OR*=0.953)[22]. Another study concerning the potential risks of long COVID specified that persistent symptoms were more common in people with older age, higher BMI, and female gender and also linked to having more than five symptoms during the first week of sickness (*OR*=3.53)[16]. Female gender, a history of anxiety or depression diagnosis or antidepressant usage, prior psychiatric disorder, and intensive care unit admission were blamed to be independent risk factors for long-COVID in different studies[23–28]. And also, it is declared that the presence of IgG antibodies was significantly associated with the occurrence of post-COVID-19 syndrome (*OR*=2.56) and median SARS-CoV-2 IgG titers were significantly higher in patients with post-COVID-19 syndrome[24]. While asthma was not reported as a factor of risk for hospitalization in some studies, its association with long COVID warrants further investigation[29]. There are conflicting results regarding the relationship between the severity of acute COVID infection and long-COVID[16,30]. Despite the fact that several researches have identified possible risk variables for long-COVID, there are proposals that this classification may not be logical due to the lack of a link between symptom severity and radiographic or laboratory abnormalities; implying that the etiology of long-COVID may not be due to the influence of SARS-CoV-2, but rather to neuropsychiatric insults[23]. Most of our findings are in line with what has been published in the literature.

To the best of our knowledge, there are very limited data about COPD as a risk factor for long-COVID. The incidence of long-term symptoms was increased 2.91 fold (95% *CI* 1.04-8.13, *P*=0.041) in the presence of COPD in our study. As known, COPD patients have an elevated risk of severe pneumonia and poor outcomes theoretically due to a lack of underlying lung reserves or condensed ACE-2 receptor expression in small airways[31]. A Spain prospective cohort study identified COPD (*OR*=5.009) as an independent risk factor for remaining symptoms; at least one symptom persisted in 80% of the people with COPD. When compared their perspective before to the COVID-19 diagnosis, 75% experienced new or exacerbated dyspnea. In the COPD group, the most prevalent symptoms were dyspnea (60%) and chest discomfort (26%)[32]. More comprehensive studies are needed to realistically evaluate the association and underlying mechanisms between COPD and long-COVID.

Pulmonary fibrosis was present in 3.4% of the retrospectively assessed group and 2.4% of the patients that admitted to the hospital for face-to-face interview at the end of the first year in our study. Considering millions of COVID-19 cases worldwide, even small proportion of post-COVID lung fibrosis is worrisome. In a study, the lung lesions of 64.7% discharged patients were fully absorbed after 4-week follow-up[33]. Another one with a mean of nearly two months follow-up, 62% of radiographs were normal, 27% demonstrated

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significant improvement, 2% were unchanged and 9% showed significant deterioration[34]. In a study, at least one of radiological abnormalities were detected in 70.91% of the participants and interstitial thickening was seen in 27% three months after discharge[35]. A Spanish prospective cohort showed relevant imaging changes in 18.9% of the participants while 52.9% of them were free of respiratory symptoms, conversely, relevant imaging changes were detected in 20.7% of patients with cough or dyspnea 10-14 weeks after acute COVID[5]. One study including severe COVID-19 cases showed that 20% of non-mechanically ventilated and 72% of mechanically ventilated individuals had fibrotic-like radiographic abnormalities at the end of 4 months[36]. In a large 6-month follow-up study, a total of 353 patients were deemed appropriate to undergo lung CT, and at least one abnormality was found in approximately 50% of them, the most common being ground glass opacities and irregular lines. While interlobular septal thickening was observed in 1% cases[20]. In the literature, data with tomography findings in long-COVID are quite scarce. This is why our study, in which we present especially long-term radiologic data, is very valuable.

There are some limitations of this study. First, not all centers in the first cohort participated in the study. As a result of applying the exclusion criteria to the participants, approximately 1/3 of the target population has been reached. Second, the study was conducted at the beginning of the pandemic, and due to policies in effect at that time, the majority of the patients were hospitalized; thus, severe patients may not have been represented well. A further limitation of our study was the simple assessment of presence of persistent symptoms; we were only able to determine whether individuals were experiencing any symptoms; we weren't able to record the severity of each symptom individually. Another limitation of this study is that the data set is in some steps of the study based on a phone consultation with no clinical, psychological, or telemedicine evaluations. These results cannot be generalized to whole population.

In conclusion, SARS-CoV-2 infects a wide range of tissues and has multi-organ and multi-system effects. On the other hand, the origin and biological basis of long-COVID are still unknown. Meanwhile, the extent, nature, and associated variables of such persisting symptoms in the post-acute phase are yet unknown. At the population level, it is critical to quantify the burden of long COVID to assess its impact on the healthcare system and appropriately distribute resources. The long-term symptoms must be contextualized and risk factors must be definitely determined to improve the treatment of these individuals.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgements

The authors thank Turkish Thoracic Society for serving as a base for the setup of the network bringing the investigators of this study together.

Funding

The authors received no extramural funding for the study.

Authors' contributions

SAB, NK, HB, OBT, PDC, FF and OI designed the study; SAB, OBT, PDC, FF, NK, SK, OK, YT, EA, MK, PAY, PPD, OK, IB, HB, IH, NK, GS, CC, HKO, HSO, BE, MH, AS, ENT, OO, TUC, IKO, VAO, FB, OA, ME, PYG, ATE, MMT, OI and HB collected the data; SK and SAB analyzed the data; SAB, OBT, PDC, FF and NK searched the literature and wrote the manuscript; SAB, OBT, FF, PDC, NK and HB edited and revised manuscript according to journal's instructions; SAB, OBT, NK and HB edited and controlled the final version of the manuscript. All the authors approved the final version of the manuscript.

References

[1] Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: An overview. *J Chin Med Assoc* 2020; **83**(3): 217-220.

[2]Worldometer. *COVID live–Coronavirus statistics*. [Online]. Available from: https://www.worldometers.info/coronavirus/. [Accessed on 23 August 2022].

[3] Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, Vera-Uribe R, Torralba Y, Alsina-Restoy X, et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Chron Respir Dis* 2021; **18**: 14799731211002240. doi: 10.1177/14799731211002240.

[4] Tleyjeh IM, Saddik B, Ramakrishnan RK, AlSwaidan N, AlAnazi A, Alhazmi D, et al. Long term predictors of breathlessness, exercise intolerance, chronic fatigue and well-being in hospitalized patients with COVID-19: A cohort study with 4 months median follow-up. *J Infect Public Health* 2022; **15**(1): 21-28.

[5] Moreno-Pérez O, Merino E, Leon-Ramirez JM, Andres M, Ramos JM, Arenas-Jiménez J, et al. COVID19-ALC research group. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *J Infect* 2021; **82**(3): 378-383.

[6] Iqbal FM, Lam K, Sounderajah V, Clarke JM, Ashrafian H, Darzi A. Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. *EClinicalMedicine* 2021; **36**: 100899. doi: 10.1016/j.eclinm.2021.100899.

[7] Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: A systematic review. *JAMA Netw Open* 2021; **4**(10): e2128568. doi: 10.1001/jamanetworkopen.2021.28568.

[8] Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufils E, Bourbao-

[Downloaded free from http://www.apjtm.org on Thursday, March 9, 2023, IP: 88.255.99.29]

Tournois C, Laribi S, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect* 2021; **27**(2): 258-263.

[9] Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: A longitudinal cohort study. *Lancet* 2021; **398**(10302): 747-758.

[10]Fernández-de-Las-Peñas C, Guijarro C, Plaza-Canteli S, Hernández-Barrera V, Torres-Macho J. Prevalence of post-COVID-19 cough one year after SARS-CoV-2 infection: A multicenter study. *Lung* 2021; **199**(3): 249-253.

[11]Bellan M, Baricich A, Patrucco F, Zeppegno P, Gramaglia C, Balbo PE, et al. Long-term sequelae are highly prevalent one year after hospitalization for severe COVID-19. *Sci Rep* 2021; **11**(1): 22666. doi: 10.1038/s41598-021-01215-4.

[12]Zhao Y, Yang C, An X, Xiong Y, Shang Y, He J, et al. Follow-up study on COVID-19 survivors one year after discharge from hospital. *Int J Infect Dis* 2021; **112**: 173-182.

[13]Kokturk N, Babayigit C, Kul S, Duru Cetinkaya P, Atis Nayci S, Argun Baris S, et al. The predictors of COVID-19 mortality in a nationwide cohort of Turkish patients. *Respir Med* 2021; **183**: 106433. doi: 10.1016/j.rmed.2021.106433.

[14]No authors listed. *COVID-19 rapid guideline: Managing the long-term effects of COVID-19*. London: National Institute for Health and Care Excellence (NICE); 2020.

[15]BSTI. *BSTI Covid-19 guidance for the reporting radiologist*. Updated version 2. [Online]. Available from: https://www.bsti.org.uk/standards-clinical-guidelines/clinical-guidelines/bsti-covid-19-guidance-for-the-reporting-radiologist/. [Accessed on 27 December 2020].

[16]Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. *Nat Med* 2021; **27**(4): 626-631.

[17]Carfì A, Bernabei R, Landi F, Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; **324**(6): 603-605.

[18]Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: A systematic review and meta-analysis. *Sci Rep* 2021; **11**(1): 16144.

[19]Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020; **81**(6): e4-e6. doi: 10.1016/j.jinf.2020.08.029.

[20]Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: A cohort study. *Lancet* 2021; **397**(10270): 220-232.

[21]Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Rodríuez-Jiménez J, Palacios-Ceña M, Velasco-Arribas M, et al. Long-term post-COVID symptoms and associated risk factors in previously hospitalized patients: A multicenter study. *J Infect* 2021; **83**(2): 237-279.

[22]Asadi-Pooya AA, Akbari A, Emami A, Lotfi M, Rostamihosseinkhani M, Nemati H, et al. Risk factors associated with long COVID syndrome: A retrospective study. *Iran J Med Sci* 2021; **46**(6): 428-436.

[23]Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 symptom burden: What is long-COVID and how should we manage it? *Lung* 2021; **199**(2): 113-119.

[24]Peghin M, Palese A, Venturini M, De Martino M, Gerussi V, Graziano E, et al. Post-COVID-19 symptoms 6 months after acute infection among hospitalized and non-hospitalized patients. *Clin Microbiol Infect* 2021; **27**(10): 1507-1513.

[25]Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One* 2020; **15**(11): e0240784. doi: 10.1371/journal.pone.0240784.

[26]Poyraz BC, Poyraz CA, Olgun Y, Gürel Ö, Alkan S, Özdemir YE, et al. Psychiatric morbidity and protracted symptoms after COVID-19. *Psychiatry Res* 2020; **295**: 113604. doi: 10.1016/j.psychres.2020.113604.

[27]Taboada M, Carinena A, Moreno E, Rodríguez N, Domínguez MJ, Casal A, et al. Post-COVID-19 functional status six-months after hospitalization. *J Infect* 2020; **82**(4): e31-e33. doi: 10.1016/j.jinf.2020.12.022.

[28]Yong SJ. Long COVID or post-COVID-19 syndrome: Putative pathophysiology, risk factors, and treatments. *Infect Dis (Lond)* 2021; **53**(10): 737-754.

[29]Robinson LB, Fu X, Bassett IV, Triant VA, Foulkes AS, Zhang Y, et al. COVID-19 severity in hospitalized patients with asthma: A matched cohort study. *J Allergy Clin Immunol Pract* 2021; **9**(1): 497-500.

[30]Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterisation of post-COVID-19 manifestations. *Int J Clin Pract* 2021; **75**: e13746. doi:10.1111/ijcp.137.

[31]Leung JM, Niikura M, Yang CWT, Sin DD. COVID-19 and COPD. *Eur Respir J* 2020; **56**(2): 2002108. doi: 10.1183/13993003.02108-2020.

[32]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* 2022; **12**(1): 3369. doi: 10.1038/s41598-022-07414-x.

[33]Liu C, Ye L, Xia R, Zheng X, Yuan C, Wang Z, et al. Chest CT and clinical follow-up of discharged patients with COVID-19 in Wenzhou City, Zhejiang, China. *Ann Am Thorac Soc* 2020; **17**(10): 1231-1237.

[34]Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, Hare SS, et al. 'Long-COVID': A cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 2021; **76**(4): 396-398.

[35]Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020; **25**: 100463. doi: 10.1016/j.eclinm.2020.100463.

[36]McGroder CF, Zhang D, Choudhury MA, Salvatore MM, D'Souza BM, Hoffman EA, et al. Pulmonary fibrosis 4 months after COVID-19 is associated with severity of illness and blood leucocyte telomere length. *Thorax* 2021; **76**(12): 1242-1245.

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