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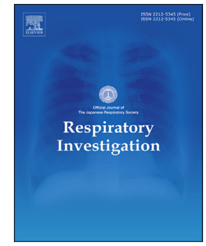

Original article

Computed tomography at every step: Long coronavirus disease

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ABSTRACT

Background: Some patients continue to experience symptoms related to Coronavirus disease (COVID-19) after the acute phase of infection. Imaging studies, especially computed tomography (CT) of the chest, have gained importance since the beginning of the pandemic. CT can help diagnose COVID-19, assess the extent of pulmonary involvement, and predict the disease severity. We aimed to define the frequency of persistent symptoms and correlate their presence with the results of laboratory findings and the severity of the disease based on the findings of chest CT.

Methods: We examined patients discharged from the hospital after treatment for COVID-19 and whose nasopharyngeal swab sample tested positive for severe acute respiratory syndrome coronavirus 2 after at least 4 weeks from the initial diagnosis. The patients were asked about the presence of persisting symptoms. In addition to the demographic data, laboratory results and severity levels seen on the chest CT were recorded.

Results: In all, 116 patients were included in the study, of which 61 reported at least one persisting symptom (52.5%). The mean age of the study population was 48.90 ± 17.74 years. The persistent symptoms included shortness of breath, chest pain, cough, muscle weakness, dizziness, headache, fatigue, and palpitations. The mean CT severity score was 3.80 ± 0.38 and it was lower in patients without any persistent symptoms.

Conclusions: Levels of C-reactive protein and fibrinogen, anemia, and female sex were associated with some of the persistent symptoms., the severity of the disease seen on CT was a successful predictor for the disease severity/prognosis and was also correlated with prolonged COVID infection and more persistent symptoms.

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1. Introduction

With an increase in the number of patients and studies focusing on the course of the coronavirus disease (COVID-19), persistent symptoms associated with the infection have been well-defined. According to recent research, some patients continue to experience COVID-19-related symptoms after the acute phase of infection. Approximately 10% of the patients with COVID-19 experience various symptoms that can last for up to 3 months after the initial diagnosis [1,2]. Currently, there is no consensus about the definition of the condition or the spectrum of the symptoms. Various terminologies, such as long COVID, post-acute COVID-19 syndrome, chronic COVID syndrome, and long-haul COVID, have been used [3,4]. Persistent symptoms Previously defined include fatigue, headaches, shortness of breath, anosmia, muscle weakness, low fever, and cognitive dysfunction (brain fog) [5–8].

Imaging studies, especially chest computed tomography (CT), have gained importance since the beginning of the pandemic. Chest CT can help diagnose COVID-19, assess the extent of pulmonary involvement, predict the disease severity/prognosis, and detect complications [9]. Qualitative and quantitative methods for calculating the CT severity index have been introduced, and CT severity values were found to be successful in predicting the disease prognosis [10]. However, to the best of our knowledge, no study in English literature has examined the correlation between CT severity and persistent post-COVID symptoms.

In the current study, we aimed to define the frequency of persistent symptoms and correlate their presence with laboratory findings and the severity of the disease based on the interpretation of the chest CT.

2. Materials and methods

The study was approved by the Institutional Ethics Committee of Erzincan Binali Yildirim University School of Medicine (KAEK 20-2-146, 25.01.21) and all participants provided written informed consent.

We attempted to contact every patient discharged from our hospital following treatment for COVID-19 and who had a positive result of the nasopharyngeal swab sample tested for severe acute respiratory syndrome coronavirus 2 at least 4 weeks after the initial diagnosis. The patients were questioned about any persistent symptoms. Patients whose CT severity values at the time of hospital admission (43 patients) were not defined and who did not/could not answer the questionnaire about persistent symptoms (21 patients) were excluded from the study. A chest disease specialist conducted the majority of the assessments over the phone.

The result of the CT examination at the time of hospital admission was used to define the CT severity value. CT severity of the patients was defined for each lung segment, and the sum of the severity value of each lobe was used to arrive at a final severity score. CT severity scores were calculated using the method described by Pan et al. [11] (Table 1) (Figs. 1 and 2). Two radiologists calculated the CT severity scores blindly. The mean value of two measurements was recorded as the final value.

Table 1 – CT severity scoring.

CT severity score	Extent of lesions for each lung lobe
0	0%
1	<5%
2	5%–25%
3	26%–50%
4	51%–75%
5	>75%

CT: Computed tomography.
Scores were defined for each lobe of the lung and the sum of the scores of the lobes constitute the total lung score.
Total score scale: 0–25.

The levels of white blood cells, hematocrit (Hct), hemoglobin (Hb), platelets (Plt), lymphocytes, neutrophils, D dimer, ferritin, fibrinogen, procalcitonin, and C- reactive protein (CRP) at the time of hospital admission were recorded. Age and sex data were also noted.

Patients were classified according to the clinical disease severity categorization suggested by Feng et al. [12]: (a) type 1, mild symptoms with no abnormal radiological findings, (b) type 2, moderate symptoms with evidence of pneumonia on chest CT, (c) type 3, either a high respiratory rate (≥30/min) or oxygen saturation (≤93%) or low oxygen partial pressure/inspired oxygen fraction (≤300 mmHg) in the arterial blood, and (d) type 4, requiring mechanical ventilation, development of shock or organ dysfunction requiring intensive care.

2.1. Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows 20 software (IBM SPSS Inc., Chicago, IL, USA). The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. Numerical variables are shown as mean ± standard deviation. Categorical variables are shown as percentages. Spearman and Pearson correlation analyses were applied to define possible correlations of the CT severity values and results of the laboratory parameters with the persistence of symptoms. Chi-square and student's t tests were used to analyze the differences in the persistent symptoms, sex, and age between patients with long COVID and those without any persistent symptoms. Logistic regression analysis was used to define the correlations between persistent COVID symptoms and age, sex, results of laboratory parameters, and CT severity values. Categorical correlation analysis (Cohen kappa values- κ) was conducted to check for interobserver agreement (Kappa results can be interpreted as follows: values ≤ 0 no agreement and 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as strong agreement). A two-tailed value of $p < 0.05$ was considered statistically significant.

3. Results

In all, 116 patients were included in the study, of which 61 reported at least one persisting symptom (61/116, 52.5%). The

Fig. 1 – Computed tomography (CT) image of a 37-year-old man with no comorbidities. A focal infiltration, presented as halo-sign, is seen at the right lower lobe, posterior segment, occupying less than 5% of the lobe (B, F). The other lobes are normal (A, C, D, E). CT severity value of the case is 1.

mean age of the population was 48.90 ± 17.74 years (13–88 years). The study population comprised 56 males (48.3%) and 60 females (51.7%). There was no significant correlation between age, sex, and persistence of symptoms ($p > 0.05$). The mean interval between the initial diagnosis and administration of the questionnaire to check for persistence of symptoms was 44.3 ± 12.4 days.

The persistent symptoms included shortness of breath, chest pain, cough, muscle weakness, dizziness, headache, fatigue, and palpitations. The frequency of each symptom is shown in Table 2. In addition to the mentioned persisting symptoms, 4 patients (3.4%) reported anxiety and 4 (3.4%) mentioned occasional hot flush. According to the results of the regression analysis, persistent shortness of breath was correlated with high CT severity index and CRP values (CT severity, OR = 2.35, $p = 0.001$; CRP, OR = 3.15, $p = 0.013$). Chest pain was correlated with higher CT severity index and fibrinogen values (CT severity, odds ratio [OR] = 1.15, $p = 0.04$; fibrinogen, OR = 3.15, $p = 0.04$). Cough was correlated with a high CT severity index (OR = 1.46, $p = 0.013$). Muscle weakness was correlated with a high CT severity index and low Hb values (CT severity, OR = 1.25, $p = 0.018$; Hb, OR = 2.63, $p = 0.001$). Fatigue was correlated with female sex (OR = 1.8, $p = 0.008$). Dizziness, headache, and palpitations were not

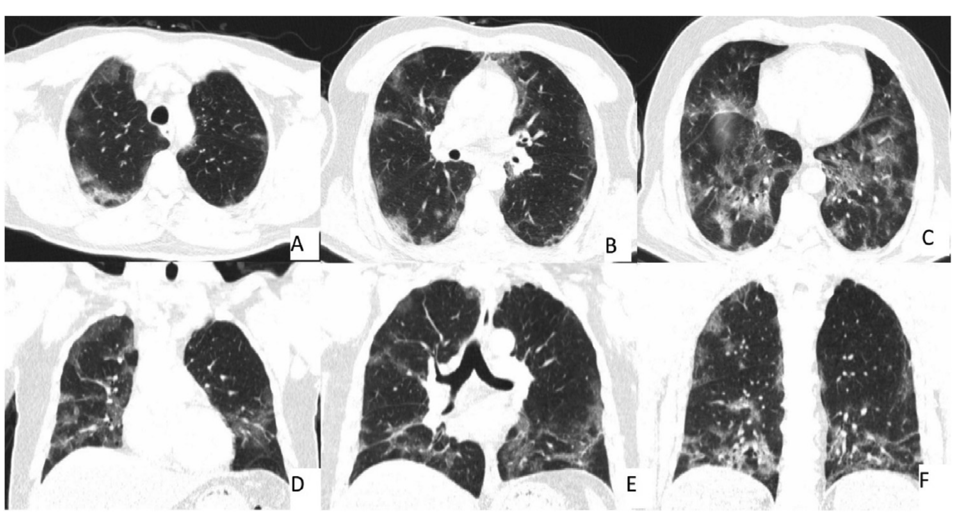

Fig. 2 – Computed tomography (CT) image of a 63-year-old woman. Diffuse, ground-glass opacities can be seen in all the lobes, located predominantly at peripheral zones (A–F). Ground glass opacities occupy 5–25% of both the upper lobes and right middle lobe, and 25–50% of both the lower lobes. CT severity value of the case is 12.

Table 2 – Frequency of persistent symptoms.

Symptom	Frequency n (%)
Shortness of breath	22 (19%)
Chest pain	7 (6%)
Cough	10 (8.6%)
Muscle weakness	24 (20.7%)
Dizziness	5 (4.3%)
Headache	11 (9.5%)
Fatigue	29 (25%)
Palpitation	5 (4.3%)

correlated with the results of laboratory parameters or CT severity index (Table 3).

Mean values of the laboratory findings are shown in Table 4.

The distribution of the patients according to the clinical severity groups is shown in Table 5. Persistent COVID symptoms were present in 10 patients (10/32, 31.25%) in type 1 clinical severity subgroup, 43 patients (43/71, 60.5%) in type 2 clinical severity subgroup, and 8 patients (8/13, 61.5%) in type 3 clinical severity subgroup. The frequency of persistent symptoms was similar in type 2 and 3 clinical severity subgroups and significantly lower in type 1 clinical severity subgroup ($p = 0.01$).

The mean CT severity score of the study population was 3.80 ± 0.38 (0–16). The mean CT severity score was lower in patients without any persistent symptoms than in those with persistent symptoms (3.02 ± 3.86 vs. 4.52 ± 3.68, $p = 0.034$). The CT severity score was positively correlated with the D dimer and CRP values and negatively correlated with the Hct and Hb values. We could not find a significant correlation with other laboratory parameters (Table 6). For the CT severity scoring, the interobserver agreement was found to be strong (κ value 0.86).

Table 3 – Persistent symptoms and related parameters.

Persistent symptom	Related parameters
Shortness of Breath	Higher CT severity index (OR = 2.35, p = 0.001)
	Higher CRP values (OR = 3.15, p = 0.013)
Chest Pain	Higher CT severity index (OR = 1.15, p = 0.04)
	Higher fibrinogen values (OR = 3.15, p = 0.04)
Cough	Higher CT severity index (OR = 1.46, p = 0.013)
Muscle Weakness	Higher CT severity index (OR = 1.25, p = 0.018)
	Lower Hb values (OR = 2.63, p = 0.001)
Fatigue	Female gender (OR = 1.8, p = 0.008)
Dizziness, Headache, and Palpitation	None

CT: Computed tomography.
CRP: C-reactive protein.
Hb: Hemoglobin.
OR: Odds ratio.

Table 4 – Mean values of the laboratory parameters.

Laboratory parameters	Mean values
White blood cell (x10^9/L)	6.53 ± 1.24
Platelet (x10^9/L)	207.24 ± 50.35
Lymphocyte (x10^9/L)	2.40 ± 5.45
Neutrophil (x10^9/L)	3.44 ± 0.22
Hematocrit (%)	57.48 ± 7.56
Hemoglobin (g/dL)	14.01 ± 1.49
D dimer (ng/mL)	550 ± 40
Ferritin (ng/mL)	188.06 ± 25.7
Fibrinogen (ng/mL)	326.48 ± 62.67
Procalcitonin (ng/mL)	0.12 ± 0.04
C-reactive protein (mg/L)	14.14 ± 1.78

4. Discussion

The research about persistent COVID symptoms is relatively new in the current times. To the best of our knowledge, there are a limited number of studies in English literature, which have defined persistent COVID symptoms, and no study has examined the relationship between persistent symptoms and CT severity. According to our first and preliminary results, fatigue, muscle weakness, and shortness of breath are the most frequent persistent COVID symptoms. The CT severity levels are related to the presence of persistent symptoms. In the previous studies, patients were asked about persistent COVID-19 symptoms until 90 days after the initial diagnosis [13]. In most studies, the interval between initial diagnosis and persistent symptoms was 30–60 days [5–7,14]. We found a median interval of 44.3 days, which in line with the published literature.

It has been reported that approximately 10–20% of the people with COVID-19 experienced persistent symptoms lasting longer than a month [15]. We defined an incidence of 52.5%. We included only patients who had undergone CT examinations; moreover, CT examination was performed in patients with severe symptoms and poor clinical condition. Thus, our study focused on patients with poor clinical condition and abnormal laboratory findings. This might explain the increased frequency of long COVID cases in our study.

The correlation between age and long COVID is debatable. While Carvalho-Schneider et al. [5] reported long COVID to be associated with age (especially in patients aged 40–60 years), some other studies [4,13] did not report any correlation. We did not find a significant correlation between age and long COVID. Elderly patients have a higher severity of COVID-19 infection; however, age is not the only predictor of disease severity [16]. The contradictory results about age and long COVID might be explained via age and disease severity

Table 5 – Distribution of the patients according to clinical severity groups.

Clinical severity group	Number (%)
Type 1	32 (27.5)
Type 2	71 (61.2)
Type 3	13 (11.2)

Table 6 – Correlations between CT severity score and laboratory parameters.

CT index	Laboratory Parameters											
	WBC	Plt	Lym	Neu	Hct	Hb	D dimer	Ferritin	Fibr	Trop	PRC	CRP
R	0.01	0.1	0.005	0.03	−0.57	−0.69	0.64	0.12	0.18	0.02	0.07	0.85
P value	0.9	0.15	0.9	0.7	0.005	0.003	0.008	0.19	0.51	0.98	0.46	0.001

WBC: White blood cells (x10^9/L).
Plt: Platelets (x10^9/L).
Lym: Lymphocytes (x10^9/L).
Neu: Neutrophils (x10^9/L).
Hct: Hematocrit (%).
Hb: Hemoglobin (g/dL).
D-dimer (ng/mL).
Ferritin (ng/mL).
Fibr: Fibrinogen (ng/mL).
Trop: Troponin (ng/mL).
PRC: Procalcitonin (ng/mL).
CRP: C reactive protein (mg/L).
CT: Computed tomography.

correlation. It can be concluded that age is not a direct predictor for long COVID; however, it can be an indirect predictor if it causes severe disease. We also did not find a significant correlation between sex and long COVID; there are also no reports in the literature contrary to the same [5–7,13].

We found a positive correlation between the clinical severity and long COVID presence. Previous studies [5,7,13] also emphasized this correlation. Although clinical severity is correlated with long COVID, young patients without any comorbidities and with a mild clinical course might also have persistent COVID symptoms [8]. We found similar results in the literature, with long COVID seen even in type 1 clinical severity subgroup.

Fatigue and shortness of breath have been reported to be the most frequent symptoms of long COVID [5–7,13]. In line with the literature, we encountered these two symptoms most frequently. However, unlike that in previous studies, we encountered muscle weakness frequently. Tenforde et al. [8] defined cough as one of the most frequent persisting symptoms. Unlike the other previous studies and the current study, Tenforde et al. questioned the patients after a short interval (approximately 16 days). Considering our results and the published literature, it can be suggested that cough as a persisting symptom might resolve earlier than fatigue and shortness of breath. Post-acute COVID-19 is often associated with low mood, hopelessness, heightened anxiety, and difficulty in sleeping [17]. In line with the previous reports, 4 patients with long COVID reported experiencing anxiety and 4 reported experiencing hot flushes, a symptom that can be related to anxious mood.

We found no correlation between dizziness, headache, and palpitations with any of the laboratory parameters and CT severity index. Meanwhile, we found that shortness of breath was correlated with high CRP levels, chest pain was correlated with high fibrinogen levels, and muscle weakness was correlated with low Hb levels. It can be inferred that high inflammatory activity represented by high CRP levels is the main cause of the persistence of shortness of breath. High fibrinogen levels can be correlated with the microangiopathic nature of COVID-19 [18]; hence one can conclude that severe microangiopathy in the lungs leads to persistent chest pain. Hypo hemoglobinemia is related to inflammation and is a cause of muscle weakness [19]. Persistent muscle weakness can be interpreted as the result and a direct sign of a previous severe COVID-19 disease. Females were found to be at a higher risk for persistent fatigue than males. We could not find a similar study in English literature that examined the correlation between the laboratory parameters, sex, and long COVID symptoms directly.

CT severity scoring systems were found to be effective in predicting the clinical severity of COVID-19. CT severity was associated with D-dimer and CRP levels. Moreover, both high severity on CT and anemia have been reported to be associated with a severe disease course [20–23]. In line with the previous studies, we found that CT severity values were correlated with CRP levels, D dimer values, and anemia. Furthermore, CT severity was reported to predict disease severity better than CRP and D dimer values [21]. Similarly, we found that CT severity values of long COVID patients were significantly high. In addition, high CT severity values were found to be correlated with persistent shortness of breath, chest pain, cough, and muscle weakness. We did not find any laboratory parameters to be correlated with as many persistent symptoms as the CT severity. This can be considered as the ability of CT to reflect the overall inflammatory level.

This study has some limitations. It was a single-center study with a limited number of participants. Further multicentric studies with large population sizes might show different results. Most of the patient information about long COVID was obtained by telephonic interviews; hence, the data on physical examination is lacking. Moreover, for elderly patients, completing the questionnaire was relatively difficult. Hence, we had to exclude more elderly patients than those in the younger age groups. Some chronic diseases can cause symptoms similar to long COVID. Although we specifically investigated for persistent symptoms, some false positive cases might have been included.

5. Conclusion

Many symptoms can persist several weeks after the initial COVID-19 diagnosis. The presence of persistent symptoms is related to disease severity. CRP and fibrinogen levels, anemia, and female sex were associated with some of the persistent symptoms. CT severity, being a successful predictor for the disease severity/prognosis, is also correlated to long COVID presence, and persistent symptoms are correlated more with CT severity than with laboratory parameters or sex.

Conflict of Interest

The authors have no conflicts of interest.

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