CT in every step: Long COVID

Abstract:

Background and aim: Some patients continue to experience symptoms related to COVID-19 after the acute phase of infection. Imaging studies, especially chest computerized tomography (CT), has been gaining importance from the beginning of the pandemic with its ability of diagnosing COVID-19, assessing the extent of pulmonary involvement, predicting disease severity. We intend to define the frequency of persistent symptoms and correlate the presence of persistent symptoms with laboratory findings and CT severity levels.

Methods and Materials: We tried to patients who had been discharged from the study hospital after the treatment and who had a positive nasopharyngeal swab result for SARS-CoV-2, after at least four weeks from the initial diagnosis. The patients were questioned for the presence of persisting symptoms. In addition to demographic data, laboratory results and CT severity levels were recorded.

Results: 116 patients were included into the study. 61 patients reported at least one persisting symptom (52.5%). Mean age of the population is 48.90±17.74 years. Shortness of breath, chest pain, cough, muscle weakness, dizziness, headache, fatigue, and palpitation were found as persisting symptoms. Mean CT severity score value of the population is 3.80±0.38. Mean CT severity score value is lower in patients without any persistent symptoms.

Conclusion: CRP, fibrinogen levels, anemia and female gender were associated with some of the persistent symptoms. CT severity, as being a successful predictor for disease severity/prognosis, is also related with future long COVID presence, and CT severity is related with more persistent symptoms than laboratory parameters.

Keywords: CT severity, post COVID, persistent symptom, CRP, D dimer

Short title: CT and Long COVID

Introduction:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the novel coronavirus disease (COVID-19) which was classified as a pandemic by the World Health Organization in March 2020. Since its first start in Wuhan Chine, COVID-19 has been effecting millions of people and has caused a lot of death [1].

Along with the increase in the patient number and studies concentrating on the course of the disease; persistent symptoms related with COVID-19 infection has become to be defined. According to recent studies; some patients continue to experience symptoms related to COVID-19 after the acute phase of infection. Currently, there is no consensus about the definition for the condition, neither for the spectrum of the symptoms. Terminology has included long COVID, post-acute COVID-19 syndrome, chronic COVID syndrome and long-haul COVID [2,3].

About 10% of the COVID-19 patients experience a range of symptoms that can last up to three months after initial diagnosis [4,5]. Previously defined persistent symptoms include fatigue, headaches, shortness of breath, anosmia, muscle weakness, low fever and cognitive dysfunction (brain fog) [6-9].

Imaging studies, especially chest computerized tomography (CT), has been gaining importance from the beginning of the pandemic with its ability of diagnosing COVID-19, as well as assessing the extent of pulmonary involvement, predicting disease severity / prognosis, and detecting complications [10]. Qualitative and quantitative methods for calculating CT severity index has been introduced, and CT severity values was found to be successful for predicting disease prognosis [11]. However, as far as we know, in English literature, there is not a study examining the relation with CT severity and persistent post-COVID symptoms.

In the current study, we intend to define the frequency of persistent symptoms and correlate the presence of persistent symptoms with laboratory findings and CT severity levels.

Materials and methods:

Approval for this study was granted by the Institutional Review Board. Informed consent was acquired from all of the participants and parents of the participants in pediatric cases.

We tried to contact every patient who had been discharged from the study hospital after the treatment of COVID-19, and who had a positive nasopharyngeal swab result for SARS-CoV-2, after at least four weeks from the initial diagnosis. The patients were questioned for the presence of persisting symptoms. The ones who did not have a proper CT scan (to define CT severity value) at the time of hospital admittance and did not/could not answer the questionnaire about persisting symptoms were excluded from the study. Most assessments were made by telephone by a chest disease specialist.

CT examinations at the time of hospital admittance were used to define CT severity value. CT severity of the patients were defined for each lung segments, then the sum of the severity values of each lobe were used to define a final severity score. CT severity scores were calculated by using Pan et al.'s method [12] (Table 1) (Figure 1 and 2).

White blood cell (WBC), hematocrit (Hct), hemoglobin (Hb), Platelet (Plt), Lymphocyte (Lym), Neutrophil (Neu), D dimer, Ferritin, Fibrinogen, procalcitonin (PCT), and C- reactive protein (CRP) values at the time of hospital admittance were recorded. Age and gender data were also noted.

Patients were also classified according to the clinical disease severity categorization suggested by Feng et al.[13] : (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 patients have either a high respiratory rate (≥ 30/min) or SaO2 (≤ 93%) or low oxygen partial pressure/ inspired oxygen fraction (≤ 300 mmHg) in arterial blood, and (d) type 4 patients need mechanical ventilation, have shock or organ dysfunction needing intensive care.

Statistical analysis: Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows 20 software (IBM SPSS Inc., Chicago, IL, USA). Normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Numerical variables were shown as mean± standard deviation values. Categorical variables were shown as percentages. Spearman and Pearson correlation analysis was applied to define possible correlations for CT severity values and laboratory parameters. Chi square and student's t test were used to analyze the differences about the persistent symptoms, gender and age between long COVID patients and the patients without any persistent symptoms. Logistic regression analysis was used to define the correlations between persistent COVID symptoms and age, gender, laboratory parameters, and CT severity values.

Results:

116 patients were included into the study. 61 patients reported at least one persisting symptom (61/116, 52.5%). Mean age of the population is 48.90±17.74 years (13-88 years). There were 56 males (48.3%) and 60 females (51.7%). We cannot detect any significant correlation between age, sex and persistent symptom presence ($p>0.05$). Mean interval between initial diagnosis and questionnaire for persisting symptoms is 44.3±12.4 days.

Shortness of breath, chest pain, cough, muscle weakness, dizziness, headache, fatigue, and palpitation were found as persisting symptoms. Frequency of each symptom can be seen in Table 2. In addition to the mentioned persisting symptoms, 4 patients (3.4%) told that they were feeling anxiety and 4 patients (3.4%) mentioned that they were experiencing hot flush occasionally. According to regression analysis results, persistent shortness of breath is correlated with higher CT severity index and CRP values (CT severity, OR=2.35, p=0.001; CRP, OR=3.15, p=0.013). Chest pain is correlated with higher CT severity index and fibrinogen values (CT severity, OR=1.15, p=0.04; fibrinogen, OR=3.15, p=0.04). Cough is correlated with higher CT severity index (OR=1.46, p=0.013). Muscle weakness is correlated with is correlated with higher CT severity index and lower Hb values (CT severity, OR=1.25, p=0.018; Hb, OR=2.63, p=0.001). Fatigue (OR=0.2, p=0.04) is related with female gender (OR=1.8, p=0.008). Dizziness, headache, and palpitation are not correlated either with any of the laboratory parameters or CT severity index.

Mean values of the laboratory findings can be seen in Table 3.

Distribution of the patients according to clinical severity groups can be seen in Table 4. 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. Frequency of persistent symptoms were similar for type 2 and 3 clinical severity subgroups, and significantly fewer in type 1 clinical severity subgroup (p=0.01).

Mean CT severity score value of the population is 3.80±0.38 (0-16). Mean CT severity score value is lower in patients without any persistent symptoms than the others (3.02±3.86 vs. 4.52±3.68, p=0.034). CT severity score is positively correlated with D dimer and CRP values, and it is negatively correlated with hematocrit and hemoglobin values. We could not find a significant correlation for other laboratory parameters (Table 5).

Discussion:

Persistent COVID symptoms is a relatively new subject which has been studied, lately. As far as we know, in English literature, there is limited number of studies to define persistent COVID symptoms, and there is not a similar study to examine the relation between persistent symptoms and CT severity of the patients. According to our first and preliminary results, fatigue, muscle weakness, and shortness of breath is the most frequent persistent COVID symptoms. CT severity levels of the patients is not related with presence of persistent symptoms.

In the literature, persistent COVID-19 symptoms were questioned until 90 days after the initial diagnosis [14]. In most of the studies the interval between initial diagnosis and persistent symptoms were between 30-60 days [6-8,15]. We have a median interval of 44.3 days, in line with the literature.

It is suggested that between approximately 10-20% of people with COVID-19 experienced persisting symptoms lasting longer than a month [16]. We defined an incidence of 52.5%. As we have included the patients with CT examinations, and generally patients with more severe symptoms and clinical condition were examined with CT; hence we have concentrated on the patients with more severe clinical and laboratory findings. This might have increased the frequency of long COVID cases.

Relation of age and long COVID is controversial. While Carvalho-Schneider et al. [6] defined long COVID to be associated with age (especially for patients with age 40 to 60 years); some other studies [3,14] did not mention any relationship. We could not define a significant correlation between age and long COVID presence. COVID-19 tends to affect older patients more severely; however age is not the only predictor for disease severity [17]. The contradictory results about age and long COVID might be explained via age and disease severity 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 gender and long COVID, we did not encounter any contradictory result in the literature, eighter [6-8,14].

We defined a positive correlation between clinical severity of the patients and long COVID presence. Previous studies [6,8,14] also emphasize such a relationship. Even though clinical severity is related with long COVID presence, young patients without any comorbidities, with a mild clinical course can reveal persistent COVID symptoms [9]. We found similar results with the literature, we encountered long COVID cases even in type 1 clinical severity subgroup.

Fatigue and shortness of breath are generally defined as the most frequent symptoms of long COVID cases [6-8,14]. In line with the literature, we frequently encountered these two symptoms. Different from the previous studies, we more frequently encountered muscle weakness. Tenforde et al. [9] defined cough as one of the most frequent persisting symptoms. Different from the other previous studies and the current study, Tenforde at al. questioned the patients after a shorter interval (approximately 16 days). Considering our results and the literature together, it can be suggested that, as a persisting symptom, cough might vanish quicker than fatigue and shortness of breath. Post-acute covid-19 is often associated with low mood, hopelessness, heightened anxiety, and difficulty sleeping [18]. In line with the literature, 4 patients with long COVID also emphasized that they had been experiencing anxiety and 4 patients said that they had experienced hot flushes, a symptom that can be related with anxious mood.

We could not correlate dizziness, headache, and palpitation with any of the laboratory parameters and CT severity index. Meanwhile, we showed 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 hemoglobin levels. It can be inferred that high levels of inflammation, presented with high

CRP levels, is the main cause for the persistence of shortness of breath. High fibrinogen levels can be correlated with microangiopathic nature of COVID-19 [19]; hence one can conclude that a severe level of lung microangiopathy creates a persistent chest pain. Hypo hemoglobinemia is related with inflammation and it is a cause of muscle weakness [20], persistent muscle weakness can be interpreted as the result and the direct sign of a previous severe COVID-19 disease. Also, female gender was found to increase the risk for persistent fatigue symptom. We could not find a similar study in English literature to examine the correlation between the laboratory parameters, gender and long COVID symptoms directly.

CT severity scoring systems was found to be effective in predicting COVID-19 clinical severity. CT severity was associated with D dimer and CRP levels. Also, both high CT severity results and anemia was defined to be associated with severe disease course [21-24]. In line with the literature, we found that CT severity values were correlated with CRP, D dimer values, and anemia. In addition, CT severity was suggested to predict disease severity better than CRP and D dimer values [22]. Similarly, we found that CT severity values of long COVID patients were significantly higher. In addition, higher CT severity values were found to be correlated with persistent shortness of breath, chest pain, cough, and muscle weakness. We could not define any laboratory parameters to be correlated with as much persistent symptoms as CT severity. This can be accepted as a confirmation for the power of CT in reflecting overall inflammatory level.

This study has some limitations worth to mention. As being a single center study with a limited number of participants, further multicentric studies with larger population numbers might change the results of the current study. Most of the patient visits for long COVID were made by telephone; hence physical examination data is lacking. Also, especially for elderly patients, completing the questionnaire was relatively difficult. As a result, we had do exclude elderly patients more than the younger ones.

Conclusions:

Many symptoms can persist after several weeks from the initial COVID-19 diagnosis. Presence of persistent symptom, so called long COVID, is related with disease severity. CRP, fibrinogen levels, anemia and female gender were associated with some of the persistent symptoms. CT severity, as being a successful predictor for disease severity/prognosis, is also related with future long COVID presence, and CT severity is related with more persistent symptoms than laboratory parameters or gender.

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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: Computerized tomography *Scores were defined for each lobe and the sum of the scores of the lobes constitute the total lung score* *Total score scale: 0-25*	

Table 2: Frequency of persisting 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%)

Table 3: 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

Table 4: 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 5: 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 cell ($x10^9$/L)
Plt: Platelet ($x10^9$/L)
Lym: Lymphocyte ($x10^9$/L)
Neu: Neutrophil ($x10^9$/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)

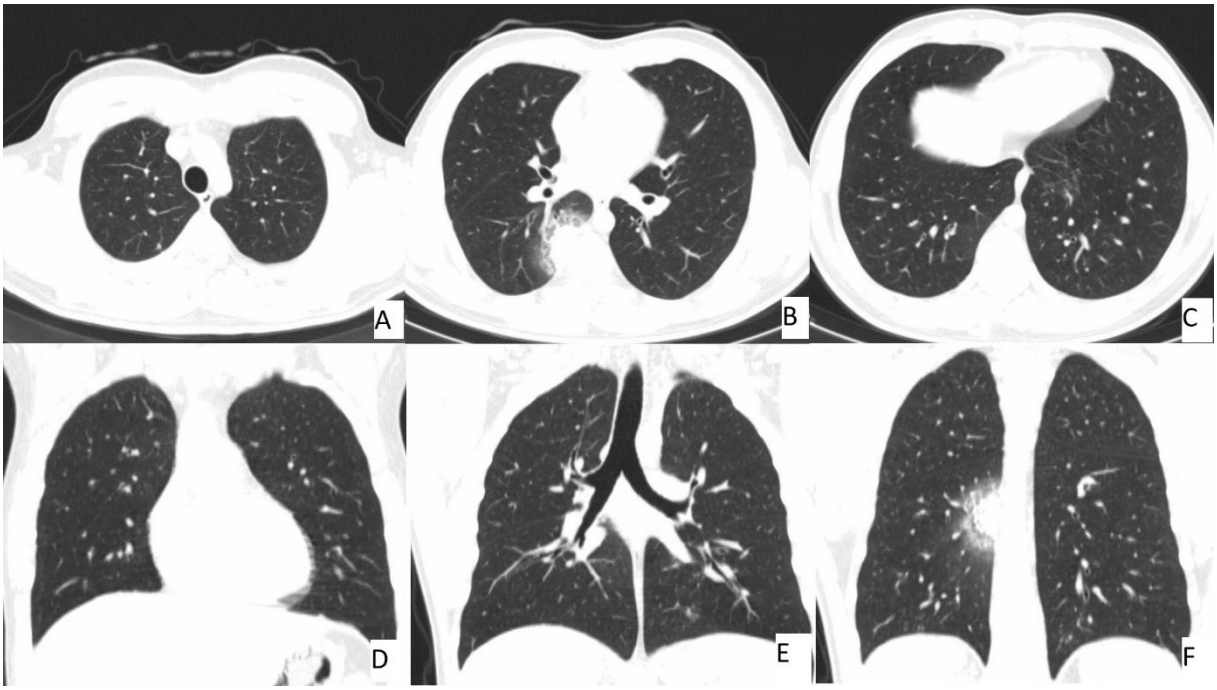

Figure 1:

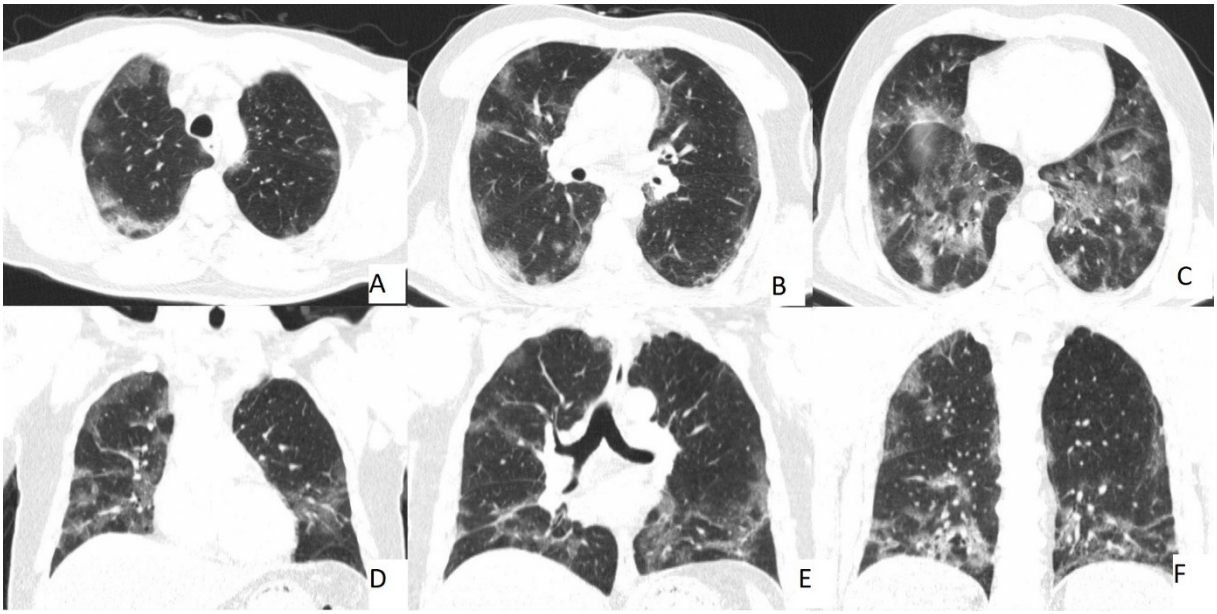

Figure 2:

Figure Captions:

Figure 1: 37- year -old man, no comorbidities. A focal infiltration, presented as halo-sign, is seen at right lower lobe, posterior segment, occupying less than 5% of the lobe (B, F). The other lobes are normal CT severity value of the case is 1.

Figure 2: 63- year-old woman. Diffuse, ground glass opacities can be seen in all of the lobes, located predominantly at peripheral zones (A-E). Ground glass opacities occupies the 5-25% of both upper lobes and right middle lobe, and 25-50% of both lower lobes. CT severity value of the case is 12.