Smyrna Tıp Dergisi ***Araştırma Makalesi***

Correlation of CT Pulmonary Inflammation Index Scores with Disease Progression and Clinical Outcome of Patients with COVID-19 Pneumonia

COVID-19 Pnömonili Hastalarda BT Pulmoner İnflamasyon İndeks Skorlarının Hastalık Progresyonu ve Klinik Sonlanım ile Korelasyonu

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Summary
Objective: Computed tomography (CT) has an important role in diagnosing and following-up COVID-19 pneumonia. Recently pulmonary inflammation index (PII) score correlated with laboratory results and disease severity, but it has not been used in a follow-up study. In this study, it was aimed to investigate the CT findings that can show disease progression and whether initial or follow-up PII scores correlate with clinical outcomes in cases with COVID-19 pneumonia.
Material and Method: On initial and follow-up chest CTs, lesion distribution, pattern, presence of pleural and pericardial effusion and mediastinal lymphadenopathy were evaluated and PII scores were calculated. Disease progression was defined as the transfer of the patients to intensive care unit or death, and regression is defined as discharge. CT findings and PII scores were compared with clinical outcomes.
Results: Seventy-three patients with a mean age of 56.95±17.8 years were included. Twenty-five (34.2%) of the patients clinically progressed and mortality rate was 9.6%. Follow-up CTs of the progressed group showed peripheral, central, diffuse, upper, middle, and lower lobe involvements, presence of consolidation, pleural and pericardial fluid and mean PII scores were significantly higher in the progressed group. The amount of mean PII score change between two CTs correlated with age, clinical progression, and mortality.
Conclusion: The progression of pneumonic infiltration to the middle-upper zones and towards the center of the lungs, diffuse involvement pattern, transformation of GGO into consolidation, pleural and pericardial effusion and the increase in PII scores indicate the progression of COVID-19 pneumonia and help to predict clinical outcome.
Key words: Computed tomography, COVID-19, pneumonia, progression, pulmonary inflammation index

Özet
Amaç: Bilgisayarlı tomografi (BT), COVID-19 pnömonisi tanı ve takibinde önemli bir role sahiptir. Son zamanlarda pulmoner inflamasyon indeksi (PII) skoru, laboratuvar sonuçları ve hastalık şiddeti ile korele bulunmakla birlikte bir takip çalışmasında kullanılmamıştır. Bu çalışmada COVID-19 pnömonisi olan vakalarda hastalığın progresyonunu gösterebilen BT bulgularını ve başlangıç veya takip PII skorlarının klinik sonuçlarla korele olup olmadığının araştırması amaçlanmaktadır.
Gereç ve Yöntem: Olguların başlangıç ve takip akciğer BT'lerinde lezyon dağılımı, paterni, plevral ve perikardiyal efüzyon varlığı ve mediastinal lenfadenopati değerlendirildi ve PII skorları hesaplandı. Hastalık progresyonu hastaların yoğun bakıma alınması veya ölümü olarak, gerileme ise taburculuk olarak tanımlandı. BT bulguları ve PII skorları klinik sonuçlarla karşılaştırıldı.
Bulgular: Çalışmaya yaş ortalaması 56.95±17.8 yıl olan 73 hasta dahil edildi. Hastaların 25'inde (%34,2) klinik olarak progresyon görüldü ve mortalite oranı %9,6 idi. Progrese olan grubun takip BT'lerinde periferik, merkezi, yaygın, üst, orta ve alt lob tutulumları görüldü. Konsolidasyon, plevral ve perikardiyal

sıvı varlığı ve ortalama PII skorları progrese olan grupta anlamlı olarak daha yüksekti. Ortalama PII skorunun değişim miktarı, yaş, klinik progresyon ve mortalite ile ilişkili bulundu.
Sonuç: Pnömonik infiltrasyonun orta-üst zonlara ve akciğerlerin merkezine doğru ilerlemesi, yaygın tutulum paterni, GGO'nun konsolidasyona dönüşmesi, plevral ve perikardiyal efüzyon ve PII skorlarındaki artış, COVID-19 pnömonisinin progresyonunu göstermekte ve klinik sonucun tahmin edilmesine yardımcı olmaktadır.
Anahtar kelimeler: Bilgisayarlı tomografi, COVID-19, pnömoni, progresyon, pulmoner inflamasyon indeksi

Kabul Tarihi: 12.Mart.2022

Introduction

COVID-19 disease is caused by a novel coronavirus (SAR-CoV-2). While most of the patients have mild symptoms, the disease can progress to severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ dysfunction and death (1). Chest computed tomography (CT) plays an important role in screening, diagnosing, and following up COVID-19 pneumonia patients (2). Various studies have been conducted to investigate how CT findings change during follow-up and they calculated the CT severity of pneumonia on basis of scoring. Although advanced methods such as artificial intelligence are used in some studies for this purpose (1), it is clear that visual quantization is much more practical and widely used as shown in most studies (3,4,5). Pulmonary inflammation index (PII) scoring established by Chongqing Radiologist Association of China provided an easy visual scoring of lung infiltrations and correlated with COVID-19 disease progression (6). There were also significant correlations found among the PII scores and the main clinical symptoms and laboratory results (7). The primary aim of this study is to investigate whether initial or follow-up PII scores correlate with clinical outcomes in cases with COVID-19 pneumonia. Secondarily it was aimed to figure out which CT findings show disease progression.

Materials and Methods

Patients
This study was performed in accordance with the Helsinki declaration. It was approved by the Turkish Ministry of Health and Institutional Review Board (the decision date/number of approval:18.06.2020/776). The informed consent form was waived because of its retrospective nature. The hospital information system was reviewed retrospectively using the ICD-10 diagnosis code for Covid-19 infection. Patients aged ≥ 18-years and hospitalized with a definite diagnosis of Covid-19 pneumonia with at least one positive RT-PCR result were identified. Among these patients, those who had initial and follow-up thoracic CT examinations in the radiology picture archiving and communication system (PACS) were included.

CT imaging and Evaluation
Thoracic CT scans were performed on a multi-slice CT device (Somatom Definition AS 128 slice, Siemens Medical Systems, Erlangen, Germany) with the patient in the supine position during breath-holding at inspiration, without administration of contrast material. Images were obtained with 120 kVp and adaptive tube current with a slice thickness of 2 mm. The images were viewed in lung window settings (width, 1000–1500 HU; level, 550-570 HU) and mediastinal window settings (width, 350–360 HU; level, 50–55 HU). Images were blindly evaluated on the PACS monitor by a single radiologist (SK) with 10 years of experience in thoracic radiology. The presence of pneumonic infiltration findings in the lung parenchyma and imaging features according to the Fleischner Community glossary of terms for thoracic imaging [ground glass opacity (GGO), consolidation, interstitial thickening, crazy paving pattern, reverse halo finding, cavitation, tree in bud finding, mediastinal lymphadenopathy, pleural fluid, pericardial fluid] were evaluated (8). The distribution of infiltrations was defined as being peripheral (involving peripheral one third of the lungs), central (involving central two thirds of the lungs), and diffuse (both peripheral and central). Lung areas were divided into three zones: The upper zone (above the carina), the middle zone (from the carina to the inferior pulmonary vein), and the lower zone (below the inferior pulmonary vein). The scores of the pulmonary inflammation index (PII) defined in the literature were calculated by using PII = (distribution score + size score)/40 x 100% formula. Distribution score was done by scoring the distribution of

GGO or consolidation, one score for each lung segment and totally 20 scores for both lungs. Dimension scoring was done by measuring the maximum diameter of the dominant lesion and the lung parenchyma in the same slice and giving one score if the lesion occupied ≥50% of the segment, and zero if it occupied <50% of the segment (7). Disease progression was defined as the transfer of the patients to intensive care unit or death, and regression is defined as discharge. By comparing the changes between the initial and follow-up CT findings with the clinical outcomes of the patients, it was investigated which finding was associated with disease progression.

Statistical Analysis

Statistical analysis was performed with SPSS (Statistical Packages for the Social Sciences) Software version 24.0 (Chicago, IL, USA). For discrete variables, number and ratio were used for descriptive statistics. For continuous variables with normal distribution, standard deviation was preferred. For continuous variables with non-normal distribution, interquartile range was utilized. Chi-square and McNemar's test were used to compare the groups involving discrete variables. Wilcoxon signed rank test was used for continuous variables. Spearman correlation test was applied to investigate the strength of the association of the statistically significant differences between the groups. $p<0.05$ was accepted as statistically significant.

Results

There were 427 patients with COVID 19 pneumonia. Seventy-three of them (45 men and 28 women) having both initial and follow-up CTs were included in the study. A total of 146 chest CT scans were acquired. The mean age was 56.95±17.8 years. Twenty-five (34.2%) of the patients clinically progressed and mortality rate was 9.6% (7 patients). Forty-eight patients recovered without any progression and could be discharged. The median follow-up time between two CT examinations was 13.3 days (range: 3-55 days). The demographic features of the patients are listed in Table 1.

Table 1. *Demographic features of patients*

	Progressed	**Non-Progressed**	**Total**	**p value**
Age (year) (mean± SD)	59.5±17.5	55.6±18	56.95±17.8	0,377
Gender (female) n (%)	10 (40)	18 (37.5)	28 (38.4)	0,728
Follow-up time (days) (mean± SD)	14.5±14.7	12.7±10.6	13.32±12.1	0,740
Need for intensive care unit stay n (%)	15 (60)	0 (0)	15 (20.5)	**0,002**
Mortality n (%)	7 (28)	0 (0)	7 (9.6)	**0,000**

There was no significant difference between the mean PII scores of initial (27,5±16,7%) and follow-up (29.6±21.9%) CTs of the non-progressed patients (p=0.236), but a significant difference was found between the mean PII scores of initial (32±25.3%) and follow-up (48.6±27.8%) CTs of the progressed patients (p=0.004). The amount of mean PII score changes between the initial and the follow up CTs was 2.14±13.32 in the non-progressed group and it was 16.6±24.33 in the progressed group and this finding was also statistically significant (p=0.012). The amount of mean PII score changes between initial and follow-up CTs was significantly positively correlated with age (p=0.03), clinical progression (p=0.011) and mortality (p=0.024) and negatively correlated with follow-up duration (p=0.008) and discharge (p=0.043). Pneumonic infiltration findings completely disappeared in 12.5% (6/48) of the follow-up CTs of the non-progressed group (p=0.031). Marked regression in the number and densities of initial patchy GGO infiltrations on the follow-up CT is shown in Fig. 1.

In clinically progressed group, central pneumonic involvement was added to peripheral involvement, patchy infiltrations turned into diffuse form and ground glass opacities transformed to mostly consolidation and to a lesser extent, linear opacities, and interstitial thickening (Fig. 2).

In the initial chest CTs, radiological findings including lower zone predominant peripheral, multifocal GGO were similar between two groups, except patchy infiltrations being significantly more frequent in the non-progressed

group (p=0.048). In the follow-up CTs, peripheral, central, diffuse, upper, middle, and lower lobe involvements, presence of consolidation (Fig.3), pleural and pericardial fluid were significantly higher in the progressed group.

Figure 1. *(a) Chest CT images of a 60-years old non-progressed male patient. On initial CT multifocal, peripheral, and lower zone predominant patchy GGO were seen and the PII score was 45%. (b) On follow-up CT, which was obtained 15 days later, the lung opacities were almost completely absorbed with a decrease in density and the PII score regressed to 15%.*

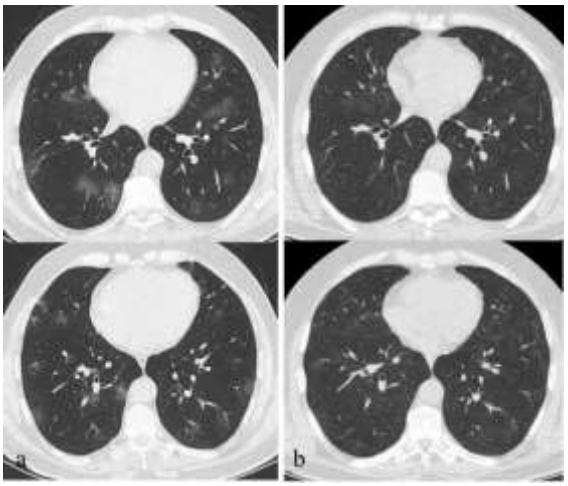


Figure 2. (a) *Chest CT images of a 56-years old progressed male patient. On initial CT there was a peripheral GGO with focal consolidation in the lateral segment of the middle lobe (arrow) and the PII score was 2,5%. (b) Ten days later he was transferred to the intensive care unit and a follow-up CT was obtained. It showed a prominent increase in lung opacities progressing towards centrally and upper zones in a diffuse pattern. Increased GGO and consolidation areas, mild traction* bronchiectasis (thin arrows) and linear opacities in lower zones (arrowheads) appeared and PII score progressed to 47,5%

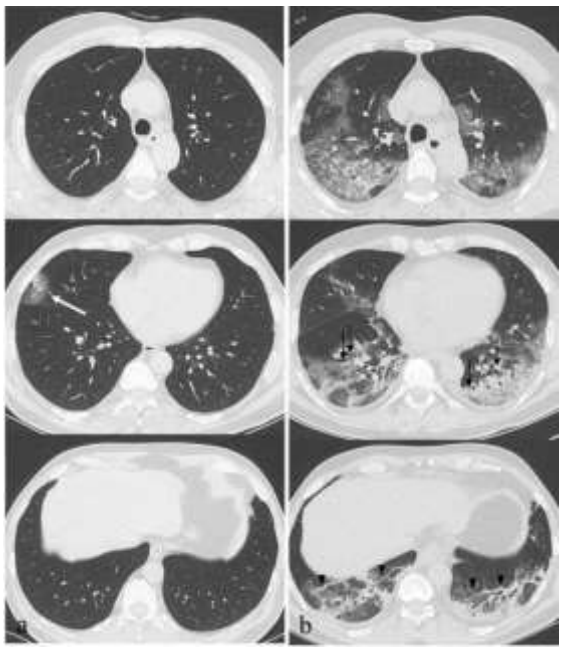
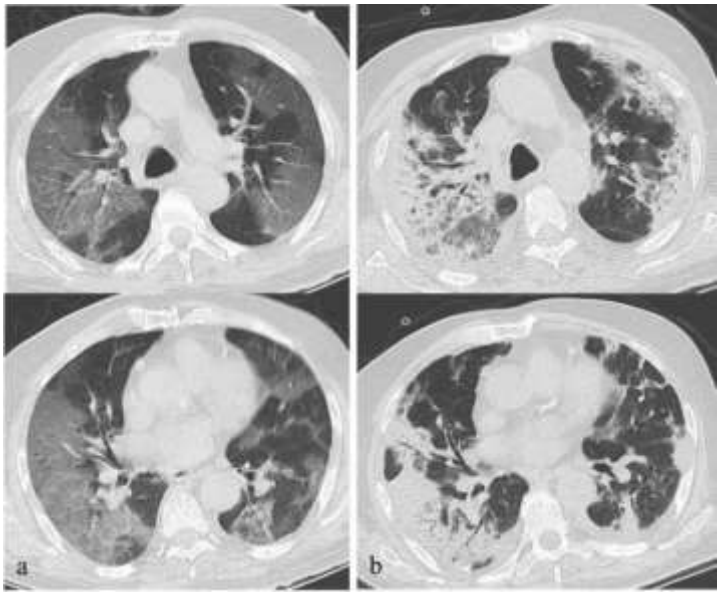


Figure 3. *(a) Chest CT images of a 79-years old progressed male patient who died on the 18th day of admission. On initial CT multifocal, peripheral diffuse GGO were seen and the PII score was 40%. (b) Twelve days later he was transferred to the intensive care unit and a follow-up CT was obtained which showed the transformation of GGO into consolidation and the PII score was 60%*



Pulmonary inflammation index scores were also significantly higher in follow-up CTs of progressed group both compared to own initial CT scores (p=0.004) and to follow-up CT scores of the non-progressed group (p=0.004). Linear opacities significantly increased in the follow-up CTs of both non-progressed (p=0.000) and progressed (p=0.012) groups compared to baseline, but no significant difference was found between the groups. Interstitial thickening was significantly seen in a higher rate in follow-up CTs of non-progressed group (p=0.031), but it did not show a significant difference between two groups. Crazy-paving, reversed halo sign, tree-in-bud sign and lymphadenopathy were rare and not significantly different in progressed group compared to non-progressed one. The initial and follow-up CT findings of the progressed and the non-progressed patient groups are listed in Table 2.

Comparison of initial and follow-up CT findings between two groups are shown in Table 3.

Discussion

Typical chest CT findings of Covid-19 pneumonia have been described as bilateral, multifocal, patchy GGO, consolidation, crazy-paving pattern with predominantly peripheral posterior and lower distribution (9,10,11). In the study similar findings were identified on initial CTs of both progressed and non-progressed patient groups. Patchy involvement was significantly more common on the initial CTs of the non-progressed group, and we think that the reason for this was the higher diffuse distribution tendency in the progressed group.

In a recent study, the appropriate CT follow-up time was recommended as approximately 12 days in progressed patients and 36 days in remission (12). In this study the median follow-up time between two CT scans was 13.3 days (12.7±10.6 days in non-progressed group, 14.5±14.7 days in progressed group). The aim of keeping the CT follow-up time shorter in the non-progressed group was to see the pneumonia resolution that would support clinical recovery and to make the decision of discharge. Lei et al. (13) stated that COVID-19 pneumonia had a typical transition from early stage with single or multiple GGO to advanced stage with consolidations and finally to dissipating stage with absorption of infiltrations. Similar studies about the temporal changes of CT findings of COVID-19 pneumonia showed that lung infiltrates rapidly changed over time (14) and the peak radiologic stage of the disease was defined between 5 and 11 days after the onset of symptoms (4, 15).

Table 2. *Initial and follow-up CT findings of progressed and non-progressed patients*

	Initial CT findings				**Follow-up CT findings**			
	Progressed n (%)	**Non-progressed n (%)**	**Total n (%)**	**p value**	**Progressed n (%)**	**Non-progressed n (%)**	**Total n (%)**	**p value**
Pneumonia	25 (100.0)	48 (100.0)	73(100.0)	1,000	25 (100.0)	42 (87.5)	67 (91.8)	0,067
Peripheral	25 (100.0)	47 (97.9)	72 (98.6)	0,470	25 (100.0)	41 (85.4)	66 (90.4)	**0,046**
Central	7 (28)	7 (14.6)	14 (19.2)	0,170	14 (56.0)	11 (22.9)	25 (34.2)	**0,005**
Patchy	23 (92.0)	48 (100.0)	71 (97.3)	**0,048**	22 (88.0)	41 (85.4)	63 (86.3)	0,762
Diffuse	9 (36.0)	8 (16.7)	17 (23.3)	0,066	19 (76.0)	18 (37.5)	37 (50.7)	**0,002**
Upper zone	14 (56.0)	29 (60.4)	43 (58.9)	0,718	20 (80.0)	25 (52.1)	45 (61.6)	**0,021**
Middle zone	15 (60.0)	37 (77.1)	52 (71.2)	0,129	22 (88.0)	31 (64.6)	53 (72.6)	**0,035**
Lower zone	24 (96.0)	43 (89.6)	67 (91.8)	0,347	25 (100.0)	38 (79.2)	63 (86.3)	**0,015**
Single lesion	2 (8.0)	6 (12.5)	8 (11.0)	0,562	1 (4.0)	3 (6.3)	4 (5.5)	0,691
Multiple lesions	23 (92.0)	43 (89.6)	66 (90.4)	0,741	24 (96.0)	39 (81.3)	63 (86.3)	0,084
GGO[#]	24 (96.0)	45 (93.8)	69 (94.5)	0,691	14 (56.0)	33 (68.8)	47 (64.4)	0,284
Consolidation	10 (40.0)	17 (35.4)	27 (37.0)	0,702	20 (80.0)	25 (52.1)	45 (61.6)	**0,021**
Interstitial thickening	3 (12.0)	6 (12.5)	9 (12.3)	0,951	7 (28.0)	16 (33.3)	23 (31.5)	0,644
Crazy paving	2 (8.0)	8 (16.7)	10 (13.7)	0,310	4 (16.0)	11 (22.9)	15 (20.5)	0,491
Reversed halo sign	0 (0.0)	1 (2.1)	1 (1.4)	0,470	0 (0.0)	2 (4.2)	2 (2.7)	0,304
Tree-in-bud sign	0 (0.0)	2 (4.2)	2 (2.7)	0,304	0 (0.0)	2 (4.2)	2 (2.7)	0,384
Linear opacity	1 (4.0)	3 (6.3)	4 (5.5)	0,691	10 (40.0)	19 (39.6)	29 (39.7)	0,973
LAP[##]	3 (12.0)	4 (8.3)	7 (9.6)	0,616	3 (12.0)	4 (8.3)	7 (9.6)	0,616
Pleural fluid	3 (12.0)	1 (2.1)	4 (5.5)	0,079	8 (32.0)	3 (6.3)	11 (15.1)	**0,004**
Pericardial fluid	0 (0.0)	0 (0.0)	0 (0)	1,000	3 (12.0)	0 (0.0)	3 (4.1)	**0,015**
PII* score (mean± SD**)	32±25.3	27.5±16.7	29±20	0,731	48.6±27.8	29.6±21.9	36.1±25.6	**0,004**

*#GGO: ground glass opacity, ##LAP: lymphadenopathy, *PII: pulmonary inflammation index, **SD: standard deviation*

Subpleural GGO on initial CTs turned to consolidation and subpleural parenchymal bands in two weeks (2). These data all seem to show the natural course of the disease. Linear opacities were previously thought to be compatible with fibrosis developing with absorption of inflammation and were seen more commonly in second CTs of non-progressive patients (15). In the presented study linear opacities significantly increased in the follow-up CTs of both groups compared to baseline, but no significant difference was found between the groups.

Although being a relatively rare finding, pleural effusion shows higher incidences among severe and critical patients of COVID-19 pneumonia (11,16). Pericardial effusion is also an uncommon finding (17). In an echocardiography study, it was found that pericardial effusion was associated with disease progression (18). Pleural and pericardial fluid was significantly higher in the follow-up CTs of the progressed group compared to initial CTs and it was correlated with the literature data.

In various studies the extent of lung involvements was calculated by using similar CT scoring systems based on visual quantification. All of them used 3-6-point scoring for the percentage area of lung opacities (3,5,16,19,20), one of them measured the lesion diameters (3) and the other one added a scoring based on the density of opacities (5) but these scoring systems are seem to be somewhat complicated as they include many grading steps. However, the results of these studies regarding disease progression or death are quite important. Ruch et al. (3) concluded that more than 50% lung involvement was significantly associated with early severe disease. In progressed patient groups extensive and diffuse distribution of lesions,

persistence of GGO, consolidation, air bronchogram, crazy-paving appearance, pleural effusion and high progressive CT scores were associated with disease progression or death (5, 16, 19, 20). In a multi-center cohort study of lung segmentation with artificial intelligence, it is found that larger areas of consolidation in upper lung zones on admission increased the risk of poor outcome in patients with COVID-19 (21).

Table 3. *Comparison of initial and follow-up CT findings between the progressed and non-progressed patient groups*

	Progressed Group			**Non-progressed Group**		
	Initial CT n (%)	**Follow-up CT n (%)**	**p value**	**Initial CT n (%)**	**Follow-up CT n (%)**	**p value**
Pneumonia	25 (100.0)	25 (100.0)	1.000	48 (100.0)	42 (87.5)	**0.031**
Peripheral	25 (100.0)	25 (100.0)	1.000	47 (97.9)	41 (85.4)	0.676
Central	7 (28.)	14 (56.0)	**0.006**	7 (14.6)	11 (22.9)	**0.000**
Patchy	23 (92.0)	22 (88.0)	0.085	48 (100.0)	41 (85.4)	**0.016**
Diffuse	9 (36.0)	19 (76.0)	**0.035**	8 (16.7)	18 (37.5)	**0.016**
Upper zone	14 (56.0)	20 (80.0)	0.420	29 (60.4)	25 (52.1)	**0.000**
Middle zone	15 (60.0)	22 (88.0)	**0.024**	37 (77.1)	31 (64.6)	**0.000**
Lower zone	24 (96.0)	25 (100.0)	1.000	43 (89.6)	38 (79.2)	**0.000**
Single lesion	2 (8.0)	1 (4.0)	1.000	6 (12.5)	3 (6.3)	**0.038**
Multiple lesions	23 (92.0)	24 (96.0)	0.763	43 (89.6)	39 (81.3)	**0.013**
GGO[#]	24 (96.0)	14 (56.0)	**0.002**	45 (93.8)	33 (68.8)	0.172
Consolidation	10 (40.0)	20 (80.0)	**0.013**	17 (35.4)	25 (52.1)	0.489
Interstitial thickening	3 (12.0)	7 (28.0)	0.826	6 (12.5)	16 (33.3)	**0.031**
Crazy paving	2 (8.0)	4 (16.0)	0.688	8 (16.7)	11 (22.9)	0.878
Reversed halo sign	0 (0.0)	0 (0.0)	X	1 (2.1)	2 (4.2)	1.000
Tree-in-bud sign	0 (0.0)	0 (0.0)	X	2 (4.2)	2 (4.2)	1.000
Linear opacity	1 (4.0)	10 (40.0)	**0.012**	3 (6.3)	19 (39.6)	**0.000**
LAP[##]	3 (12.0)	3 (12.0)	1.000	4 (8.3)	4 (8.3)	1.000
Pleural fluid	3 (12.0)	8 (32.0)	0.063	1 (2.1)	3 (6.3)	0.500
Pericardial fluid	0 (0.0)	3 (12.0)	0.250	0 (0.0)	0 (0.0)	x
PII* score (mean± SD**) ***	32±25.3	48.6±27.8	**0.004**	27.5±16.7	29.6±21.9	0.236

*#GGO: ground glass opacity, ##LAP: lymphadenopathy, *PII: pulmonary inflammation index, **SD: standard deviation, x: p value could not be calculated, ***Wilcoxon signed rank test was used.*

In the study the follow-up CTs of the progressed group showed increased central infiltrations besides peripheral involvement persistency and opacities spread towards the middle and upper zones of the lungs, the involvement pattern transformed from patchy to diffuse distribution and GGO mainly turned into consolidation. These findings were similar with literature data. Pulmonary inflammation index (PII) scoring was established by Chongqing Radiologist Association of China and used to quantify the chest CT findings of patients with mild and severe COVID-19 pneumonia. They found the mean PII score 13.7% in the mild and 58% in the severe group and concluded that a score between 20% and 50% might require close monitoring for the development of severe pneumonia (6). But the temporal change of PII score over time was not investigated in this study. In our study we had follow-up CT scans and we found a significant difference between the mean PII scores of initial (32±25.3%) and follow-up (48.6±27.8%) CTs of the progressed patients (p=0.004). Follow-up CT scans may be useful for the patient group with PII scores between 20-50%. Significant increase in their PII scores compared to the baseline may indicate a poor clinical course. Another study by Wu J et al. (7) showed that PII was significantly correlated with clinical and laboratory findings such as body temperature, lymphocyte and monocyte counts, C-reactive protein and procalcitonin but they did not mention if it could be used as a predictive parameter for clinical outcome and they did not have follow-up imaging studies.

Finally, there were some limitations to this study. First the number of patients included in the study was small. Second, we only followed the patients during their hospitalization, and we did not

include the data of those who were followed-up after discharge. Third we could not investigate dynamic CT changes in different stages. Last, we did not evaluate clinical data and associated comorbidities that could indicate disease progression. We think that PII should be evaluated in larger patient series in long-term follow-up and should be compared with clinical data to better elucidate its value in showing disease progression.

In conclusion, the progression of pneumonic infiltration to the middle-upper zones and towards the center of the lungs, diffuse involvement pattern, transformation of GGO into consolidation, pleural and pericardial effusion, and the increase in PII scores indicate the progression of COVID-19 disease and help to predict clinical outcome.

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