Diagn Interv Radiol 2023; DOI: 10.5152/dir.2022.211090

CHEST IMAGING

ORIGINAL ARTICLE

Long-term lung perfusion changes related to COVID-19: a dual energy computed tomography study

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PURPOSE

Although the findings of acute new coronavirus disease (COVID-19) infection on dual-energy computed tomography (DECT) have recently been defined, the long-term changes in lung perfusion associated with COVID-19 pneumonia have not yet been clarified. We aimed to examine the long-term course of lung perfusion in COVID-19 pneumonia cases using DECT and to compare changes in lung perfusion to clinical and laboratory findings.

METHODS

On initial and follow-up DECT scans, the presence and extent of perfusion deficit (PD) and parenchymal changes were assessed. The associations between PD presence and laboratory parameters, initial DECT severity score, and symptoms were evaluated.

RESULTS

The study population included 18 females and 26 males with an average age of 61.32 ± 11.3 years. Follow-up DECT examinations were performed after the mean of 83.12 ± 7.1 (80–94 days) days. PDs were detected on the follow-up DECT scans of 16 (36.3%) patients. These 16 patients also had ground-glass parenchymal lesions on the follow-up DECT scans. Patients with persistent lung PDs had significantly higher mean initial D-dimer, fibrinogen, and C-reactive protein values than patients without PDs. Patients with persistent PDs also had significantly higher rates of persistent symptoms.

CONCLUSION

Ground-glass opacities and lung PDs associated with COVID-19 pneumonia can persist for up to 80–90 days. Dual-energy computed tomography can be used to reveal long-term parenchymal and perfusion changes. Persistent PDs are commonly seen together with persistent COVID-19 symptoms.

KEYWORDS

DECT, COVID-19, follow-up, perfusion deficit, lung

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Received 14 October 2021; revision requested 15 November 2021; last revision received 15 February 2022; accepted 16 March 2022.

Epub: 23.01.2023

Publication date: 31.01.2023

DOI: 10.5152/dir.2022.211090

The novel coronavirus disease (COVID-19) is caused by coronavirus 2 that results in severe acute respiratory syndrome. In March 2020, the World Health Organization declared it a pandemic. Since the first cases were reported in Wuhan, China, COVID-19 has infected millions of people and killed thousands.[1]

A diagnosis of COVID-19 has been associated with both systemic coagulation abnormalities and microangiopathy. In COVID-19 patients, D-dimer and fibrinogen degradation product levels can be elevated, and these elevated levels have been associated with poor prognoses. Vasculopathy is more prevalent in the vessels of the lungs.[2] In COVID-19, the rate of pulmonary embolism (PE) is increased (20.6%–40%), and the presence of PE is associated with a severe disease course.[3,4] In comparison to standard computed tomography (CT) pulmonary angiography, dual-energy computed tomography (DECT) can provide sufficient diagnostic

You may cite this article as: Aydın S, Karavaş E, Ünver E, Şenbil DC, Kantarcı M. Long-term lung perfusion changes related to COVID-19: a dual energy computed tomography study. *Diagn Interv Radiol.* 2023;29(1):103-108.

information about the presence of PE and lung perfusion in a single session without increasing the radiation dose. A sufficient consistency between perfusion on DECT and scintigraphy has also been shown.[5,6] Additionally, DECT has recently proven to be effective in detecting changes in lung perfusion in patients with COVID-19 pneumonia who do not have PE.[7-9]

Endotheliitis-induced pulmonary microvascular damage and occlusion/vasoconstriction has previously been defined as the primary cause of perfusion deficit (PD) in COVID-19 pneumonia, particularly parenchyma, which is commonly observed.[7,10] PD can also occur in opacified-lung parenchyma due to a degraded ventilation–perfusion (V/Q) ratio. Previously, severe V/Q mismatches were defined in COVID-19 pneumonia cases.[11,12]

Although the DECT findings of acute COVID-19 infection have recently been defined,[7,9,13,14] the long-term changes in lung perfusion associated with COVID-19 pneumonia have yet to be clarified. The current study sought to investigate the long-term course of lung perfusion in COVID-19 pneumonia cases using DECT, as well as to correlate changes in lung perfusion with clinical and laboratory findings.

Methods

The Institutional Review Board of Erzincan Binali Yıldırım University approved this retrospective study (protocol number: KAEK-EBYU-2020/03/11). Due to the retrospective nature of this study, informed consent was waived.

Between July 2020 and January 2021, patients with a positive reverse transcription polymerase chain reaction (RT-PCR) result for COVID-19 were examined. Patients with two DECT scans with a minimum interval of three weeks were included in the study. Patients with non-contrast enhanced CT scans, mono-energy CT scans, low-quality DECT scans, insufficient clinical/laboratory data, or pulmonary comorbidities were excluded (five patients). In addition, patients diagnosed with pneumonia in the second DECT examination were also excluded (two patients). Subsequently, a total of 44 patients were enrolled in the study.

Main points

- The presence of ground-glass opacities and lung perfusion deficits (PDs) of coronavirus disease-2019 (COVID-19) pneumonia can continue for as long as 80–90 days.
- Dual-energy computed tomography can be used to reveal both long-term parenchymal and perfusion changes.
- Computed tomography severity values, D-dimer, and C-reactive protein levels can be useful in predicting future persistent PD presence.
- Persistent PDs are commonly observed along with persistent COVID-19 symptoms.

Data on age and gender were gathered. At the time of the first and second DECT scans, D-dimer, white blood cell, platelet, lymphocyte, neutrophil, fibrinogen, and C-reactive protein (CRP) levels were measured. (± 2 days before/after DECT scans). At the time of the first and second DECT scans, the patients' symptoms were also recorded.

The CT severity scores of the patients were calculated and recorded at the time of COVID-19 diagnosis using the Pan et al.[15] method (Table 1).

The DECT examinations were performed with a third-generation device (Somatom Force, Siemens Healthineers, Erlangen, Germany). Intravenous administration of 50–60 mL iohexol (rate = 4.0 mL/s) through the antecubital vein was followed by a 40-mL saline bolus. Following the acquisition of scouts, imaging was performed in the supine position, scanning in the cranio-caudal direction with the following parameters: 80/140 Sn kVp, 60 mAs, rotation time 0.33 s. Slice thickness was 1.5 mm. Image reconstruction was performed in the axial, coronal, and sagittal planes.

On a workstation, the DECT images were evaluated (Syngo.via, Siemens Healthineers, Erlangen, Germany). Two radiologists evaluated the images and clinical data blind. A third radiologist's opinion was sought in cases where the two radiologists disagreed, and consensus was reached. Images of perfusion blood volume (PBV) were used to detect PD.

Along with PBV images, iodine maps were generated. The ground-glass opacities' (GGO) and consolidations' iodine uptake values were determined by placing region-of-interest (ROI) circles on the iodine maps. Three ROI circles were placed on the lesions, and the final value was calculated as the mean of the three measurements.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) for Windows 20 software was used to analyze the data (IBM SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to determine whether the data conformed to a normal distribution. Numerical variables with a normal distribution were represented as mean ± standard deviation values, and categorical variables as numbers (n) and percentage values (%). The Student's t-test was used to compare patients with and without persistent lung perfusion. To define cutoff values for the prediction of future PDs, receiver-operating-characteristic (ROC) analysis was used. The chi-square test was used to compare two groups of categorical variables. Interobserver agreement was assessed using categorical correlation analysis (Cohen kappa values).

Statistical significance was defined as a two-tailed value of $P < 0.050$.

Results

The study population included 18 females (40.9%) and 26 males (59%) with an average age of 61.32 ± 11.3 years (range, 22–87 years).

On the initial DECT examinations performed within one week of a positive RT-PCR result for COVID-19, all of the patients had PDs. All of the PDs were found near parenchymal pneumonia lesions.

Follow-up DECT examinations were performed at mean of 83.12 ± 7.1 days (range: 80–94 days) after the initial DECT scan. No PDs were detected on the follow-up DECT examination of 28 (63.6%) patients (Figures 1-4). Of these 28 patients, ground-glass parenchymal lesions (regressed in comparison with the initial CT scans) were determined in 4 patients

Table 1. CT severity scoring

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

Each lobe was assigned a score, and the sum of the lobe scores equals the total lung score.
Scale of total points: 0–25. CT, computed tomography.

on the follow-up DECT scans, and the other 24 patients had normal lung parenchyma.

PDs were determined on the follow-up DECT scans of 16 (36.3%) patients (Figures 5-8). All 16 patients also had ground-glass parenchymal lesions on the follow-up DECT scans. Of these 16 patients, the ground-glass parenchymal lesions and PDs were seen to be regressed in comparison with the initial CT scans in 15 cases. Only one patient (an 87-year-old female, finally diagnosed as non-specific interstitial pneumonia after COVID-19 infection) was seen to have progression of the ground-glass parenchymal lesions and PDs. In all patients, parenchymal abnormalities involved the same lung regions where PDs were detected.

Interobserver agreement for PD presence and change was strong (κ values of 0.86 and 0.84, respectively).

The laboratory data and symptoms of the patients were compared based on the presence of persistent PDs. Patients with persistent lung PDs had a significantly higher mean age than patients without PDs (72.13 ± 8.9 years vs. 60.8 ± 10.3 years, $P < 0.001$). There was no gender difference in the presence of persistent lung PDs ($P = 0.105$). Patients with persistent lung PDs had significantly higher initial mean D-dimer, fibrinogen, and CRP values than patients without PDs. Patients with persistent lung PDs had significantly higher mean CT severity scores at the time of COVID-19 diagnosis (Table 2). According to the ROC analysis, D-dimer and CRP levels were the best predictors of a future persistent PD. Measures of D-dimer, CRP, CT severity scoring, and fibrinogen had area-under-the-curve values with 95% confidence intervals (CIs) of 0.725 (0.67–0.78, 95% CI), 0.693 (0.635–0.751, 95% CI), 0.587 (0.526–0.648, 95% CI), and 0.522 (0.457–0.587, 95% CI), respectively (Figure 9, Table 3).

A D-dimer value >1,315 was determined to predict persistent PD presence with a sensitivity of 87.5% and specificity of 100%. A CRP value >92 was seen to predict persistent PD presence with sensitivity of 75% and specificity of 100%.

Patients with persistent lung PDs had significantly higher mean CRP and D-dimer values at PF.

Dyspnea, coughing, and fatigue were observed as persistent symptoms in the interval between the two DECT examinations. Patients with persistent PDs had significantly higher rates of persistent symptoms (Table 4). Dyspnea was not found in any of the patients who did not have persistent PDs. Coughing was present in only two patients without PDs, and both of these two patients were determined to have GGOs that had regressed but still persisted in the second DECT examination.

Consolidations derived from iodine uptake maps had a higher mean Hounsfield Unit value than GGOs (–91.11 ± –8.61 vs. –573.9 ± –100.7, respectively).

All patients were given 6,000 anti-Xa IU/0.6 mL enoxaparin in accordance with the Turkish Ministry of Health's treatment guidelines after initial diagnosis. None of the patients had a history of being admitted to the intensive care unit due to COVID-19.

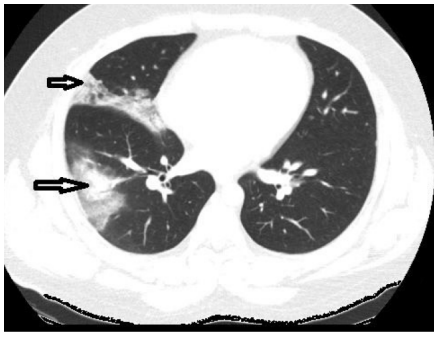


Figure 1. Thirty-two-year-old male. Initial dual-energy computed tomography image. Consolidations (arrows) are present.

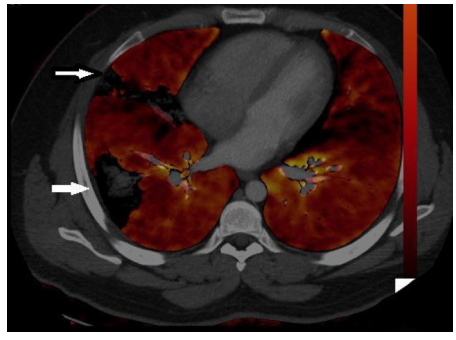
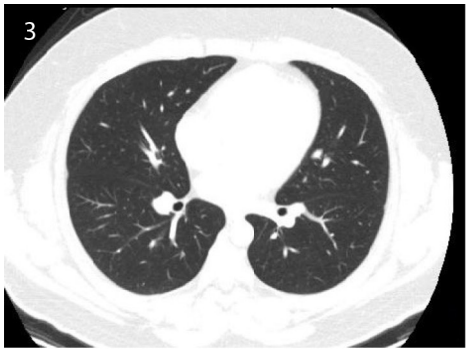


Figure 2. The same patient as in **Figure 1.** Initial dual-energy computed tomography images. Consolidation-related perfusion deficits are observed (arrows).



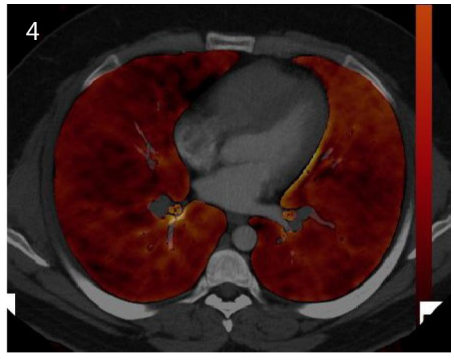


Figure 3, 4. Follow-up (after 87 days) dual-energy computed tomography (DECT) images of the same patient as in Figures 1 and 2. Follow-up DECT scan reveals no parenchymal (**Figure 3)** or perfusion (**Figure 4)** abnormality.

Discussion

The findings of this study show that lung perfusion abnormalities caused by COVID-19 pneumonia can last for up to two to three months. Persistent PDs are associated with laboratory markers and persistent symptoms.

As the number of patients with COVID-19 infections has grown, and research has focused on the disease's progression, the symptoms that persist after infection have now been identified. It has been found that 10% of COVID-19 patients experience a variety of symptoms that can last for up to three months following the initial diagnosis.[16,17]

Research has shown DECT to be effective at detecting small PEs that are missed by conventional CT angiography, as well as parenchymal PDs.[18] Although a number of recent studies have defined the changes in lung perfusion associated with COVID-19 pneumonia,[8,9] to our knowledge, no study in English literature has examined long-term lung perfusion changes in COVID-19 cases treated with DECT during follow-up.

The absorption stage of GGOs of COVID-19 pneumonia can last for as long as one month after the initial diagnosis,[19] and although at a smaller prevalence, GGOs may be detected up to 100 days after the initial diagnosis.[20] Similar to findings in the literature, GGOs were determined after a mean of 83 days in the current study. These persistent GGOs were mostly accompanied by persistent PDs. GGOs and PDs had generally regressed by the time of the follow-up examinations with the exception of one patient who was eventually diagnosed with interstitial lung disease. Regression of lung manifestations of COVID-19 is a known and expected enti-

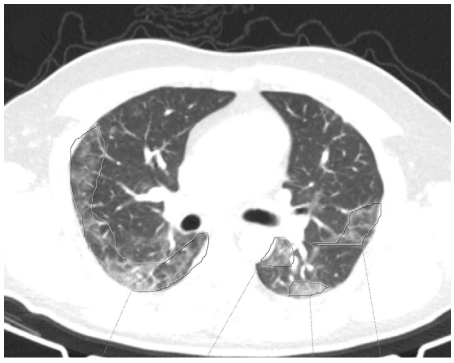


Figure 5. Fifty-year-old male. Initial dual-energy computed tomography images. Ground-glass opacities (arrows) are marked.

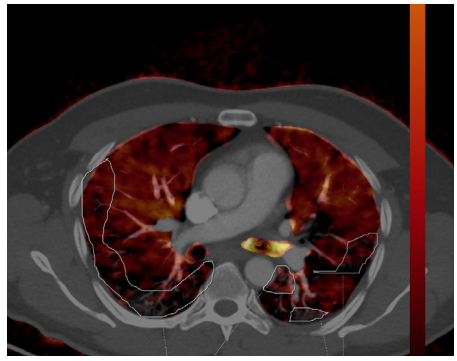
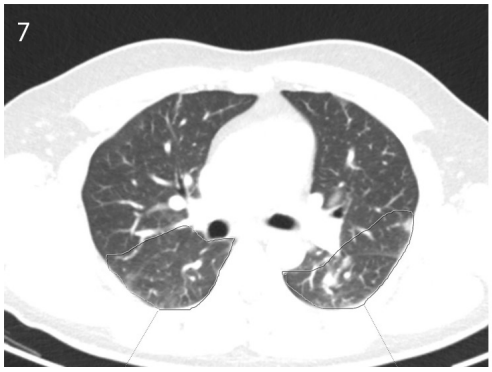
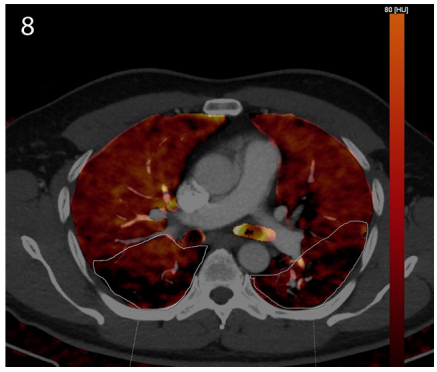


Figure 6. The same patient as in **Figure 5.** Initial dual-energy computed tomography images. Consolidation-related perfusion deficits are marked.





Figures 7, 8. Follow-up (after 81 days) dual-energy computed tomography images of the same patient as in Figures 5 and 6. The regressed parenchymal opacities (**Figure 7)** and their corresponding regressed perfusion deficit (**Figure 8)** are indicated.

Table 2. Mean values of the parameters at the time of the initial DECT scan based on the presence of persistent PD

Parameters	Patients without persistent PD	Patients with persistent PD	*P* value
CT severity score	**5.3 ± 2.34**	**9.75 ± 3.29**	**0.004**
D-dimer (µg/L)	**571.23 ± 21.87**	**1.225.23 ± 112**	**0.001**
Fibrinogen (mg/dL)	**365.23 ± 54.01**	**423.12 ± 64.43**	**0.003**
CRP (mg/dL)	37.17 ± 8.3	83.72 ± 5.3	0.001
Platelet (×10^9/L)	214.21 ± 63.14	243.15 ± 25.16	0.072
Neutrophil count (×10^9/L)	4.45 ± 1.48	5.83 ± 2.01	0.120
White blood cell (×10^9/L)	5.45 ± 0.3	6.25 ± 0.3	0.090

Bold indicates statistical significance. DECT, dual-energy computed tomography; CT, computed tomography; CRP, C-reactive protein; PD, perfusion deficit.

ty,[19] although, as in the above-mentioned case, irreversible pulmonary fibrosis has also been previously reported.[21] No data could be found in the literature pertaining to the persistence of lung PD, so the information presented in this study can be considered of value as it may alter the perceptions of the content and extent of COVID-19 sequelae.

COVID-19 has a greater impact on older patients, and persistent COVID-19 symptoms are associated with age.[22,23] Furthermore, CT severity values, CRP, and D-dimer levels have been discovered to be good predictors of disease course, severity, and persistence symptoms of COVID-19.[24,25] The data of the current study demonstrated that in addition to their ability to predict severe disease, these parameters are also associated with long-term PD presence. D-dimer is an important indicator of the microangiopathic nature of COVID-19. The association between D-dimer and long-term PD also confirms the microangiopathic damage of COVID-19 pneumonia and reveals its extent. Fibrinogen levels are another indicator of the microangiopathic nature of COVID-19-related pneumonia. Levels of CRP have been defined as a significant indicator of a severe disease course due to their role as a major marker of inflammation. Additionally, it was discovered that CT severity values were correlated with both CRP levels and clinical disease severity. The CRP and D-dimer values were also found to be positively correlated, implying that increased inflammation is associated with more severe angiopathy.[25,26] It was also previously emphasized that severe disease course was associated with more frequent post-COVID-19 symptoms.[25,27] As previously stated, the presence and severity of a PD is consistent with a severe inflammatory/microangiopathic process. Similarly, we believe that the persistence of PDs and their association with post-COVID-19 symptoms, D-dimer, CRP, fibrinogen, and CT severity values can be explained by an inflammatory/microangiopathic etiology. The current study results also revealed that the presence of persistent PDs was more common in older patients, which is consistent with previously known data that the presence of post-COVID-19 symptoms increases with age.[28]

Defining the presence of long-term PD raises the question of its clinical importance. Although a relatively small population was included in this current study, all the patients with persistent PDs also had persistent COVID-19 symptoms. Dyspnea, in particular, was found to be strongly associated with PD presence, and can thus be accepted as a finding that confirms the importance of PDs as a secondary sign for the hypoxemia associated with PDs.

There was a significant difference in iodine density values between the consolidations and GGOs. Similar findings have been reported in other studies.[7,14]

Despite the fact that all of the patients were provided with enoxaparin, a significant number of them had long-term PDs. It has been proposed that thrombosis prevention should include not only anticoagulant therapy but also antiplatelet agents.[7,29] The use of aspirin has recently been linked to improved outcomes.[30] When the presence of long-term PDs in patients taking enoxaparin treatment are considered, the presented data can point to the need for an additional antiplatelet agent. In addition, a reconsideration of the dosage of enoxaparin might be needed. None of the patients included in the study had a history of intensive care admission due to COVID-19. Nonetheless, we discovered persistent PDs in some of these patients. Similarly, clinical severity was previously associated with long COVID-19 symptoms; however, young patients with no comorbidities were found to have persistent COVID-19 symptoms as well.[25,31]

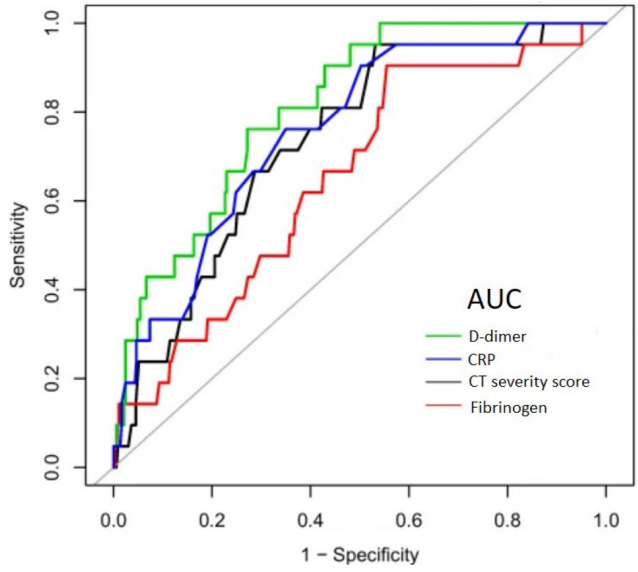


Figure 9. Receiver-operating-characteristic curve of the D-dimer, C-reactive protein, computed tomography severity index, and fibrinogen levels to predict future perfusion deficits. AUC; area under the curve; CT; computed tomography; CRP, C-reactive protein.

Table 3. Mean values of the parameters at the time of the second DECT scan based on the presence of persistent PD

Parameters	Patients without persistent PD	Patients with persistent PD	*P* value
D-dimer (µg/L)	**236.17 ± 78.52**	**613.18 ± 76.39**	**0.005**
Fibrinogen (mg/dL)	215.73 ± 22.91	288.43 ± 51.39	0.320
CRP (mg/dL)	**9.23 ± 1.46**	**33.64 ± 11.4**	**0.001**
Platelet (×10^9/L)	197.15 ± 66.18	211.23 ± 27.28	0.061
Neutrophil count (×10^9/L)	4.27 ± 0.97	4.83 ± 1.34	0.590
White blood cell (×10^9/L)	5.26 ± 1.8	6.15 ± 2	0.700

Bold indicates statistical significance. DECT, dual-energy computed tomography; CRP, C-reactive protein; PD, perfusion deficit.

Table 4. Distribution of the frequency of persisting symptoms according to persistent perfusion deficit presence

Symptom	Frequency n (%)		*P* value
	Patients without persistent PD	Patients with persistent PD	
Dyspnea	0 (0%)	16 (16/16, 100%)	$P < 0.001$
Cough	4 (4/28, 14.2%)	10 (10/16, 62.5%)	$P = 0.003$
Fatigue	8 (8/28, 28.5%)	12 (12/16, 75%)	$P = 0.010$

PD, perfusion deficit.

This study had some limitations, the most notable of which was the relatively small number of patients due to it being a retrospective, single-center study. Further studies using a greater number of patients would be better able to reveal the extent and duration of the sequelae of GGOs and PDs. This study looked at the long-term presence of PDs and their connection to clinical and laboratory data, but it did not investigate the extent and severity of PDs or their connection with other conditions or symptoms. There were insufficient data about the non-pulmonary comorbidities of the patients; as a result, the presence of comorbidities could not be correlated with PDs.

In conclusion, these preliminary results have demonstrated that the presence of GGOs and lung PDs related to COVID-19 pneumonia can last for as long as 80–90 days. In addition, DECT can be used to reveal both long-term parenchymal and perfusion changes. CT severity values, D-dimer, and CRP levels can be useful for the prediction of future persistent PDs. Persistent PDs are commonly seen together with persistent COVID-19 symptoms.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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