

Extrapulmonary Findings Predicting Intensive Care Support in Coronavirus Disease 2019 at Initial Computed Tomography

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Abstract

Objective: To determine the possible extrapulmonary factors that can predict the need for intensive care support with initial computed tomography and predict mortality.

Methods: Computed tomography analysis was performed to determine the extrapulmonary findings, grouped under 4 categories: mediastinal, vascular, pleural, and intraabdominal. Pulmonary involvement of each lobe was scored between 0 and 5 points on computed tomography. In addition to ground-glass opacity, the computed tomography score increased by 1 point per lobe in the presence of a crazy-paving pattern and 2 points for consolidation.

Results: There was a significant difference in pulmonary parenchymal involvement between intensive care unit and in/outpatient groups (16 vs 8, $P < .0001$). Among the extrapulmonary computed tomography findings, the best predictor variable was lymphadenopathy, detected in 60 (25%) of the total cases and the majority (75%) of the intensive care unit patients (odds ratio 0.04, 95% CI = 0.02-0.08). Other parameters that predict the worse outcome were age (odds ratio 1.093, 95% CI = 1.057-1.136), presence of comorbidities (odds ratio 0.15, 95% CI = 0.08-0.28), and male gender (odds ratio 2.18, 95% CI = 1.17-4.1). Pericardial thickening was found to be higher in the intensive care unit group, while liver density was found to be lower. Pleural thickening was the most common pleural change with no morbidity or mortality prediction.

Conclusion: The most crucial extrapulmonary variable to predict intensive care unit admission is the presence of mediastinal lymphadenopathy in addition to pulmonary parenchymal involvement in a patient with COVID-19 pneumonia. This finding can guide the clinical management, can be easily detected with non-enhanced computed tomography, and can be obtained at the time of presentation of the patient.

Keywords: COVID-19, computed tomography, extrapulmonary, mediastinal lymphadenopathy

Introduction

Since December 2019, a novel coronavirus named “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2), affected millions of lives. The illness it causes was termed coronavirus disease 2019 (COVID-19) by World Health Organization. It reached pandemic status by March 2020 and has put enormous strain on intensive care units (ICUs) worldwide, both by overdemand for limited ICU capacity and lack of treatment options.¹ The most prominent symptoms are nonspecific findings such as fever, cough, dyspnea, and weakness. Reverse transcriptase-polymerase chain reaction (RT-PCR) test is used for diagnosis.² However, in the light of up-to-date information, false-negative test results are considerably high and computed tomography (CT) is used to aid diagnosis or when necessary in the later stages of the disease.^{3,4}

Computed tomography imaging is performed without contrast in the routine management of COVID-19 patients. Various parenchymal involvement patterns and scoring systems have been defined

for CT findings to date.⁵⁻¹¹ The typical CT pattern is ground-glass opacity (GGO) and is reported at a systematic review with a frequency of 88%.⁶ In some cases, crazy-paving pattern or consolidation can also be seen, and fibrotic changes can be observed according to the stage of the disease.^{6,10} Apart from these typical findings, various atypical findings such as tree-in-bud pattern, cavitation, and mediastinal lymphadenopathy (LAP) have been described for COVID-19 pneumonia.^{6,12} In addition, a strong relationship between the CT score and the prognosis has been reported in several studies.^{11,13-15}

The virus-infected host may not present symptoms, or s/he may face a severe clinical situation that may lead to acute respiratory distress syndrome (ARDS) and require intensive care support.¹⁶ Besides parenchymal involvement, any finding that can help the clinician affect the treatment process and prognosis is valuable in this clinical complexity. Therefore, it is the duty of every radiologist who performs a thoracic evaluation to demonstrate all of the significant findings with initial CT. This study aims to determine the possible extrapulmonary factors that can predict the patient group who will need intensive care support with initial CT and predict mortality and the clinical course.

Material and Method

The Institutional Review Board approved this study of the University of İstanbul University-Cerrahpaşa. We retrospectively

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studied the patients suspected of COVID-19 pneumonia from March 2020 to July 2020 in our hospital. Written informed consent was waived because of retrospective nature of the study.

A total of 237 patients, including 92 women and 145 men, were included in the study, who had typical findings for COVID-19 pneumonia and/or had positive PCR tests. Patients with typical findings for bacterial or other viral pathogens, lobar atelectasis, or segmentectomy/lobectomy secondary to malignancy and patients with clinical suspicion of COVID-19 pneumonia but with 3 negative PCR tests and no CT findings have been excluded from the study.

All patients included in the study were evaluated by CT scans obtained 24 hours after admission to the hospital. Although they did not have any complaints, the number of patients who underwent CT was 12 because the PCR test was positive. A CT scan was performed on average 6 days after the onset of symptoms in the remaining cases.

Computed Tomography Protocol

Patients suspected of COVID-19 pneumonia were examined on a dual-source (2 × 64 detectors) CT scanner (SOMATOM Definition AS, Siemens Healthcare, Forchheim, Germany). Chest CT examinations were performed at the end of the inspiration in a supine position. The CT scan parameters were as follows: 100 kV tube voltage with automatic tube current modulation (120-280 mA), pitch 1.25, matrix 512 × 512, slice thickness of 1.5 mm, intersection space 1.5 mm. Except for 9 cases (3.7%) with pulmonary thromboembolism (PTE) suspicion at the time of admission to the hospital, all CT examinations were obtained with the non-contrast CT protocol.

Image Analysis

The CT scans were evaluated in 3 orthogonal views for lung involvement pattern and percentage. The CT images were reviewed in consensus by 2 radiologists with over 10 (S.A.K.) and 5 (S.Ş.) years of clinical experience, who were blinded to the RT-PCR results and the clinical status of the patients.

We used an upgraded version of CT scoring criteria to evaluate the pulmonary involvement, defined by Huang et al.¹⁰ According to the involvement of lobes, scores were defined as follows: 0 expressed no involvement; 1, less than 5% involvement; 2, 5%-25% involvement; 3, 26%-49% involvement; 4, 50%-75% involvement; and 5, more than 75% involvement. The typical parenchymal findings were investigated: presence or absence of GGO, crazy-paving pattern, and consolidation.

If the crazy-paving pattern appeared in 1 lobe, the CT score increased by 1 point and, if consolidation appeared, the score increased by 2 points. The final CT score was defined as the total of the scores for each of the 5 lobes. This score ranged from 0 to 35.

Extrapulmonary CT findings were investigated under 4 main headings:

- A. Mediastinal findings: Cardiothoracic ratio (CTR), pericardial effusion and pericardial thickening, and presence of LAP
- B. Vascular findings: Diameters of pulmonary truncus and right and left main pulmonary arteries and presence of PTE
- C. Pleural signs: Pleural effusion and pleural thickening
- D. Intraabdominal solid organs: Liver density and length of the spleen.

The CTR was calculated by proportioning the heart's projection over the thoracic wall at the largest chest diameter (Figure 1). The

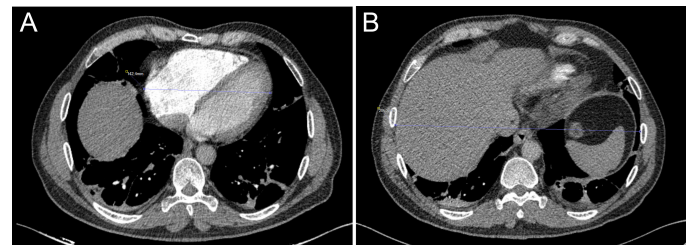


Figure 1. A, B. Cardiothoracic ratio measurement. (A) The projection of the heart over the thoracic wall. (B) Largest chest diameter.

presence of a lymph node in the mediastinum window with a short axis of more than 10 mm at all lymphatic levels was considered LAP. Regardless of lymph node size, patients with a diagnosis of lung cancer were excluded from the study. In addition, we did not include any calcific lymph nodes typical for granulomatous and some other diseases in the study. Vascular diameter measurements of the pulmonary truncus, right and left main pulmonary arteries were made on the axial plane. In addition, the presence of pleural/pericardial effusion and pleural/pericardial thickening was evaluated. Liver density was measured in the axial plane, from the subcapsular area in the right lobe, without any major vascular structures in the region of interest. The spleen completely entered the field of view, except for 4 patients with splenectomy. The kidneys were not included in the study since most CT examinations were done without contrast material.

Statistical Analysis

Population distribution was assessed with Kolmogorov-Smirnov and Shapiro-Wilk tests. Parameters with normal distribution are reported as mean ± SD, and parameters that do not have normal distribution are reported as median (interquartile range).

Patients were split into 2 groups according to intensive care admission. Continuous and normally distributed parameters were analyzed with the unpaired *t*-test, and nonnormally distributed parameters were analyzed with Mann-Whitney test. Categorical variables were assessed with Fisher's exact test. A multiple logistic regression test with significantly different results was performed. A 2-sided *P*-value < .05 was reported as statistically significant in each test. A subsequent receiver operator characteristic (ROC) curve was calculated to show the performance of the model.

Results

Of the cases included in the study, 65 were ICU patients and 172 were outpatients. While the RT-PCR test of all cases in the ICU group was positive, it was negative in 49 patients (28.4%) despite typical CT findings in the in/outpatient group. Sixty-five (27.5%) of the patients received intensive care support at the time of the first arrival from the emergency room (*n* = 41) or during treatment from the ward (*n* = 24); the treatment of the remaining patients (72.5%) was provided in their own home (outpatient) or hospital, under appropriate isolation conditions, in inpatient services reserved for these patients. Of those treated in the third-level ICU, 42 patients (65%) were demised due to refractory shock and respiratory failure. No deaths occurred in the group who were only treated in the ward or outpatients.

The male patient population (73%, *n* = 48) was more dominant in the ICU group than the outpatient group (56%, *n* = 97). One hundred two patients (43%) had various comorbidities. While the rate of comorbidity was 30% in the outpatient group, it reached

Table 1. Patient Characteristics and CT Findings

CT Variables	Intensive Care Unit (n = 65)	In/Outpatient (n = 172)
Age (18-94) (mean)	32-94 (69)	18-77 (47)
Gender (male) (%)	48 (73)	97 (56)
Presence of comorbidity (%)	49 (75)	53 (30)
CT Score (median)	19	9
LAP	45	15
CTR (median)	0.48	0.42
Pericardial effusion	10	2
Pericardial thickening	13	8
Pulmonary truncus diameter, mm (median)	27	24
Right pulmonary artery, mm (median)	23	18
Left pulmonary artery, mm (median)	21	18
Pleural effusion	18	1
Pleural thickening	61	109
Liver density, HU (n = 248) (median)	41	45
Spleen length, mm (n = 233) (median)	109	112
Total	65	172

CT, computed tomography; CTR, cardiothoracic ratio; ICU, intensive care unit; HU, Hounsfield unit.

75% in the ICU group. Patients' characteristics and CT findings are listed in Table 1.

Imaging Findings

All of the patients had typical pulmonary parenchymal findings for COVID-19 pneumonia. The CT findings were predominantly composed of GGOs, mainly in the lower lobe and posterior segments. This involvement was generally in more segments and a wider area in the intensive care group, and this finding was often accompanied by consolidation (Figure 2). Due to this situation affecting the CT score directly, the CT score (whose mean was ten overall) was 19 in intensive care patients and 8 in the other patient group.

Lymphadenopathy was detected in 60 (25%) of the cases, and the majority (75%) were in intensive care patients with a mean

age of 66 (Figure 3). Lymphadenopathy was detected in 87% of the patients admitted to the ICU from the emergency department and 61% of the patients coming from the ward. The mean CT score was 19 ± 7.6 in cases with LAP, while it was 12 ± 7.9 in all patients. The number of patient death while being followed up in ICU with LAP was 29 (44% of all ICU cases, 48% of all LAP-positive cases, and 69% of all deceased cases). There were only 11 patients with various malignancies, and no LAP was detected in 3 of them, while 8 patients with a mean age of 64 were positive for LAP. The stations of pathological lymph nodes are listed in Table 2.

The average length of stay in the ICU was 11.3 ± 8.1 days. There was no significant difference between this duration of stay in the ICU according to the presence or absence of LAP. Also, no significant difference was found between the 2 groups in terms of age.

The CTR was calculated as 0.48 in the intensive care group and 0.42 in the other group. The mean CTR value in the patients who succumbed was 0.50. Pericardial effusion and thickening were positive in 10 patients (4.2%) and 13 patients (5.5%) receiving intensive care support, while positive only in 2 (0.8%) patients and 7 (3%) patients outside this group, respectively. The CTR rates of these groups were 0.54 and 0.53, respectively, and were above the general average.

Although no significant pathological increase was observed in pulmonary truncus and main pulmonary artery diameters, it was noted that these values were higher in patients followed up in the ICU than in the other group.

No embolism was detected in any of the patients examined with contrast-enhanced CT with a preliminary diagnosis of PTE. However, 3 (1.2%) patients in the intensive care group developed PTE at follow-up.

It is noteworthy that all of the cases with pleural effusion, except 1 case, were in the group followed in the ICU. In the majority of cases (72%), there was an increase in pleural thickness. This increase in pleural thickness was more prominent around the proximity of subpleural lesions (Figure 4).

In our study, there was no patient with chronic liver disease or malignancy. Liver density could not be measured in 8 patients because of intravenous (IV) contrast material administration. However, in the remaining patients, liver density was lower in the intensive care group than in the other group.

As for the spleen size, in the intensive care group, 11 patients were at the physiological upper limit, and 8 patients had increased size, while in the other group, the number of patients with the size of the physiological upper limit was 21. The number of patients with increased size was 20.

Statistical Findings

A consequent multivariable logistic regression test to predict ICU admission was performed statistically significantly between



Figure 2. A-C. Typical parenchymal involvements at initial chest computed tomography (CT) imaging. (A) A 44-year-old man with posterior weighted ground-glass opacity (CT score 10). (B) A 80-year-old man followed up in the intensive care unit (ICU) with a crazy-paving pattern (CT score 23). (C) An 82-year-old man who died while being followed up in the ICU had significant involvement with consolidation (CT score 34).



Figure 3. A-C. Lymphadenopathies (LAPs). (A) A 64-year-old man with subcarinal LAP died while being followed up in the intensive care unit (ICU) (computed tomography (CT) score 19). (B) A 67-year-old woman with paratracheal LAP died while being followed up in the ICU (CT score 25). (C) A 44-year-old man with hilar LAP followed up in the inpatient service (CT score 23).

the 2 groups. Variance inflation factor parameters lower than <2.5 were taken into the final analysis to avoid multicollinearity. Age, CT score, CTR, pulmonary truncus diameter, liver density, gender, presence of comorbidities, LAP, pleural/pericardial effusion, and pleural thickening were used to predict ICU admission. Age, gender, CT score, and presence of LAP were statistically significant predictors of ICU admission. The parameters of continuous and categorical variables are listed in Tables 3, 4, and 5.

The area under the ROC curve for all parameters was 0.95 (95% CI 0.91-0.98), $P < 0.0001$. Thus, the negative predictive power of the model was 92.1%, while the positive predictive power was 84.8%. These values were found statistically significant in multiple logistic regression analysis to predict admission to intensive care and death.

Table 2. Lymphadenopathy Stations

Station	Intensive Care Unit (n = 65)	In/Outpatient (n = 172)	P
Subcarinal	28	9	
Lower paratracheal	27	8	
Upper paratracheal	7	3	
Hilar	24	9	
Prevascular	4	2	
Para-aortic	2	2	
Subaortic	4	3	
Axillary	1	1	
Supraclavicular	1	1	
Total positive stations	98 (n = 45)	38 (n = 15)	.0001

Discussion

In this retrospective study, we showed that the presence of LAP along with age, gender, comorbidity, and CT score can predict intensive care admission. Identifying all potential poor prognostic factors for COVID-19 pneumonia in initial CT makes it possible to predict the need for intensive care and support clinical management. The SARS-CoV-2 pandemic significantly increased the burden on healthcare systems, and the increase in the demand for mechanical ventilation for severe patients was the most challenging aspect of the pandemic. Studies have shown that the relationship between CT findings and the course of the disease is quite strong.^{2,17}

In our study, variables other than parenchymal involvement and the demographic data were collected in 4 categories. These categories were mediastinal, vascular, pleural signs, and intraabdominal solid organ findings at the initial CT. Among all the variables, the only variable to predict ICU admission was the presence of LAP in the category of mediastinal findings. Lymph nodes with a short axis above 1 cm were present in 60 patients, giving a prevalence of 25%. Twenty-nine of these patients with mediastinal LAP died in the follow-up in the ICU. In both groups, the stations with the most LAP were subcarinal, lower paratracheal, and hilar stations, respectively. Sardanelli et al¹⁸ reported that the sample they formed with 410 patients collected from 3 hospitals consisted of lower-severity illness and low LAP prevalence.¹⁸ According to Sardanelli et al, the relatively higher number of the ICU patient group in our study (27% vs 15%) can be explained by the fact that the sample belongs to the period when the pandemic was most intense in our study region and our providing tertiary health care. However, mortality rates were almost equal in the presence of LAP (48% vs 49%).

Acute respiratory distress syndrome is a heterogeneous disease caused by various organisms (pulmonary or extrapulmonary), trauma, or inflammation.^{19,20} As Simon et al²¹ stated, a CT scan provides a comprehensive assessment of parenchymal and extra-parenchymal findings in patients, especially followed up with

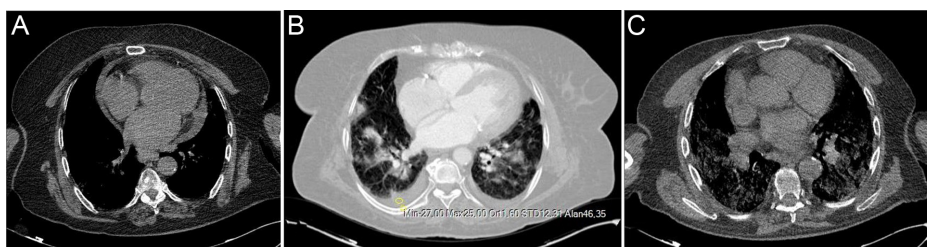


Figure 4. A-C. Mediastinal extrapulmonary findings. (A) A 79-year-old man with pericardial effusion (computed tomography (CT) score 17). (B) A 67-year-old woman with pleural effusion (CT score 25). (C) An 82-year-old man with pleural thickening adjacent to the parenchymal involvement (CT score 34).

Table 3. Comparison of Continuous Variables

	ICU vs In/ Outpatient	P	95% CI (Difference Between Median Values)
Age (n = 237)	66 vs 46	<.0001	16.2-24.4
CT score (n = 237)	19 vs 8	<.0001	8-12
Cardiothoracic ratio (n = 237)	0.48 vs 0.42	<.0001	0.05-0.08
Pulmonary truncus (n = 237)	27 vs 24	<.0001	2-4
Right pulmonary artery (n = 237)	23 vs 18	<.0001	4-6
Left pulmonary artery (n = 237)	22 vs 18	<.0001	3-5
Liver density (n = 228)	41.5 vs 47	.015	(-8) to (-1)
Spleen length (n = 233)	108 vs 111	.22	(-8) to (2)

CT, computed tomography; ICU, intensive care unit.

ARDS.²¹ In addition, similar to our results, the presence of mediastinal LAP was reported as 66.7% in their study, including 204 patients.²¹ Although nonspecific, the presence of LAPs may indicate significant inflammation and a more severe clinical course. The high metabolic activity of the virus can cause cytokine storm and lung injury through the immunological response in lymphoid tissues, especially in severe diseases.²² Coronavirus disease 2019

Table 4. Comparison of Categorical Values

n = 237	ICU vs In/ Outpatient	P	Odds Ratio (95% CI)
Gender (Female)	26% vs 43%	.0167	0.46 (0.24-0.85)
Presence of comorbidities	75% vs 30%	.0001	0.15 (0.08-0.28)
Lymphadenopathy	75% vs 25%	.0001	0.04 (0.02-0.08)
Pleural effusion	28% vs 1%	.0001	0.02 (0.001-0.09)
Pericardial effusion	16% vs 1%	.0001	0.06 (0.01-0.29)
Pleural thickening	94% vs 63%	.0001	0.11 (0.04-0.31)

ICU, intensive care unit.

Table 5. Multiple Logistic Regression Analysis (1: ICU Admission, 0: In/Outpatient)

Parameters	Odds Ratio	95% CI	P
Age	1.093	1.057- 1.136	<.0001
Gender (female)	0.17	0.05-0.46	.001
CT score	1.17	1.088-1.272	<.0001
Lymphadenopathy	7.93	3.1-21.6	<.0001

CT, computed tomography; ICU, intensive care unit.

is known to trigger an inflammatory response in the host, as shown by the increased interleukin-6 (IL-6) levels comparable to non-COVID-19 ARDS or sepsis.^{21,22} It is possible that more severe patients had intensive inflammation, which led to the increased number of LAPs in our cohort. The mean CT score was higher in the patients with LAP than those without, suggesting that LAP may be associated with viral load and supports the earlier results. However, we were unable to measure IL-6 levels, and we cannot exclude the contribution of older age.

The number of patients in our series is considerable, and the fact that LAP presence is similar to those previously defined in critically ill patients and even at a higher rate constitutes an antithesis to recognizing this finding as an atypical finding.

From a radiologist's perspective, the strongest predictor for poor prognosis is undoubtedly the degree of parenchymal involvement.^{6,8,11,16,24} In our study, the mean CT score was 19 in cases admitted to the ICU, while in other patients, this rate was 8. It has been shown by various studies that as the degree of parenchymal involvement increases, the morbidity and mortality of the disease increase proportionally.^{6,8,11,16,24} Our study supports this result.

Another extrapulmonary variable, pleural thickening, was determined as the most common pleural change. Pleural effusion was present in only 19 cases (8%), while pleural thickening was observed in 170 patients (71.7%). We believe that pleural thickening is a significant finding independent of effusion. In the Middle East respiratory syndrome coronavirus (MERS)-CoV infection, pleural thickening was associated with a poor prognosis.²⁵ Although there was a significant difference between the groups in our study, pleural thickening was not a predictor of morbidity and mortality. On the contrary, pericardial thickening associated with high inflammatory viral load in previous studies increased in intensive care patients, especially in the deceased group.²⁶

Studies have reported coagulation disorders and associated microvascular thrombotic events in patients infected with SARS-CoV-2.²⁷⁻³⁰ In our patient group, PTE was detected in only 3 patients while being treated. This small number of patients can be explained by initially obtaining CT imaging in the early phase of the disease and almost all without contrast material, excluding patients with lung cancer, surgery, and atelectasis. No significant expansion was seen in pulmonary vascular structures. Wider vascular structures found in the intensive care group can be related to age and comorbid factors.

It is known that SARS-CoV-2 also affects the myocardium and cardiac involvement is frequent in hospitalized patients.^{31,32} This situation was also observed in the SARS and MERS epidemics. Researchers have tried to explain this by different mechanisms such as systemic inflammatory response, direct damage to myocardial cells, and impairment of myocardial oxygenation.^{31,32} Although cardiac evaluation with initial CT is limited, CTR can be measured simply. The CTR was higher in the ICU group. To the best of our knowledge, this is the first study to address CTR in COVID-19 in the literature.

In previous studies, liver damage was detected in 60% of patients with SARS-CoV.³³ The SARS-CoV-2 has also been associated with liver damage or dysfunction.³⁴ We know that liver-related enzyme values such as aspartate aminotransferase (AST) and alanine transaminase (ALT) increase in patients with COVID-19 pneumonia.³⁵ We investigated the relationship between liver density and morbidity and mortality in patients infected with SARS-CoV-2 with this knowledge. Liver density was found to be lower in the patient group followed up in the ICU. That this finding may be significant in high-risk patients has been supported by several studies.^{36,37}

When the cut-off value was accepted as 40 Hounsfield units, the difference between the 2 groups was significant, albeit with low specificity and sensitivity rates. However, no significant contribution was found in predicting morbidity or mortality.

In addition to the systemic inflammatory response caused by the cytokine storm, hemostatic abnormalities detected are also encouraging to investigate splenic involvement of SARS-CoV-2. Splenic infarct has been described in several cases so far³⁸ due to the potential to affect the spleen at the macro and micro levels. When the spleen was examined in non-contrast-enhanced initial CT in patients infected with SARS-CoV-2, no density change was detected in our patients, and the size of the spleen was investigated as single quantitative data. In total, 12% of cases had increased spleen size. However, there was no significant difference between the groups. To the best of our knowledge, this is the first study to examine solid organs with initial CT, such as CTR, liver density, and spleen size in patients with COVID-19 pneumonia.

Similar to the literature, there was a significant difference between the groups in predicting morbidity and mortality compared to age, male gender, and comorbidities.^{2,15,18} These comorbidities mainly were hypertension, diabetes, and cardiovascular diseases, respectively, in our sample. Remarkably, 75% of patients in the ICU group had at least 1 comorbidity.

There are several limitations of our study. First and foremost, our study was retrospective in design. However, the researchers were blinded to the outcome of the patients and the PCR tests. Second, the ICU patient population can be considered small, but it is comparable to the literature.^{18,39} Additionally, all of the extrapulmonary findings were analyzed with non-enhanced CT imaging. Finally, we could not measure laboratory values for our cohort, as most outpatients did not have a complete blood test.

Conclusion

The most crucial variable that radiologists and other clinicians should focus on is the presence of mediastinal LAP, in addition to pulmonary parenchymal involvement in a patient who is admitted with COVID-19 pneumonia and examined with CT. This finding can guide clinical management and can be easily detected with the non-enhanced CT obtained at the time of the presentation of the patient.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of İstanbul University-Cerrahpaşa (Date: 16/06/2020, Number: 73270).

Informed Consent: Written informed consent was waived because of retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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