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EVALUATION OF INDETERMINATE LESIONS ON COMPUTED TOMOGRAPHY IN PATIENTS WITH COVID-19 PNEUMONIA PRESENTED TO THE EMERGENCY DEPARTMENT

ACİL SERVİSE BAŞVURAN VE COVID-19 PNÖMONİSİ OLAN HASTALARDA BİLGİSAYARLI TOMOGRAFİDEKİ BELİRSİZ LEZYONLARIN DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: Indeterminate CT findings can complicate and delay the diagnosis of COVID-19 pneumonia in the emergency department in comorbid patients. The aim of the study is to analyze indeterminate chest CT findings and differentiate predictive features in RT-PCR positive and negative patients, which can be diagnostic for COVID-19 pneumonia.

Methods: In this cross-sectional study, patients suspected of COVID-19 pneumonia whose CT reports were indeterminate were retrospectively reviewed. All CT variables and comorbidities were recorded blindly. Lesions were compared by means of location, multiplicity, configuration, distribution, and margin characteristics between RT-PCR positive and negative patients.

Results: A total of 81 patients were enrolled in the study. Thirty-five (43.2%) had positive RT-PCR tests, and 46 (56.8%) had negative tests. Well-defined central GGO and tree-in-bud nodules were frequently seen in RT-PCR negative patients (p=0.016 and p=0.027, respectively). The lesions were located in the left lower lobe in 16 (45.7%) of the RT-PCR positive patients and 34 (73.9%) of the RT-PCR negative patients (p=0.010). Non-dependant location was recorded in 68.6 % of the RT-PCR positive patients and 54.3% of the negative patients. Regarding the binary regression analysis, only the presence of non-dependent density (OR: 4.91, 95% CI:1.12–20.21) and the absence of tree-in-bud nodules (OR: 0.15, 95% CI:0.03–0.78) were found to be independent predictors of positive RT-PCR test results.

Conclusion: Lesions in the non-dependent part of the lung may be related to positive RT-PCR test results. The presence of tree-in-bud nodules may be a predictor of negative results.

Keywords: Computed tomography, pneumonia, coronavirus, COVID-19

ÖZ

Amaç: Belirsiz BT bulguları, acil serviste komorbiditeleri olan hastalarda COVID-19 pnömonisi tanısını zorlaştırabilir ve geciktirebilir. Bu çalışmanın amacı, belirsiz akciğer BT bulgularını analiz etmek ve COVID-19 pnömonisi için tanısal olabilecek RT-PCR pozitif ve negatif hastalarda prediktif özellikleri ayırt etmektir.

Yöntem: Bu kesitsel çalışmada, BT raporlarında belirsiz olarak tanımlanan lezyonları olan ve COVID-19 pnömonisinden şüphelenilen hastalar retrospektif olarak incelendi. Tüm BT değişkenleri ve komorbiditeler kör olarak kaydedildi. Lezyonlar, RT-PCR pozitif ve negatif hastalar arasında yer, çokluk, konfigürasyon, dağılım ve sınır özellikleri açısından karşılaştırıldı.

Bulgular: Araştırmaya toplam 81 hasta dahil edildi. Hastaların 35'inin (%43,2) RT-PCR testi pozitifken, 46'sının (%56,8) negatifti. RT-PCR negatif hastalarda iyi tanımlanmış merkezi GGO ve tomurcuklu ağaç nodülleri sıklıkla görüldü (sırasıyla p=0,016 ve p=0,027). RT-PCR pozitif hastaların 16'sında (%45,7), RT-PCR negatif hastaların 34'ünde (%73,9) lezyonlar sol alt lob yerleşimliydi (p=0,010). RT-PCR pozitif hastaların %68,6'sında ve negatif hastaların %54,3'ünde non-dependan yerleşim olduğu izlendi. Regresyon analizi sonucuna göre; non-dependan yerleşim varlığı (OR: 4,91, %95 GA: 1,12–20,21) ve tomurcuklanan ağaç nodüllerinin olmaması (OR: 0,15, %95 GA: 0,03–0,78) pozitif RT-PCR test sonucunun bağımsız belirteçleri olarak bulundu.

Sonuç: Akciğerde non-dependan lezyonların görülmesi ve tomurcuklanan ağaç nodüllerinin görülmemesi; pozitif RT-PCR test sonucu ile ilişkili olabilir.

Anahtar Kelimeler: Bilgisayarlı tomografi, pnömoni, koronavirüs, COVID-19

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Introduction

Coronavirus disease 2019 (COVID-19) was confirmed as a pandemic by the World Health Organization. To date, over 500 million confirmed cases and over 6 million deaths were reported.[1] Although different disease variants were previously documented, typical clinical findings were reported as fever, cough, dyspnea, and myalgia, although some patients may be asymptomatic.[2] Early and accurate diagnosis of COVID-19 is quite challenging and demands a cohesive approach among clinical, radiological, and laboratory data. A definitive diagnosis of COVID-19 is based on laboratory testing, which is most often the reverse transcriptase-polymerase chain reaction (RT-PCR) test assay. The RT-PCR test detects viral RNA and the inadequate technique and timing of sampling may cause false-negative results. The sensitivity of RT-PCR testing in clinical practice was reported to be between 42% and 83%.[3,4]

Typical computed tomography (CT) findings for COVID-19 pneumonia were reported as bilateral, multifocal, peripheral ground-glass (GGO) opacities and consolidations with a rounded or confluent pattern.[5-7] The halo and atoll signs were also described.[6-8] Although the sensitivity of chest CT in detecting COVID-19 pneumonia was reported as high as 56–98%, many other conditions may resemble its appearance, including pneumonia due to other viruses and organizing pneumonia.[9] Standardized nomenclature and categorized reporting of chest CT for suspected COVID-19 cases have great importance in these circumstances. The recent Radiological Society of North America expert consensus statement on chest CT reporting proposed four categories (*typical appearance, indeterminate appearance, atypical appearance, and negative for pneumonia*).[9] Indeterminate CT findings are reported by radiologists when it is not possible to completely rule out the disease radiologically[9]. In certain patients with other clinical conditions, such as congestive heart disease, lung edema, interstitial lung disease, and chronic obstructive pulmonary disease (COPD), both clinical symptoms and chest CT findings may overlap. Due to higher COVID-19 mortality rates in the elderly and those with other comorbidities, accurate and rapid diagnosis is vital.[10, 11]

The purpose of this study was to assess the features of indeterminate CT findings that can influence the diagnosis of COVID-19 pneumonia in patients in the emergency department with appropriate clinical symptoms.

Methods

Patients

This was a cross-sectional study of retrospectively collected single-center data on patients with clinically suspected COVID-19 infection between March and April 2020. Ethical committee approval was obtained before the study started.

All patients who had presented to the emergency department with suspected symptoms of COVID-19 pneumonia were enrolled in the study. The RT-PCR test results were extracted from each patient's electronic medical record in the hospital data system. Patients were grouped according to their latest RT-PCR test results if the test had been repeated.

Adult patients with clinically suspected COVID-19 pneumonia and indeterminate chest CT findings were enrolled in the study. Patients with normal chest CT findings, patients with typical chest CT findings for COVID-19 pneumonia, patients having a different diagnosis after chest CT, and patients without RT-PCR test results were excluded from the study.

CT Technique and Interpretation

CT examinations were performed on a 16-section scanner (Toshiba Aquilion 16, Toshiba Medical Systems, Otawara, Japan). The low-dose, non-contrast chest CT scanning variables were as follows: tube voltage, 120 kVp; tube current, 60 mAs; detector thickness, 1 mm; rotation time, 0.75 seconds; pitch, 1.5; reconstruction interval, 1.0–5.0 mm. Two thoracic radiologists, one with 15 and the other with four years of experience, who were blinded to the RT-PCR test results reviewed the CT images on the same day. All images were viewed on both lung (width, 1500 HU; level, -700 HU) and mediastinal (width, 350 HU; level, 40 HU) settings. The basic CT terminology described by the Fleischner Society glossary was used.[12]

Indeterminate CT findings included; non-peripheral (central or peribronchovascular), diffuse, or amorphous GGO / consolidations, and coexisting findings such as nodules, effusions, or septal lines.

For each patient, the following CT variables were evaluated:

Lesions: Ground-glass opacity, consolidation, tree-in-bud nodules, interlobular septal thickening, subpleural band, halo sign, atoll sign, pleural effusion, and pericardial effusion.

Location of the lesion: Lesions locations were categorized as peripheral or non-peripheral (central / peribronchovascular). The lesion was recorded as peripheral if located in the outer one-third of the lobe. Otherwise, it was defined as a central lesion. Dependent or non-dependent localization of lesions was also recorded.

Configuration, multiplicity, and margins of the lesion: Lesions were categorized as round, amorphous, and diffuse in terms of their configurations. Lobar or segmental distribution was recorded if present. The number of lesions was recorded as solitary, few (1-5), or multiple (more than 5). Margin characteristics were recorded as well-defined or unidentifiable margins.

Statistical Analysis

Data analysis was performed using SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA). The

Shapiro-Wilk test was used to test normal distribution of continuous variables. Continuous variables were tested using the Mann-Whitney U test and expressed as median and interquartile ranges. Categorical variables were tested using the Chi-square test and Fisher's exact test. A multivariable logistic regression model was performed to evaluate independent predictors of positive RT-PCR test results. Only variables that were statistically significant at a level of p<0.25 were included in the multivariable model. Before the final model was established, a multicollinearity analysis was performed. The Hosmer-Lemeshow test was used to assess the fitness of the model, and the effects sizes were expressed with odds ratios (ORs) and 95% confidence intervals (CIs). All the statistical analyses were two-sided, and an alpha value <0.05 was considered to be the nominal level of significance.

Results

During the study period, a total of 262 adult patients with suspected COVID-19 were assessed for eligibility. Eighty patients were excluded because of entirely normal chest CT findings, and 39 were excluded because they had typical findings for COVID-19 pneumonia. Another 62 patients were excluded because their chest CT findings were consistent with other pathologies and atypical for COVID-19. The remaining 81 patients with indeterminate CT findings were ultimately included in the study.

Of the 81 patients, 35 (43.2%) had positive and 46 (56.8%) had negative RT-PCR test results. Demographic characteristics, RT-PCR test results, CT variables, and comorbidities are shown in Table 1.

Table 1. Univariate comparisons of variables regarding to RT-PCR status

	PCR (+) n=35	PCR (-) n=46	p value
Age, yr (IQR)*	46 (32-60)	58 (39-71)	**0.048**
Lesions			
Peripheral GGO**, well-defined margins, n (%)	19 (55.9%)	14 (30.4%)	**0.022**
Peripheral GGO, unidentifiable margins, n (%)	20 (57.1%)	29 (63.0%)	0.590
Peripheral GGO, diffuse, n (%)	1 (2.9%)	3 (6.5%)	0.630
Central GGO, well-defined margins, n (%)	7 (20.0%)	21 (45.7%)	**0.016**
Central GGO, unidentifiable margins, n (%)	3 (8.6%)	2 (4.3%)	0.647
Consolidation, well-defined margins, rounded or amorphous, n (%)	8 (22.9%)	15 (32.6%)	0.335
Consolidation, lobar- segmental distribution, n (%)	3 (8.6%)	1 (2.2%)	0.311
Tree-in-bud nodules, n (%)	3 (8.6%)	13 (28.3%)	**0.027**
Halo sign, n (%)	3 (8.6%)	1 (2.2%)	0.311
Interlobular septal thickening, n (%)	1 (2.9%)	8 (17.4%)	0.070
Pleural efusion, n (%)	4 (11.4%)	14 (30.4%)	**0.042**
Pericardial efusion, n (%)	1 (2.9%)	6 (13.0%)	0.133
Non-dependent location, n (%)	24 (68.6%)	25 (54.3%)	0.195
Subpleural discoid bands, n (%)	3 (8.6%)	8 (17.4%)	0.335
Lesion number			
Multiple (>5), n (%)	19 (54.3%)	36 (78.3%)	**0.022**
Few lesions (1-5), n (%)	16 (45.7%)	10 (21.7%)	
Lesion location			
Right upper lobe, n (%)	13 (37.1%)	15 (32.6%)	0.671
Right middle lobe, n (%)	14 (40.0%)	22 (47.8%)	0.483
Right lower lobe, n (%)	29 (82.9%)	38 (82.6%)	0.977
Left upper lobe, n (%)	13 (37.1%)	14 (30.4%)	0.526
Left lower lobe, n (%)	16 (45.7%)	34 (73.9%)	**0.010**
Comorbidities			
Bronchopneumonia or aspiration pneumonia, n (%)	5 (14.3%)	4 (8.7%)	0.490
Increased cardiothoracic ratio, n (%)	4 (11.4%)	16 (34.8%)	**0.016**
Malignancy, n (%)	3 (8.6%)	2 (4.3%)	0.647
Chronic obstructive pulmonary disease or severe emphysema, n (%)	2 (5.7%)	8 (17.4%)	0.174

*IQR: interquartile range
**GGO: ground-glass opacity

According to the univariate analysis results, patients with negative RT-PCR test results were older (p=0.048). Peripheral GGO lesions with well-defined margins were recorded in 19 of the positive RT-PCR test group (55.9%)

and 14 of the negative RT-PCR test group (30.4%). In contrast, centrally located GGO with well-defined margins were predominantly seen in patients in the negative RT-PCR test group (n=21, 45.7%), whereas only in the 7 (20.0%) of the patients in the positive RT-PCR test group. Similarly, tree-in-bud nodules and pleural effusion were more frequently reported in the RT-PCR negative patients (28.3% vs 8.6% and 30.4% vs 11.4%, respectively). Multiple lesions were reported in 36 (78.3%) patients in the RT-PCR negative group and 19 (54.3%) patients in the positive group. Regarding comorbidities, patients with increased cardiothoracic ratio were predominantly seen in the RT-PCR negative patients (34.8% vs 11.4%).

Only the variables that had an alpha value under 0.25 in the univariate hypothesis tests were included in the final multivariate model. According to multicollinearity analysis, a high correlation between the increased cardiothoracic ratio and pleural fluid was observed ($r=0.658$, $p<0.001$), and only cardiothoracic ratio was included in the final model. Model fitness was established in the multivariate model (Hosmer-Lemeshow test, $p=0.613$).

Regarding the results of the binary regression analysis, the non-dependent location of the lesion and absence of tree-in-bud nodules were found to be independent predictors of positive RT-PCR test results. The absence of tree-in-bud nodules increased approximately 6.7 times (OR: 0.15, 95% CI: 0.03–0.78), and the presence of non-dependent location of the densities increased 4.9 times (OR: 4.91, 95% CI: 1.12–20.21) the positive RT-PCR test diagnosis (Table 2).

Table 2. Multivariate logistic regression model for independent predictors of positive RT-PCR result

	Wald	**Odds ratio (95% CI)**	**p value**
Age, yr	0.716	0.98 (0.95 - 1.02)	0.398
Peripheral GGO*, well-defined margins	0.538	1.59 (0.46 - 5.53)	0.463
Central GGO, well-defined margins	2.291	0.35 (0.09 - 1.37)	0.130
Multiple lesions (>5)	0.021	1.12 (0.24 - 5.30)	0.884
Left lower lobe location	1.993	0.37 (0.09 - 1.47)	0.158
Tree-in-bud nodules	5.114	**0.15 (0.03 - 0.78)**	**0.024**
Increased cardiothoracic ratio	0.278	0.59 (0.08 - 4.22)	0.598
Interlobular septal thickening	0.347	0.43 (0.03 - 7.14)	0.556
Non-dependent location	4.892	**4.91 (1.12 - 20.12)**	**0.027**
Subpleural discoid bands	0.672	0.34 (0.03 - 4.47)	0.412
Pericardial efusion	1.422	0.19 (0.01 - 2.94)	0.233
Severe emphysema	1.015	0.35 (0.05 - 2.71)	0.314

*GGO: ground-glass opacity

Discussion

Establishing a common and standard language in the radiological reporting of COVID-19 pneumonia is important in the emergency department where rapid diagnosis is vital. To achieve this, RSNA has created 4 categories in the standard COVID-19 pneumonia reporting system published in 2020.[9] In the category defined as indeterminate, the lesions are not specific to COVID-19 and have a wide differential diagnosis. There may be an increase in indeterminate chest CT lesions with increasing patient age and the coexistence of pulmonary comorbidities in COVID-19 patients. Pulmonary comorbidities complicate CT diagnosis of COVID-19 pneumonia for radiologists and necessitate scrupulous attention to detail because patients with comorbidities have poorer clinical outcomes than those without.[10]

In our study, well-defined peripheral GGO lesions were observed more frequently in RT-PCR positive patients, whereas well-defined central GGO lesions, tree-in-bud nodules, pleural effusion, multiple lesions, left lower lobe localization, and the increased cardiothoracic ratio were more prominent in RT-PCR negative patients. Among the variables in the study, it was determined that the factors most strongly predicted RT-PCR positivity were the non-dependant localization of the GGO/consolidations and the absence of the tree-in-bud nodules.

Similar to previous studies, we observed in our study that peripheral GGO lesions were more common in RT-PCR positive patients, while central GGO lesions were less common.[13-16] But it seems that it is not very accurate to speculate about RT-PCR positivity based on GGO lesions according to the multivariate analysis results of our study. It is also inappropriate to predict the COVID-19 status based solely on the presence of single or multiple GGO lesions. In addition, halo and atoll signs have been highly described for COVID-19 pneumonia in the literature, but their frequency in our study was quite low.[14,15] This may be related to the very early CT imaging of patients in the emergency department.

In our study non-dependent location of the lesions in chest CT was an independent predictor for RT-PCR positivity (Figure 2). In previous studies, COVID-19 lesions were detected more often in the posterior portions of the lung.[6,9,17] However, in these studies, patients were generally in the group who applied to the outpatient clinic and had low comorbidities, and typical COVID-19 lesions were investigated. Since our patient group consists of patients who presented to the emergency department, their comorbidities were probably high. Most of the accompanying lesions such as edema, pleural fluid, compressive atelectasis, and aspiration in these patients may involve the posterior dependant regions of the lungs, which may reinforce the importance of evaluating the non-dependent portions of the lung for COVID-19 pneumonia.

Positive RT-PCR test results also had a significant negative relationship with tree-in-bud lesions. Tree-in-bud lesions are more specific for airway diseases and non-COVID-19 infections.[9,16] Therefore these nodules are described in the atypical category for COVID-19 pneumonia in the literature.[7,9,13] However, since these nodules often accompany GGO, they are included in the indeterminate group in another study like ours.[16] In our study, of the 16 patients who had tree-in-bud nodules, only three had positive RT-PCR test results (3/16, 18.75%). All three had peripheral ground-glass lesions together with nodules, and one patient had bacterial co-infection clinically in addition to COVID-19 pneumonia (Figure 1). Even in the presence of ground-glass opacifications, tree-in-bud nodules may discourage the diagnosis of COVID-19 pneumonia.

Figure 1. A 60-year-old man with a positive RT-PCR test presents with fever and dyspnea
a: Chest CT shows bilateral, peripheral located, rounded ground-glass lesions and consolidations with well-defined margins (arrows)
b: There are also centrilobular and tree-in-bud nodules (arrow) not consistent with COVID-19 infection in the same patient. The patient is diagnosed with COVID-19 pneumonia with co-infection

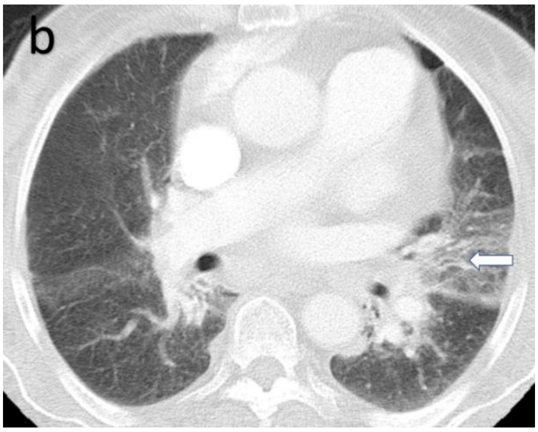

Figure 2. a: An 81-year-old man with a positive RT-PCR test. Chest CT shows bilateral, peripheral, amorphous ground-glass lesions with well-defined margins in the non-dependant region of right upper and lower lobes (arrows)
b: A 70-year-old woman presents with dyspnea and cough with a negative RT-PCR test, who has a history of cardiovascular disease and pulmonary hypertension. Chest CT shows amorphous, ground-glass lesions in the dependent portion of the left upper lobe (arrow)

Although pleural effusion was revealed as atypical for COVID-19 pneumonia in many reports of RT-PCR test-positive patients, its association with cardiac comorbidities was not mentioned before.[17-19] In our study pleural effusion had a strong relationship with increased cardiothoracic ratio but not with positive RT-PCR test.

There are several limitations to this study. First, it is a retrospective study from a single center. Second, a larger sample size of patients with a wide range of co-morbidities with indeterminate lesions in different patients would reflect more precise results. Third, some patients had difficulty breathing during their CT scans due to comorbidities, so their images were expiratory and had motion artifacts. As a result, it was difficult to evaluate the images in this population. Fourth, other atypical infections that can mimic COVID-19 pneumonia were absent from the study because they were categorized as atypical for COVID-19 pneumonia. There could be atypical appearances of COVID-19 pneumonia in that group, and including these patients would affect the results.

Conclusion
Our study evaluated the indeterminate chest CT findings in patients with suspected COVID-19 pneumonia who applied to the emergency department. The differential diagnosis of GGO/consolidations for COVID-19 pneumonia is difficult in this patient group due to comorbidities and advanced age. The localization of GGO lesions in non-dependent areas strongly supports the diagnosis of COVID-19 pneumonia. Tree-in-bud nodules and radiological clues of congestive heart failure, such as increased cardiothoracic ratio and pleural fluid, may distract us from the diagnosis of COVID-19 pneumonia.

Compliance with Ethical Standards
Ethical committee approval was obtained from Kocaeli University (KÜ-GOKAEK-2020/09.25).

Conflict of Interest
None declared.

Author Contribution
NOD, SD: Design, ED, EA, AK, MK: Patients, NOD: Methodology-Statistics, SD: Writing, NOD: Critical Revision.

Financial Disclosure
None declared.

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