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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA MAKALESİ

The Relation of Polymerase Chain Reaction and Computed Tomography Infiltrations of Suspected Covid-19 Patients in Emergency Department

Acil Serviste COVID-19 Şüpheli Hastaların Polimeraz Zincir Reaksiyonu ve Bilgisayarlı Tomografi İnfiltrasyonları Arasındaki İlişki

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ABSTRACT

Aim: Considering the limitations of Polymerase Chain Reaction (PCR) in the Emergency Department (ED), alternative confirmation methods for assessing COVID-19 are needed. This study aimed to evaluate the performance of Thorax-Computed Tomography (T-CT), following Radiological Society of North America (RSNA) recommendations, for suspected COVID-19 patients with pulmonary infiltrations.

Material and Methods: From March to August 2020, 324 ED patients with suspected COVID-19 underwent T-CT scans. Blinded radiologists independently assessed T-CT scans based on RSNA guidelines. Reverse-transcriptase polymerase chain reaction (RT-PCR) served as the reference test.

Results: Of 324 patients, 35% tested positive via RT-PCR. T-CT categories were typical (35.2%), indeterminate (47.5%), and atypical (11.1%). Using a typical T-CT category threshold resulted in 66% sensitivity, 81% specificity, 65% positive predictive value (PPV), 82% negative predictive value (NPV), and 76% accuracy. Subgroup analysis of repeat RT-PCR tests improved performance: 80% sensitivity, 79% specificity, 76% PPV, 83% NPV, and 79% accuracy. Combining RT-PCR and T-CT in the ED achieved 95.5% sensitivity, 79% PPV, and 86.4% accuracy.

Conclusion: Following RSNA guidelines, T-CT exhibits moderate sensitivity and high specificity for detecting COVID-19. In ED settings with suspected cases, T-CT aids in recommending retesting after an initial negative RT-PCR result, facilitating early management and timely isolation measures. The combined use of RT-PCR and T-CT enhances diagnostic performance, emphasizing the potential benefits of integrating these methods.

Keywords: Computed Tomography, COVID-19, emergency Department, RT-PCR

ÖZ

Amaç: Polimeraz Zincir Reaksiyonunun (PCR) sınırlamaları göz önüne alındığında, Acil Serviste COVID-19'u değerlendirmek için alternatif doğrulama yöntemlerine ihtiyaç vardır. Bu çalışmanın amacı, pulmoner infiltrasyonları olan şüpheli COVID-19 hastalarında Kuzey Amerika Radyoloji Derneği (RSNA) tavsiyelerine uygun olarak rapor edilmiş Toraks Bilgisayarlı Tomografisinin (T-BT) performansını değerlendirmektir.

Gereç ve Yöntemler: Mart-Ağustos 2020 tarihleri arasında, COVID-19 şüphesi olan 324 acil servis hastasına T-BT taraması yapılmıştır. Kör radyologlar, T-BT taramalarını RSNA kılavuzlarına göre bağımsız olarak değerlendirmiştir. Referans test olarak ters transkriptaz polimeraz zincir reaksiyonu (RT-PCR) kullanılmıştır.

Bulgular: 324 hastanın %35'inde RT-PCR testi pozitif çıkmıştır. T-BT kategorileri tipik (%35,2), belirsiz (%47,5) ve atipik (%11,1) olarak belirlenmiştir. Tipik T-BT kategorinin eşik olarak kullanılması %66 duyarlılık, %81 özgüllük, %65 pozitif prediktif değer (PPV), %82 negatif prediktif değer (NPV) ve %76 doğruluk ile sonuçlanmıştır. Tekrarlanan RT-PCR testi yapılanlarda uygulanan alt grup analizi tanısal performansı iyileştirmiştir: %80 duyarlılık, %79 özgüllük, %76 PPV, %83 NPV ve %79 doğruluk. Acil serviste RT-PCR ve T-BT'nin birlikte kullanılması ise %95,5 duyarlılık, %79 PPV ve %86,4 doğruluk sağlamıştır.

Sonuç: RSNA kılavuzları uyarınca değerlendirilen T-BT, COVID-19'u tespit etmek için orta düzeyde hassasiyet ve yüksek özgüllük sergilemektedir. Şüpheli vakaların bulunduğu acil servis ortamlarında T-BT, ilk negatif RT-PCR sonucunun ardından yeniden test yapılmasını önermeye yardımcı olarak erken yönetimi ve zamanında izolasyon önlemlerini kolaylaştırır. Çalışmamız, RT-PCR ve T-BT'nin birlikte kullanımı tanısal performansı artırarak bu yöntemlerin entegre edilmesinin potansiyel faydalarını vurgulamaktadır.

Anahtar Kelimeler: Bilgisayarlı Tomografi, COVID-19, Acil Servis, RT-PCR

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Introduction

Coronavirus Disease-2019 (COVID-19) has emerged as a global pandemic in the 21st century, spreading rapidly and reaching uncontrollable levels worldwide. Efforts to curb its spread have led to progress in many regions. The pandemic nearly ended, but COVID-19 infections are still prevalent. This ongoing presence underscores the importance of maintaining vigilance and implementing effective management strategies.

The first strategy in controlling highly contagious infections such as COVID-19 is early detection and isolation of positive cases. However, many patients exhibit either no symptoms or mild symptoms, and the clinical manifestations of the disease are not specific, making it challenging to diagnose based on clinical findings alone. Since its authorization, the reverse-transcriptase polymerase chain reaction (RT-PCR) test has been the gold standard for diagnosing COVID-19. However, this test has limitations, including high false-negative rates of up to 40% and a relatively long turnaround time for results (1-4). These challenges become even more critical in emergency departments (EDs) with limited space and high patient volume, where isolating suspected COVID-19 patients until test results are available and making decisions regarding hospitalization can be complicated.

Although COVID-19 can infest different organ systems, the lungs remain one of the commonly affected organs, albeit not as prominently as at the onset. Management and treatment strategies for lung involvement differ from those required for other systems. Emergency medicine physicians frequently encounter cases requiring differential diagnosis on the frontline. Thorax-computed tomography (T-CT) is an evidenced imaging tool that has been shown to confirm the diagnosis of COVID-19 cases when the lung is involved. It is suggested to be an alternative diagnostic tool due to its high sensitivity in detecting lower respiratory tract pathologies for suspected cases, according to algorithms. T-CT is the most sensitive imaging test for detecting COVID-19 pneumonia, and several radiology societies have approved it as a second-line technique.

In studies investigating the diagnostic capacity of T-CT, high sensitivity rates of up to 97% have been reported in diagnosing COVID-19 pneumonia with T-CT (5). However, the low specificity of T-CT (25%) presents a challenge due to the overlapping of COVID-19 findings with other viral infections such as influenza, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), which has led to ongoing debate regarding its utilization as a diagnostic tool. While routine use of T-CT is not recommended for diagnosing COVID-19, data in the literature suggests that T-CT can serve as an alternative to RT-PCR in patients with possible lung involvement. The question arises whether it is appropriate to act based on T-CT findings instead of waiting for the RT-PCR result in cases where T-CT has already been performed on patients suspected of having COVID-19. This study aims to investigate the diagnostic performance of T-CT, following the recommendations of the Radiological Society of North America (RSNA), in patients with suspected COVID-19 and pulmonary infiltrations.

Material and Methods

Patients' Selection

Between March 1st and August 30th, 2020, patients who presented to our Emergency Department (ED) and were identified as possible COVID-19 cases were included in this study. The patient records were retrospectively examined using the Hospital Information Management System. Only patients who underwent RT-PCR testing and had a T-CT scan were selected for the study. Exclusion criteria comprised patients below 18 years of age, individuals not initially suspected of having COVID-19 but were incidentally diagnosed with it, and patients with missing or inaccessible medical records. Furthermore, patients without any lung infiltrations on their initial T-CT scan and with a consensus agreement from two blinded radiologists indicating the absence of infiltrations upon reassessment were excluded. The definition of patients as possible/suspected COVID-19 cases was determined based on the Possible Case Definitions outlined in the Republic of Turkey Ministry of Health COVID-19 Guidelines, as detailed in supplementary data A.

RT-PCR Test and Thorax Computed Tomography Scanning Procedure and Reporting

Supplementary data A provides details regarding the RT-PCR test and T-CT scanning procedures. In line with the procedure applied in the ED, the on-duty radiologist promptly assessed T-CT scans and reported them as either showing infiltrations or no infiltrations. Patient management decisions were based on these initial results. After database research, only patients identified as having infiltrations in the initial assessment were included in the present retrospective study.

For this study, T-CT scans were re-evaluated by two independent blind radiologists (RS and HT) with 8 and 10 years of thorax imaging experience, respectively. The re-evaluation process followed the guidelines outlined in the Expert Consensus Document on Reporting Thoracic CT Findings Related to COVID-19 by the Radiological Society of North America (RSNA) (6). Blinded radiologists categorized each T-CT scan into one of four categories: typical appearance, indeterminate appearance, atypical appearance for COVID-19 pneumonia, or negative for pneumonia.

Statistical analysis

Mean and standard deviation (SD) were reported for normally distributed data, while median and interquartile range (IQR) values were provided for non-normally distributed data. Categorical data were summarized with counts (n) and percentages (%).

The t-test and the Mann-Whitney U test were used for continuous variables with two independent groups. In cases involving more than two independent groups, the Kruskal-Wallis Analysis of Variance was applied, and post hoc analyses were conducted using the Kruskal-Wallis Multiple Comparison Test to determine group differences. Nominal variable group comparisons utilized the Chi-square and Fisher's Exact tests, each serving specific purposes in distinct analyses.

Interobserver agreement was assessed using Kappa analysis. In instances where the two radiologists assigned inconsistent categories during the examination, Latent Cluster Analysis (LCA) was performed to determine the final

RSNA category for the T-CT scans, using the RT-PCR test as the reference.

To evaluate the diagnostic performance of T-CT, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated by establishing various thresholds based on RSNA categories.

The Latent Gold 3.0 program was employed for LCA, while all other statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software version 21 (SPSS Inc., Chicago, IL, USA). The Type I error probability (α) was 0.05 for all hypothesis tests.

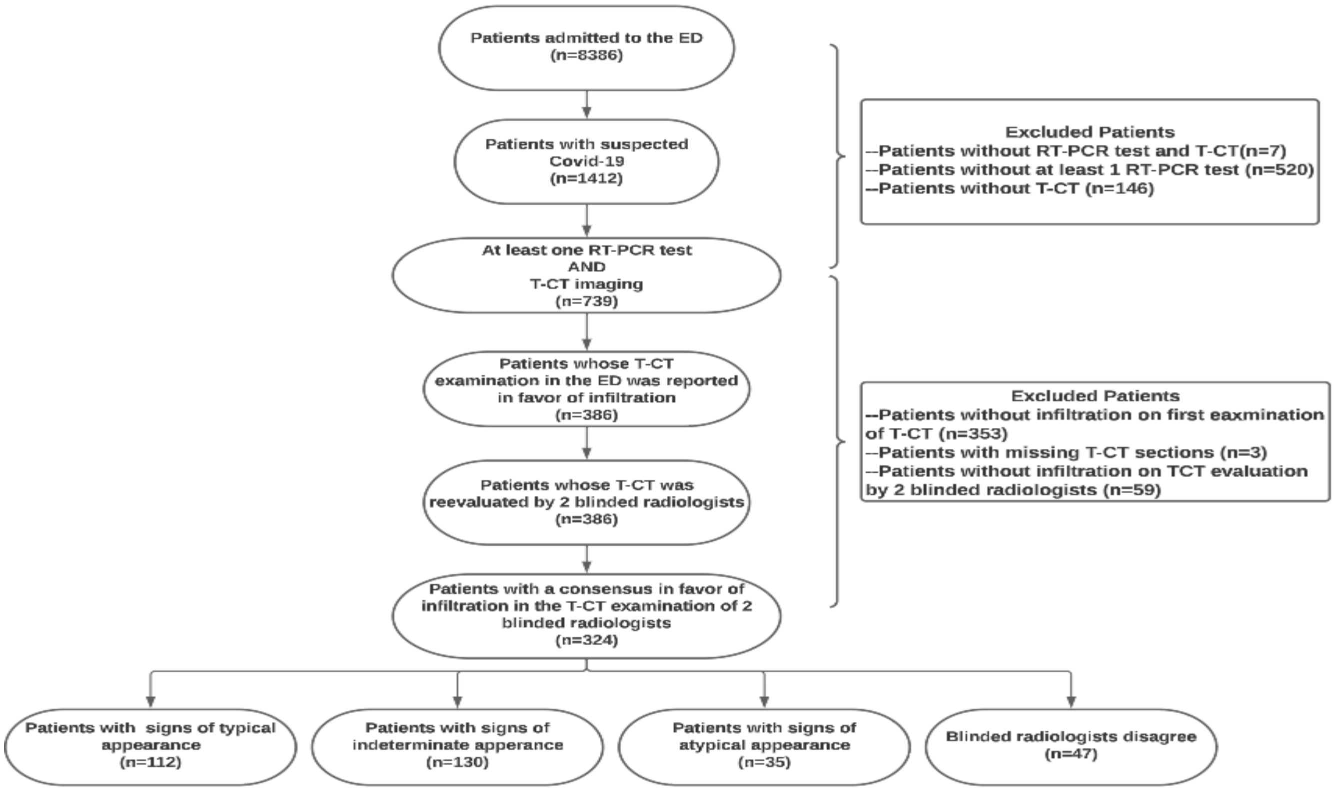

Figure 1. The patient selection diagram

This retrospective study adhered to the institutional and national research committee's ethical standards, the 1964 Helsinki Declaration, and its subsequent amendments or comparable ethical guidelines. The study received approval from the Baskent University Local Ethics Committee (registration number: KA20/225).

Results

Patient Characteristics

The patient selection diagram depicting the process is presented in Figure 1. Detailed patient characteristics can be found in Table 1.

RT-PCR Test Results

When the initial and all subsequent test results were evaluated collectively, at least one RT-PCR test was positive in 112 (34.6%) patients. These 112 patients were considered COVID-19 positive and represented the positive cases in assessing the diagnostic power of T-CT. Among the total population, 20 patients (6%) initially tested negative but subsequently positive in at least one follow-up RT-PCR test. The results of consecutive test outcomes are schematized in Figure 2.

Variable	Median (IQR) or n (%)
Age (years)	66 (50-79)
Sex	
Female	176 (54)
Male	148 (46)
Smoking status	
Actively smoking	47 (15)
Ex-smoker	40 (12)
No smoking history	237 (73)
COVID-19 Contact	
No/unknown	273 (84)
Yes	51 (16)
Comorbidity	
Yes	245 (76)
No	79 (24)
Number of complaints	
≤1	100 (31)
>1	224 (69)
Complaints	
Fever	121 (37)
Cough	96 (30)
Fatigue	75(23)
Shortness of Breath	107 (33)
Chest Pain	25 (8)
Myalgia	48 (15)
Diarrhea	19 (6)
Sore Throat	30 (9)
Headache	12 (4)
Loss of Taste and Smell	9 (3)
'Other'	151 (46)

Table 1. Patient characteristics

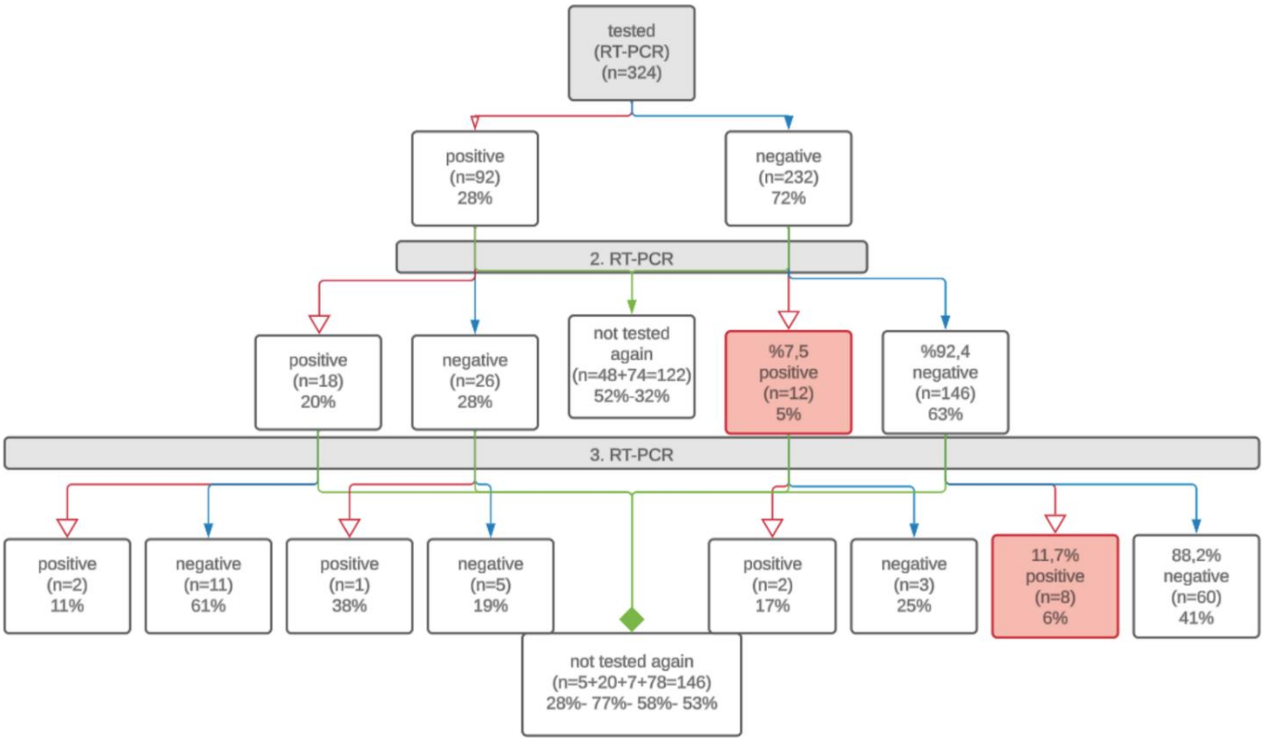

Figure 2. RT-PCR tests and results
Red arrow indicates COVID-19 positive cases, blue arrow indicates negative cases, and green arrow indicates cases not tested for a reevaluation
abbreviations: RT-PCR: reverse transcriptase-polymerase chain reaction

Thorax Computed Tomography Findings

Two independent blinded radiologists retrospectively re-evaluated T-CT images. Radiologist number 1 (R1) classified 124 patients (38.3%) as having typical pneumonia, 146 patients (45.1%) with indeterminate pneumonia, 46 patients (14.2%) with atypical pneumonia, and determined that eight patients (2%) showed no signs of pneumonia. Radiologist number 2 (R2) classified 130 patients (40.1%) as having typical pneumonia, 153 patients (47.2%) with indeterminate pneumonia, 39 patients (12%) with atypical pneumonia, and determined that two patients (0.6%) showed no signs of pneumonia. In the evaluations of both radiologists, the indeterminate category was the most prevalent, followed by the typical category. The most common finding in patients classified as typical pneumonia by both radiologists was a "peripheral ground glass view." For the indeterminate category, the most common finding was a "non-round lesion," for the atypical category, it was an "isolated segmental consolidation without ground glass." Figure 3 displays T-CT images of representative cases for three different RSNA categories.

Although inconsistency among radiologists was observed in 47 patients (14.5%), a statistically significant agreement was found between observers (kappa (κ) 0.765, $p < 0.001$). Following LCA, the final T-CT categorization was approved as typical for 114 patients (35.2%), indeterminate for 154 patients (47.5%), and atypical for 36 patients (11.1%). The T-CT category for 20 patients was considered as No Sign of Pneumonia.

Collective assessment of T-CT and RT-PCR

The RT-PCR test results were compared according to the T-CT category, and a significant correlation (dependence) was observed between them ($p<0.001$). As the category progressed from typical to atypical, an increasing rate of negative PCR test results was observed. The phi coefficient, which shows the relationship size between these two variables, was calculated as 51.4%. The distribution of patients according to RT-PCR test results and T-CT categories after LCA is presented in Table 2.

		T-CT				p
		Typical	**Indeterminate**	**Atypical**	**No**	
RT-PCR	**Positive (n=112)**	**74 (64.9)**	**24 (15.6)**	**3 (8.3)**	**11 (55.0)**	**<0.001**
	Negative (n=212)	40 (35.1)	130 (84.4)	33 (91.7)	9 (45.0)	

Table 2. Patient distributions against T-CT and RT-PCR

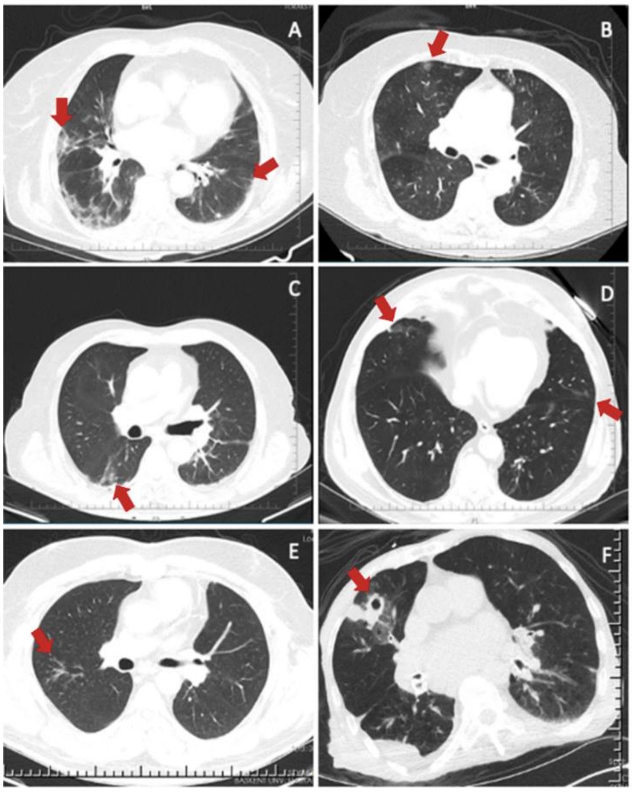

Figure 3. Representative T-CT images according to three different RSNA categories
A. Typical: Peripheral, bilateral, ground-glass opacities; **B.** Typical: Peripheral, multifocal, rounded ground-glass opacities; **C.** Indeterminate: Peripheral and non-peripheral, non-rounded ground-glass opacities; **D.** Indeterminate: Non-rounded, non-peripheral, multifocal ground-glass opacities; **E.** Atypical: "tree-in-bud" appearance; **F.** Atypical: Lung cavitation and consolidation.

False-negative RT-PCR test
The most assigned T-CT category in 20 patients who underwent repeat PCR and were subsequently confirmed as positive was typical pneumonia (60%). There were no atypical categorized cases among these patients. Indeterminate pneumonia findings were observed in 6 patients (30%), and no sign of pneumonia was observed in 2 patients. Due to the very small number of patients in these groups, no statistical analysis could be performed except for the proportional evaluation.

Diagnostic Performance of T-CT Findings in The Diagnosis of COVID-19
The diagnostic power of T-CT was evaluated by accepting the typical, indeterminate, and atypical categories as thresholds, respectively. The diagnostic performance measurements of T-CT for different threshold categories are presented in Table 3. As the threshold category progressed from typical to atypical, sensitivity increased, but specificity, PPV, NPV, and accuracy decreased.
Based on the diagnostic performance analyses' results, it was concluded that using the indeterminate and atypical categories as the positive-negative threshold for T-CT would not be suitable for routine use, as the PPV and accuracy would fall below 50%. Therefore, the typical category was considered the positive-negative result threshold for T-CT in subsequent analyses.
Individuals who underwent multiple RT-PCR tests were analyzed separately to account for the possibility of reduced false-negative PCR results. In this subgroup analysis, significant improvements in diagnostic power were observed, including a sensitivity of 80%, specificity of 79%, positive predictive value (PPV) of 76%, negative predictive value (NPV) of 83%, and an overall accuracy of 79%.
The diagnostic power of combined utilization of RT-PCR and T-CT was also calculated. In that case, patients with positive initial RT-PCR and/or typical category T-CT were considered COVID-19. It was observed that the diagnostic performance increased in the case of combined use, with 95.5% sensitivity, 79% PPV, and 86.4% accuracy.

Discussion
In addressing the urgent need for swift and accurate COVID-19 diagnosis, especially in emergency department (ED) settings, this study investigated the potential of T-CT as a supplementary tool to the standard RT-PCR, which has known limitations (1-4). The diagnostic performance of T-CT, categorized following RSNA guidelines, was assessed in 324 suspected COVID-19 patients. Our findings indicated that utilizing indeterminate and atypical categories as thresholds for routine T-CT diagnosis is unsuitable due to their lower positive predictive value (PPV) and accuracy, falling below 50%. Instead, adopting the typical category as the positive-negative threshold for T-CT is proposed, showcasing a sensitivity of 66%, specificity of 81%, PPV of 65%, NPV of 82%, and an accuracy of 76%.

	Typical category threshold	**Indeterminate category threshold**	**Atypical category threshold**
Sensitivity	66.1%	87.3%	90.2%
Specificity	81.1%	19.8%	4.2%
Positive predictive value	64.9%	36.5%	33.2%
Negative predictive value	82.9%	75.0%	45.0%
Accuracy	75.9%	43.2%	33.9%

Table 3. The diagnostic performance measurements of T-CT for different threshold categories

Previous studies have reported varying results for non-categorized T-CT sensitivity and specificity, ranging from 37% to 98% and 25% to 95%, respectively (5,7-10). However, these studies, often retrospective and potentially biased, displayed methodological errors and diverse patient recruitment criteria. Two large European studies found sensitivities ranging from 79% to 84% and PPVs from 86% to 88% in patients with suspected COVID-19 (11). A Cochrane review reported a T-CT sensitivity of 86.2% and specificity of 18.1% (12). These results align closely with our study's retested subgroup, where repeat testing minimized the false-negative rate attributed to RT-PCR, showing an improved diagnostic accuracy with sensitivity of 80%, specificity of 79%, PPV of 76%, NPV of 83%, and accuracy of 79%.

T-CT's diagnostic efficacy is contingent on observer expertise and reporting accuracy. Distinguishing COVID-19 pneumonia from other viral pneumonia poses a challenge, emphasizing the need for globally standardized reporting. Radiology societies recommend using internationally recognized stratified reporting methods, such as the RSNA classification (6). Our study categorized patients' T-CT scans according to RSNA recommendations to enhance diagnostic accuracy, involving two radiologists in the evaluation process.

The diagnostic performance of T-CT, using RSNA categorization with the typical category as a threshold, has been widely studied, displaying a range of sensitivity (64%-92%), specificity (73-97%), PPV (23-97%), NPV (79-95%), and accuracy (78%-91%) (13-17). Our study's measurements align with these ranges. For instance, Cicaresse et al. retrospectively reviewed T-CT scans of 460 patients, reporting a sensitivity of 71.6%, specificity of 71.6%, and PPV of 87.8% using the typical category threshold. Another study of 773 patients with suspected COVID-19 reported a sensitivity of 90.7% and PPV of 86.4% with the indeterminate category threshold (13). Our study observed a similar sensitivity but a PPV of 36.5% using the same threshold, likely due to differences in RT-PCR positivity rates. Another study with 71 patients reported a sensitivity of 83% and specificity of 97% for T-CT (18). However, the sample composition differed from real-world scenarios. A retrospective study analyzing 160 RSNA-based T-CT scans reported 98.5% specificity for the typical category, with 88.3% sensitivity and 79.0% specificity for the indeterminate category (15). The main difference is that all patients in that study were confirmed COVID-19 cases. A prospective study in the UK involving 259 patients with acute surgical emergencies revealed a sensitivity of 58%, specificity of 73%, and NPV of 77.69% (16).

A study examining the RSNA COVID-19 consensus reporting guidelines in over 200 patients reported a sensitivity of 68% and a PPV of 52%, similar to our findings (19). The researcher attributed this to the low prevalence of COVID-19 and noted increased diagnostic accuracy from April 2020 to March 2021.

Barbosa et al. retrospectively evaluated T-CT accuracy by RSNA categories in 91 suspected COVID-19 patients at a cancer center (17). In scenario one, considering only typical findings as positive, sensitivity, specificity, and accuracy were 64.0%, 84.8%, and 79.1%. In scenario two, considering both typical and indeterminate findings as positive, they were 92.0%, 62.1%, and 70.3%. Results were similar to our study, with diagnostic performance decreasing when applying the indeterminate category threshold.

Combining RT-PCR and T-CT notably enhanced diagnostic performance, achieving a sensitivity of 95.5%, PPV of 79%, and an overall accuracy of 86.4%. While T-CT alone cannot replace RT-PCR as the gold standard, the combined approach offers a more comprehensive and accurate diagnostic strategy.

Finally, it is noteworthy to mention a significant point: today, the course of the disease has notably changed compared to the pandemic, leading clinicians to adopt a more conservative approach to testing. In settings such as EDs, where COVID-19-positive cases and patients with complex conditions, such as those with neutropenic fever, are often monitored in close proximity, T-CT images of patients made for other reasons may provide a diagnostic contribution to identifying COVID-19 without the need for testing. This capability potentially allows for the diagnosis of COVID-19 without the necessity of conducting diagnostic tests.

Limitations

The retrospective nature of our study necessitates a cautious interpretation of the results. It is important to acknowledge the limitations arising from the diagnostic power of the reference test, RT-PCR, which is inherently limited. Therefore, the possibility of false negatives among patients who did not undergo repeat RT-PCR testing despite negative initial results should be considered. Studies indicate that T-CT findings may precede positive RT-PCR results, highlighting the potential for early detection (5,20). Another limitation lies in the potential variation in diagnostic performance based on the stage of the disease, exacerbated by the absence of time-related information in our study. The unknown timing of the second and third RT-PCR tests and symptom onset is unreliable, as viral detection by PCR diminishes over time.

Moreover, since all our patients were symptomatic, caution should be exercised when extrapolating our findings to the general population. It is important to note that this study was conducted during an ongoing phase of the pandemic, and therefore, disease characteristics such as transmissibility and manifestations may differ from the current period. Considering these factors is crucial when generalizing the results of our study to current patients. Moving forward, prospective studies are needed to address these limitations and provide a more comprehensive understanding of T-CT's diagnostic capabilities at different stages of COVID-19.

Conclusion

In conclusion, T-CT cannot replace the gold standard RT-PCR in detecting COVID-19 due to their lack of specificity and potential confusion with other viral pneumonia, but they still hold value in the clinical decision-making process. Based on the RSNA consensus guideline recommendations, T-CT demonstrates a moderate sensitivity of 66% and a high specificity of 81% for diagnosing COVID-19. In the context of suspected cases in EDs, T-CT can aid in advising retesting following an initial negative RT-PCR result, facilitating early management, and enabling timely isolation measures. It is important to note that the indeterminate and atypical categories as thresholds for T-CT in COVID-19 diagnosis are not recommended, as they exhibit lower positive predictive value (PPV) and accuracy below 50%. Instead, the typical category is proposed as the positive-negative threshold for T-CT. Moreover, the combined utilization of RT-PCR and T-CT demonstrates enhanced diagnostic performance, highlighting the potential benefits of integrating these two methods.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Authors' Contribution: SBK: Content planning, Literature search and review, data collection or management, data analysis, writing - original draft. BS: content planning, literature search, editing - original Draft. RS: data collection or management, data analysis, editing - original draft.HT: data collection or management, data analysis, editing - original draft. MSA: Data collection or management, data analysis, editing - original draft. EK: Data collection or management, data analysis, editing - original Draft. EGA: content planning, data analysis, editing - original Draft. MYC: content planning, data analysis, editing - original Draft. All authors reviewed and approved the final version of the manuscript for submission.

Ethical Approval: This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Local Ethics Committee approved this study. The study received approval from the Baskent University Local Ethics Committee (registration number: KA20/225)

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