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Should CT be used for the diagnosis of RT-PCR-negative suspected COVID-19 patients?

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Abstract

Introduction: The diagnosis of patients with Coronavirus disease 2019 (COVID-19) suspicion but negative reverse transcriptase-polymerase chain reaction (RT-PCR) test is challenging.

Objective: We aimed to investigate the diagnostic value of chest computed tomography (CT) in RT-PCR-negative patients with suspected COVID-19.

Materials and methods: The study included patients who were admitted to our hospital with the suspicion of COVID-19 between 1 April 2020 and 30 April 2020 and tested negative after RT-PCR test, and underwent CT for further diagnosis. Initial CT findings were classified as typical, indeterminate, and atypical for COVID-19, and negative for pneumonia. Incidental findings on CT were noted.

Results: Of the 338 patients with a mean age of 57 years (min 18 years–max 96 years), 168 (49.70%) were male and 170 (50.29%) were female. The most common symptoms were cough (58.87%), fever (40.82%), and dyspnea (39.34%). The CT findings were typical for COVID-19 in 109 (32.24%) patients, indeterminate in 47 (13.90%) patients, and atypical in 77 (22.78%) patients. The CT findings of 105 (31.06%) patients were negative for pneumonia. Incidental lung nodules suspicious of malignancy were identified in seven patients. Seventy-seven patients (22.78%) had extrapulmonary incidental findings

Conclusion: The diagnostic value of CT in RT-PCR-negative patients with suspected COVID-19 is not very high. Based on clinical, laboratory, and chest x-ray findings, it may be more appropriate to refer patients to CT after the first triage, when necessary.

KEYWORDS

chest, computed tomography, coronavirus, COVID-19, negative RT-PCR, pneumonia, viral

1 | INTRODUCTION

COVID-19 pneumonia, which first emerged in China in December 2019 and was declared a pandemic in a short period of time, remains a serious public health issue worldwide.[1] Although fever and dry cough are the major symptoms, the common symptoms also include dyspnea, myalgia, loss of taste and smell, nausea, and diarrhea.[2,3] Because of its rapid spread from person to person, the history of contact is of importance in the diagnosis.[4] However, in epidemic areas where there are many patients, most patients do not have a specific history of close contact.[5]

Reverse transcriptase-polymerase chain reaction (RT-PCR) viral nucleic acid testing is the reference method for the diagnosis of the disease.[6] However, its sensitivity is low and has been reported between 42% and 71% in previous studies.[7-10] It may yield significantly high false-negative results in patients with symptoms and a history of close contact who have a high clinical probability.[11,12] In addition, the test is unstable and some patients initially tested negative have been found to be positive

in repeat studies.[13] There are many factors affecting the result, including inappropriate and insufficient sampling, sampling time, low viral load, and the detection rate of the kit used.[12,14] In cases of high patient load, access to the test is a problem. One of the disadvantages of the test is that it is time-consuming.[15] During this period of time, CT has started to be used frequently for the diagnosis and follow-up. Its sensitivity is higher than that of RT-PCR and it provides results faster.[10,16-19] Visualization of peripheral ground-glass density or patchy consolidations on CT allows patients to be considered as a COVID-19 case and to initiate treatment rapidly.[20-22] However, CT emits ionizing radiation, creates a workload, and increases the risk of transmission in hospital.[23-25]

The aim of our study was to investigate the CT findings of high-probability COVID-19 patients with symptoms and a history of close contact but a negative RT-PCR result, as well as the role of CT in the diagnosis of COVID-19.

2 | MATERIALS AND METHODS

This study was approved by the National Ministry of Health, General Directorate of Health Services and the ethics committee of our institution (approval number 2020-05-01T09_16_08.xml). According to the Council for International Organizations of Medical Sciences guidelines, the requirement to obtain informed consent from patients was waived.

We retrospectively evaluated the data of patients who were admitted to our hospital with high case density in our country between 1 April 2020 and 30 April 2020, who underwent RT-PCR on the suspicion of COVID-19 based on clinical evaluation and epidemiological history, but who tested negative for COVID-19 with RT-PCR, and who were treated inpatiently. History of close contact and the number of RT-PCR tests were evaluated. The symptoms examined included fever, cough, dyspnea, myalgia, sore throat, loss of taste and smell, headache, nausea and vomiting, diarrhea, chest and back pain. The study included patients with at least two clinical symptoms or those with at least one clinical symptom and a history of contact. RT-PCR was studied from nasopharyngeal swab samples, and it was studied at least once, at most five times (1.54 on average). All of the initial tests were negative. The tests took 1-5 days to complete. CT examination was performed on the same day as RT-PCR or 1 day after RT-PCR. The initial CT examination of the patients was evaluated, and those without CT examination were excluded from the study.

The CT examinations were performed on two separate devices, 128-slice Philips Ingenuity Multidetector CT (Philips Medical Systems, Best, The Netherlands) and 16-slice Toshiba Alexion CT Scanner (Toshiba Medical Systems, Kyoto, Japan). The parameters used for CT scans were, respectively, as follows: tube voltage, 100-120 kVp; tube current, standard (reference mAs; 200-50); slice thickness, 5.0-5.0 mm; pitch 1.558-1.293. The scans were obtained in the supine position during normal respiration. No intravenous contrast agent was used.

The CT examinations were separately assessed on the EIZO GS520 workstation by two radiologists with 6 and 9 years of experience in the field of thoracic imaging. Indeterminate cases were evaluated jointly and the final decision was made together. The evaluations were carried out in the parenchymal (width 1500 HU; level − 700 HU) and mediastinal (width 350 HU; level 40 HU) window settings. The images were classified as typical for COVID-19, indeterminate for COVID-19, atypical for COVID-19, and negative for pneumonia based on the reporting system proposed by Simpson et al.[26] Accordingly, those with bilateral, peripheral ground-glass opacity accompanied by consolidation or not, and those with a finding of organized pneumonia such as a reversed halo sign were considered typical for COVID-19. Those with diffuse or perihilar ground-glass opacity accompanied by consolidation lacking a specific distribution or not were classified as indeterminate. Lesions other than these were considered atypical.

All statistical analyses were performed using the R software (version 3.6.0; http://www.Rproject.org). Continuous variables were represented as means and standard deviations, while categorical variables were expressed as counts and percentages.

3 | RESULTS

Of the 366 PCR-negative patients treated inpatiently for suspected COVID-19, 28 without CT examination were excluded. The mean age of the remaining 338 patients was 57 years (min 18 years–max 96 years). Of the patients, 168 (49.70%) were male and 170 (50.29%) were female.

In total, 333 of the patients were symptomatic. The most common symptoms were cough (58.87%), fever (40.82%), and dyspnea (39.34%). The symptoms of the patients are illustrated in detail in Table 1. Of these patients, 59 had a history of close contact. Five patients were asymptomatic, but had a strong history of close contact.

Of the 338 patients, 109 (32.24%) had CT findings consistent with typical COVID-19 pneumonia (Figure 1). The CT findings of 47 (13.90%) patients were indeterminate, and the findings of 77 (22.78%) patients were atypical for COVID-19 (Figure 2). Of the patients, 105 (31.06%) had no pneumonia on CT. Typical CT findings were present in 31.88% of the patients with fever and in 32.91% of the patients with both fever and cough (Table 2). Seven patients had a solitary pulmonary nodule, and some with a suspicious appearance for malignancy (Figure 3). Seventy-seven patients (22.78%) had non-pulmonary incidental findings (Figures 4 and 5). These included renal cyst (n = 26), liver mass (n = 15), gallstone (n = 11), thyroid nodule

(n = 9), adrenal mass (n = 5), renal stone (n = 3), hydronephrosis (n = 3), costal lesion (n = 3), suspicious malignant breast lesion (n = 1), and vascular variation (n = 1) (Table 3).

4 | DISCUSSION

The most common reported CT findings of COVID-19 pneumonia are bilateral, ground-glass opacity in the lower lobes, consolidation, and crazy-paving pattern.[9,27-29] It is suggested that CT can be used for the diagnosis of COVID-19.[10,12,14,18]

TABLE 1 Demographic and clinical characteristics of patients

Characteristics	All patients (n = 338)
Age	
Mean	57
Range	18-96
Sex, n (%)	
Male	168 (49.70)
Female	170 (50.29)
Symptoms at presentation, n (%)	
Fever	138 (40.82)
Cough	199 (58.87)
Dyspnea	133 (39.34)
Sore throat	25 (7.39)
Loss of taste-smell	4 (1.18)
Headache	25 (7.39)
Gastrointestinal symptoms (nausea-vomiting, diarrhea)	46 (13.60)
Myalgia	79 (23.37)
Chest and back pain	23 (6.80)
No symptoms	5 (1.47)

It manifests findings in the early stages of the disease, even before the onset of symptoms.[30] Patients with negative initial CT findings have been observed to have positive CT findings again.[31] Its sensitivity and specificity have been reported between 60%–98% and 5%–53%, respectively.[9,10,16] Although the sensitivity of CT has been reported to be high in some studies, its specificity is not high. Therefore, some studies suggest that CT can be used as a supportive tool, but not as a screening test for diagnosis of COVID-19.[9,30,32] Since some studies have found that the negative predictive value of CT as modest, it is not recommended as a screening test.[9] CT has been found to be useful for monitoring COVID-19 pneumonia. Different CT findings have been described in the onset, progression, and resolution stages of the disease.[21,28,33-38] Ground-glass opacity has been frequently reported in the early period, and crazy paving and consolidation during the progression period.[21,33,35,37,38] A gradual decrease in consolidation and ground-glass opacity has been detected during the healing period.[21,33,35,37,38] An increase in fibrous lesions has been observed in the late period.[33,35,37] Pulmonary findings have been found to peak on days 6-11.[21,33,36-38] Previous studies have shown an increase in the number, extent, and density of pulmonary lesions during the progression stage of the disease.[21,32,33,35-38] The extent of pulmonary lesions has been determined to be correlated with clinical and laboratory findings.[36,38] A study by Zhao et al found that bronchiectasis, architectural distortion, and pleural effusion were more common in the severe and fatal patient group than in the mild and common patient group. Again, scoring based on the area of involvement was higher in the severe and fatal patient group.[39]

The American College of Radiology suggested the use of chest x-ray (CXR) for the diagnosis of COVID-19 to minimize the risk of cross-infection and reduce the density in the radiology department.[25] Italian and British hospitals use CXR as a first-line triage tool.[40,41] Some authors have suggested

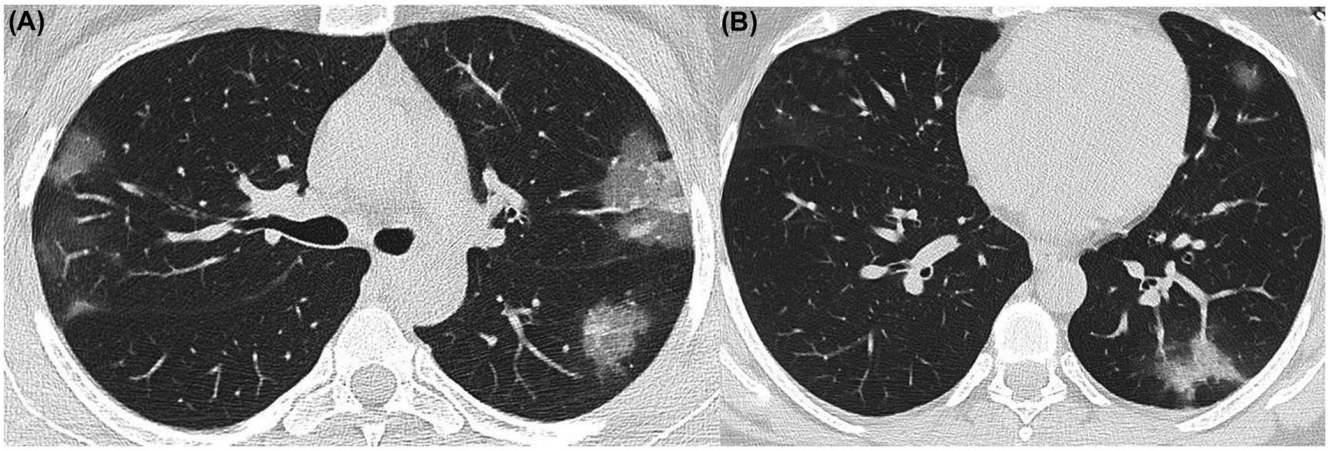

FIGURE 1 Chest CT of a 35-year-old woman with PCR-negative COVID-19 pneumonia. An axial CT image showing multiple ground-glass opacities with superimposed interlobular and intralobular septal thickening

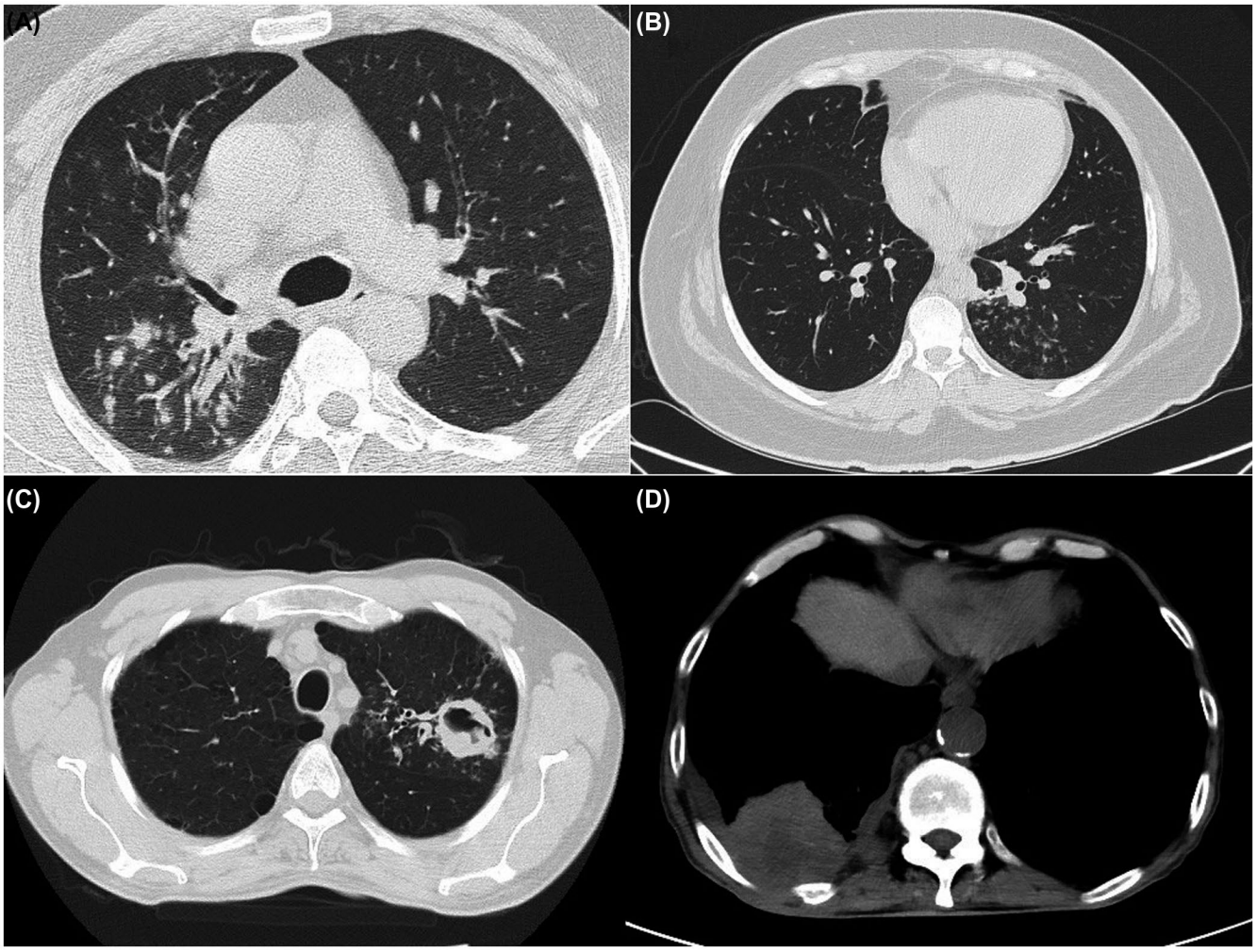

FIGURE 2 Of the RT-PCR-negative patients who underwent chest CT on suspicion of COVID-19 but whose findings were inconsistent with COVID-19. A, A 59-year-old male patient with centrilobular nodular infiltration in the superior segment of the right lung lower lobe. B, A 34-year-old female patient with a tree-in-bud sign in the posterior segment of the left lung lower lobe. C, A 48-year-old male patient with a thick-walled cavitary lesion with a peripheral tree-in-bud sign in the posterior segment of the left lung lower lobe, which is an indicative of tuberculosis or malignancy in the foreground. D, A 72-year-old male patient with a pleural-based mass lesion with a necrotic center posterior to the right lung lower lobe, accompanied by minimal pleural effusion

TABLE 2 Classification of patients by CT findings

	Typical for COVID-19, n (%)	Indeterminate for COVID-19, n (%)	Atypical for COVID-19, n (%)	Negative for penumonia, n (%)
All patients (n:338)	109 (32.24)	47 (13.90)	77 (22.78)	105 (31.06)
Patients with fever (n:138)	44 (31.88)	22 (15.94)	23 (16.66)	49 (35.50)
Patients with fever and cough(n:79)	26 (32.91)	13 (16.45)	13 (16.45)	27 (34.17)

that CXR may have a place in the diagnosis of COVID-19. The most commonly described lesions in these studies were peripheral ground-glass opacity, consolidation, and reticular pattern in the middle and lower zones.[42-44] In their study on the RT-PCR-positive, symptomatic patient group, Vespro et al evaluated CXR as pathological in 80.3% of patients. Of the patients with follow-up CXR, 68.6% had deterioration and 12.3% had improvement in the findings, while 19.1% had no significant change.[43]

In our study, a total of 46.14% of the patients had suggestive findings for COVID-19, with 32.24% typical and 13.90% indeterminate. Among the patients with fever and cough,

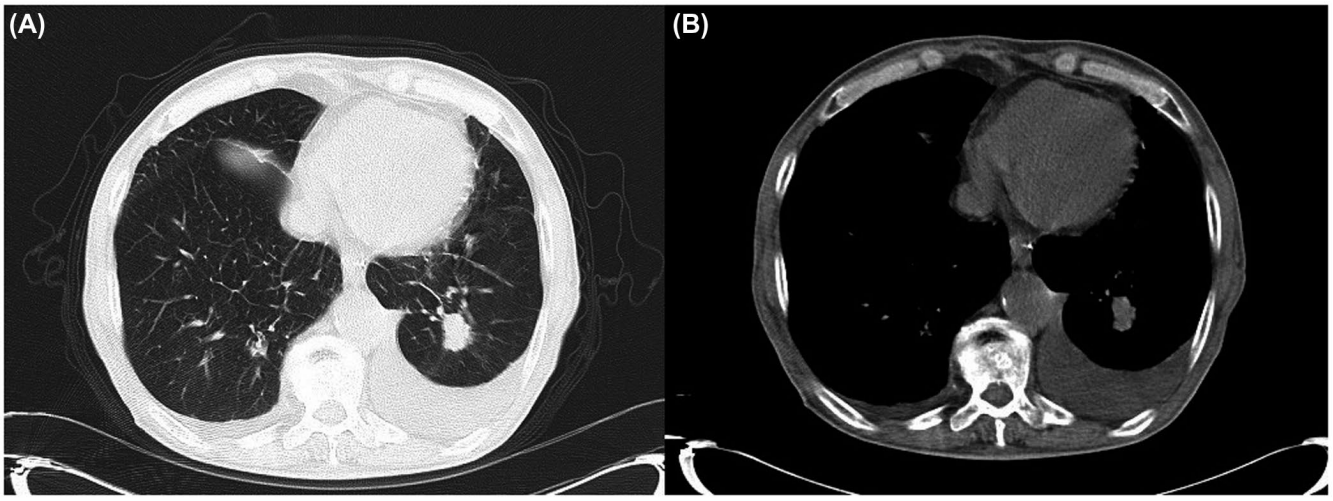

FIGURE 3 Chest CT of a 77-year-old male patient showing a solitary pulmonary nodule suspicious of malignancy and pleural effusion in the posterior segment of the left lung lower lobe in the parenchymal window (A) and the soft tissue window (B)

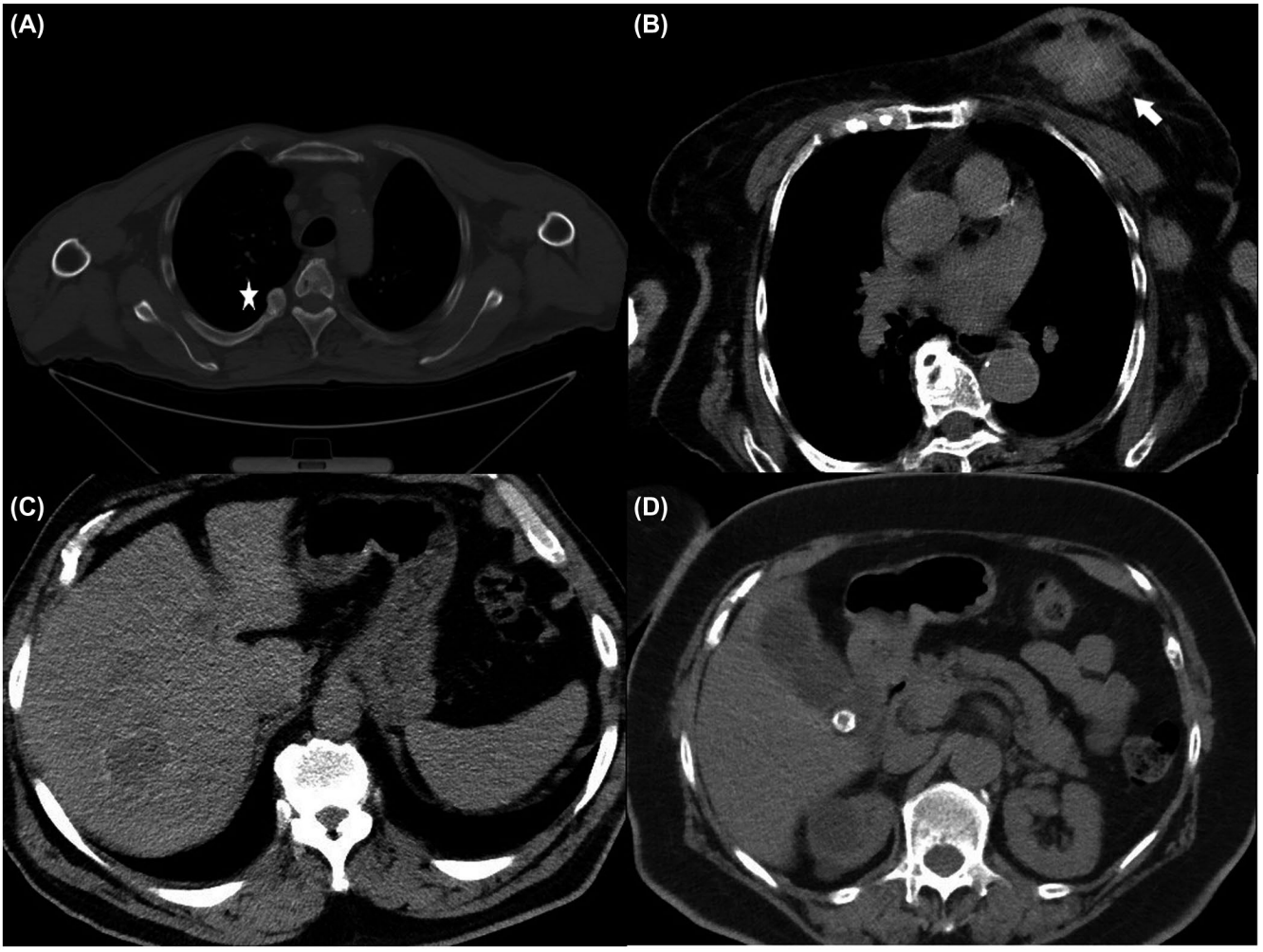

FIGURE 4 Among extrapulmonary incidental findings, A, A 70-year-old female patient with a smooth and well-demarcated lesion (star) at the posterior segment level of the right lung upper lobe, which expands the rib at the costal head on the right. B, A 86-year-old female patient with a mass (arrow) with irregular contour suspicious for malignancy in the left breast. C, A 69-year-old female patient with cholelithiasis and two cortical cysts in the upper pole of the right kidney

FIGURE 5 Among the extrapulmonary incidental findings, A, A 81-year-old male patient with hydronephrosis on the right. B, A 59-year-old male with a renal stone in the lower pole of the left kidney. C, A 72-year-old male patient with a mass lesion (arrowhead) in the right adrenal gland

TABLE 3 Non-pulmonary İncidental findings

Non-pulmonary İncidental CT findings	All patients (n = 77)
Renal cyst	26
Liver mass	15
Gallstone	11
Thyroid nodule	9
Adrenal mass	5
Renal stone	3
Hydronephrosis	3
Costal lesion	3
Malignant breast lesion	1
Vascular variation	1

which are the most common symptoms of the disease, we determined typical CT findings in 31.88% of those with fever and in 32.91% of those with both fever and cough. The diagnostic value of CT was low, even in patients with the most common symptoms. In our study, 31.06% of all patients had no findings of pneumonia. We could detect positive findings on the follow-up CTs. However, follow-up CT scans will increase the radiation dose exposed by patients. According to our results, CT is not an appropriate method as a screening test in RT-PCR-negative patients. Based on our results, CT does not have a high success in diagnosing COVID-19 in RT-PCR negative but clinically suspected patients. Therefore, we are of the opinion that patients who will benefit from CT can be selected under the guidance of clinical and laboratory findings and CXR. The use of CT for determining the severity of the disease and monitoring it will be useful in clinical follow-up. In this way, an elimination will reduce the workload on the radiology departments and increase the availability of CT rooms. Sufficient time can be allocated between scans to adequately disinfect the CT room. Thus, cross-infection risk will be decreased. Since the risk of being infected for healthcare professionals will decrease, the labor loss will decrease in the fight against this pandemic with a rapidly increasing number of patients. Since performing CT on all patients for the diagnosis will increase the radiation dose to which patients will be exposed, the risk of undesired long-term side effects will increase, especially for young patients.

Among the extrapulmonary incidental findings we found, renal stones and gallstones are pathologies that require to be evaluated and treated electively. It is, therefore, important to indicate these pathologies in the CT report. Whether renal cysts, thyroid nodules, hepatic and adrenal masses, and rib lesions are benign or malign should be investigated. The irregular contour of the breast mass we noted in one patient was quite significant for malignancy. Again, indicating for further evaluation of the solitary pulmonary nodule we found in seven patients will increase the survival in malignant lesions. In order to characterize these lesions, further investigations are required. The identification of these lesions is very valuable for early diagnosis and treatment.

In conclusion, we investigated the diagnostic value of CT in RT-PCR-negative patients with suspected COVID-19 in our study. Based on CT findings, we determined typical, indeterminate, atypical, and normal groups for COVID-19. We found a low rate of patients with typical findings for COVID-19 with 32.24%. We noted incidental findings for which early diagnosis and treatment are important. The retrospective nature of the study and not evaluating follow-up CTs are among the limitations of our study.

AUTHOR CONTRİBUTİONS

Concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article, statistics, data collection: G. Rona. *Concept/design, data analysis/interpretation, critical revision of article, approval of article, data collection*: M. Arifoğlu. *Concept/design, data analysis/interpretation, critical revision of article, approval of article*: N. Voyvoda. *Data collection*: A. Batırel.

ETHICS

This study was approved by the National Ministry of Health, General Directorate Of Health Services and the

ethics committee of our institution (approval number 2020-05-01T09_16_08.xml).

CONFLICTS OF INTEREST

The authors and their institutions declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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