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Coronavirus Pandemic

Computed tomography findings in COVID-19 and atypical pneumonia: a comparative study

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Abstract

Introduction: Computed tomography (CT) has an important role in the rapid diagnosis, treatment, and management of lower respiratory tract infections. This study aimed to explore different imaging characteristics between Coronavirus disease 2019 (COVID-19) and atypical pneumonia (non-COVID-19) on chest CT of patients admitted to the emergency department.

Methodology: CT features of 120 patients with positive Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by reverse transcriptase-polymerase chain reaction (RT-PCR) and 83 patients with negative SARS-CoV-2 by RT-PCR but positive respiratory tract sample test results for other respiratory pathogens were retrospectively evaluated, findings were recorded and compared between the two groups.

Results: Compared to non-COVID-19, COVID-19 patients were more likely to have a peripheral (60.5% vs. 23.8%, $p < 0.001$) and bilateral distribution (72.3% vs. 41.3%, $p < 0.001$), patchy consolidations (45% vs. 28.9%, $p = 0.021$), ground glass opacity (GGO) (94.2% vs. 83.1%, $p = 0.011$), crazy paving patterns (55% vs. 31.3%, $p < 0.001$); but less likely to have centrilobular nodules (15% vs. 62.7%, $p < 0.001$), pleural effusion (3.3% vs. 10.8%, $p = 0.032$), multifocal consolidations (7.5% vs. 21.7%, $p = 0.003$), and random distribution (1.7% vs. 46.3%, $p < 0.001$).

Conclusions: There were significant differences between the CT patterns of patients with COVID-19 and other atypical pneumonia. The presence of patchy consolidations, GGO, crazy paving patterns with typical peripheral, bilateral distribution, and absence of centrilobular nodules, pleural effusion, and multifocal consolidations may help to differentiate COVID-19 from atypical pneumonia.

Key words: atypical pneumonia; computed tomography; COVID-19.

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Introduction

Coronavirus disease 2019 (COVID-19), which was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first emerged in Wuhan, China in December 2019 and spread all over the world [1,2]. Though the number of COVID-19 deaths has been declining due to intensive vaccination, it still causes nearly 50,000 deaths weekly. According to the WHO statistics, while over 54,000 new deaths were reported during the week of 27 September to 3 October 2021, over 48,000 new deaths were reported between 1 to 7 November 2021 [3,4]. Despite the decreasing trend in weekly death numbers, COVID-19 could be a chronic seasonal disease in the coming period considering the anti-vaccine movement, lack of complete immunity against infection by vaccines, the probability, and frequency of emergence of new variants, and the lack of efficiency of currently available vaccines against some variants [5].

Respiratory tract specimens tested with reverse transcriptase-polymerase chain reaction (RT-PCR) is the reference standard to confirm the positive diagnosis of COVID-19 infection. SARS-CoV-2 RT-PCR has a high false-negative rate of 21% - 67% [6]. Due to differences in treatment protocols and the prognosis, the differential diagnosis between SARS-CoV-2 and other respiratory pathogens should be made quickly and accurately. Chest computed tomography (CT) not only plays an essential role in the primary diagnosis of COVID-19 but also predicts the severity of the disease [7]. Fang *et al.* found that the sensitivity of chest CT was greater than that of RT-PCR (98% vs 71%) [8]. Some authors recommend chest CT as a primary diagnostic method for detecting COVID-19 in epidemic areas in the initial presentation [9]. The specificity of chest CT in the diagnosis of COVID-19 is very low (19% - 30), depending on age, and gender [9]. Many types of viruses cause acute respiratory infections. The

imaging findings of viral pneumonia are diverse and overlap with those of other non-viral infections, and inflammatory conditions; can be seen in even healthy asymptomatic patients [10,11].

Radiological Society of North America Expert Consensus recommended a standardized CT reporting language of COVID-19 based on current literature in March 2020. Typical CT features seen in COVID-19, more specifically, are peripheral, bilateral, ground-glass opacities (GGO) with or without consolidation, crazy-paving patterns, and reverse halo sign. Indeterminate features have been reported in COVID-19 but are not specific enough to arrive at a relatively confident radiologic diagnosis. Those imaging features are multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation which makes no specific distribution and non-rounded or non-peripheral involvement. Atypical features are reported to be uncommon or not related to COVID-19 and are more typical findings of other diseases. Those imaging features are isolated lobar or segmental consolidation without GGO, discrete small nodules which make tree-in bud patterns, lung cavitation, and smooth interlobular septal thickening with pleural effusion [12]. It is crucial to differentiate COVID-19 from other cases of pneumonia, as the management and treatment protocols are different. However, it may be difficult for radiologists to make differential diagnoses of viral pneumonia due to similar clinical, and imaging findings. In this paper, we aimed to compare different imaging characteristics between COVID-19 and atypical pneumonia on chest CT in patients admitted to the emergency radiology department.

Methodology

Patient selection criteria

Patients with complaints of fever, cough, sore throat, shortness of breath, etc., who were admitted to the emergency department and COVID-19 outpatient clinic of Ankara City Hospital and referred to the emergency radiology department for chest CT with suspicion of COVID-19 between March 2020 and June 2020, were evaluated retrospectively. The study was approved by the ethics committee of our hospital (Approval Number: E1-20-685). Written informed consent was waived for this retrospective study. The RT-PCR and respiratory tract sample test (nasopharyngeal or oropharyngeal swab) were extracted from the hospital information system of the patient's electronic medical records. Patients older than 18 years old, who had a non-enhanced chest CT scan, positive Swab sample test for SARS-CoV-2 by RT-PCR (Bio-Speedy COVID-19 qPCR Detection Kit, Cat No: BS-SY-WC-305, Bioeksen, Turkey) and negative SARS-CoV-2 by RT-PCR but positive respiratory tract sample test for Influenza A virus, Influenza A(H1N1) swl virus, Influenza B virus, Human Rhinovirus, Human Coronavirus NL63, 229E, OC43, and HKU1; Human Parainfluenza 1, 2, 3 and 4; Human Metapneumovirus A/B, Human Bocavirus, Human Respiratory Syncytial Viruses A/B, Human Adenovirus, Enterovirus, Human Parechovirus, *Mycoplasma pneumoniae* (Fast Track FTD Respiratory Pathogens 21 kit, Fast Track Diagnosis, Luxembourg) were included in the study population.

Our exclusion criteria were (1) patients younger than 18 years, (2) patients who had their symptom onset for less than 14 days on their hospital admission day, (3) immunocompromised patients, (4) having positive RT-PCR results for both SARS-CoV-2 and other atypical pathogens, (5) patients with artifacts on CT images (6) patients who had positive CT findings but negative RT-PCR results.

Image acquisition

All CT studies were performed with two devices with 128-detector systems (*GE Revolution EVO 128 Slice CT Scanner, GE Medical Systems, Milwaukee, WI, USA)* specially reserved for patients who were suspected of being COVID-19 positive. All scans were performed without intravenous contrast media, from the first rib to the adrenal glands, with the patient in the supine position during end-inspiration, using the following parameters; tube voltage of 100 kV, tube current of 90-300 mAs, spiral pitch factor of 0.98, collimation width of 0.625 mm, and slice thickness of 1.3 mm with a sharp reconstruction kernel.

Image interpretation

Two emergency radiologists (with 14 and 6 years of experience) evaluated the CT images by consensus. CT findings were defined and recorded in accordance with the Fleischner Society glossary of terms criteria [13]. The CT images were examined for the presence or absence of the following findings: patchy consolidation (≥ 1 cm or more than 1 segmental level), multifocal consolidations (< 1 cm and more than 3 in number), GGO, centrilobular nodules (CLN), bronchial wall thickening, interlobular septal thickening, crazy paving patterns, air bronchogram, pleural effusion, halo sign, pericardial effusion, tree-in-bud sign, vascular thickening, atelectasis, and lymphadenopathy (which was defined as a lymph node > 1 cm in short-axis diameter), and normal appearance. The anatomic

distribution of the lesions was also recorded as following findings; laterality (right lung/left lung/ bilateral lungs), affected lobes (right upper/ middle/ lower lobe, left upper/lower lobe), distribution (peripheral, central, diffuse, random), and lesion number (single/multiple lesions).

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA). In descriptive statistics, the continuous variables were expressed as mean ± SD, while categorical variables were expressed in numbers and percentages. The Mann-Whitney U test was used to compare the continuous variables of the two groups. Differences between categorical variables are calculated by the Chi-Square test. A p value of < 0.05 was considered statistically significant.

Results

Our study consists of 203 (88 female, 115 male) patients. There were 120 (49 female, 71 male) SARS-CoV-2 RT-PCR positive patients (COVID-19 group) and 83 patients (39 female, 44 male) who had one or two other respiratory pathogens positive Multiplex RT-PCR (non-COVID-19 group). The non-COVID-19 group consisted of, Enterovirus (n = 4), Human Adenovirus (n = 11), Human Bocavirus (n = 3), Human Coronavirus NL63 (n = 2), Human Metapneumovirus A/B (n = 16), Human Parainfluenza B (n = 2), Influenza A, B (n = 10), Human Respiratory Syncytial Viruses A/B (n = 9), Human Rhinovirus (n = 18), *Mycoplasma pneumoniae* (n = 10) patients. Two patients had positive Multiplex RT-PCR test for two viruses, one of them positive for Metapneumovirus and Rhinovirus together and the other had a positive result for Metapneumovirus A/B and Enterovirus together.

The comparison of clinical characteristics, including age, gender, comorbidities, mortality, and intensive care hospitalisation between the two groups, was shown in Table 1. The mean age was 47.9 years (range of 18-88) in the COVID-19 group and 45.4 years (range of 20-87) in the non-COVID-19 group; there was no significant difference in terms of age ($p = 0.204$) and gender ($p = 0.384$) between both groups.

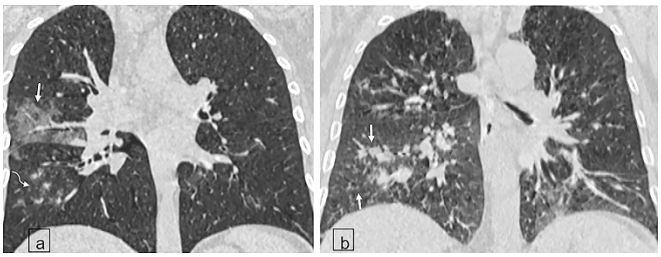
Chronic lung disease was significantly higher in the non-COVID-19 group than in the COVID-19 group (16 (19.3%) vs 7 (5.8%), $p = 0.003$).

One (0.8%) patient with positive SARS-CoV-2 PCR had no lung involvement on CT, while two patients (2.4%) with Rhinovirus positive Multiplex RT-PCR respiratory sample test had either no lung involvement on CT.

The distribution of the lesions was listed in Table 2 and CT features are listed in Table 3.

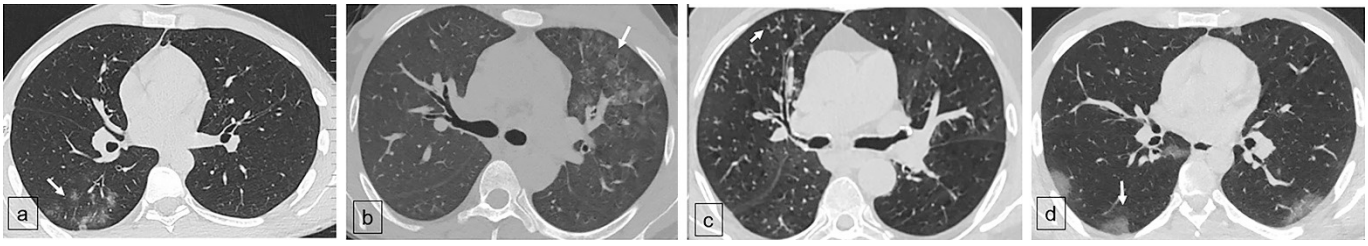
Compared to non-COVID-19, COVID-19 lesions were more likely to be bilateral (72.3%), peripheral (60.5%), with lower lobe predominance (right 84.2%, left 71.7%) ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p = 0.004$ respectively).

Figure 1. Thorax CT images of two non-COVID-19 patients.



Coronal reformatted images of non- contrast chest CT (**a**) reveals right upper lobe GGO (*white arrow*) and right lower lobe CLN with multifocal consolidation (*curved arrow*) in a 41-year-old female patient with influenza pneumonia; and (**b**) reveals CLN, GGO and consolidation (*white arrow*) in a 73 -year-old female patient with Human Respiratory Syncytial Virus pneumonia. (CLN, centrilobular nodules; GGO, ground-glass opacities)

Figure 2. Thorax CT images of non-COVID-19 and COVID-19 patients.



Non-contrast chest CT images (**a**) in a 20-year-old male with Metapneumovirus pneumonia; shows right lower lobe GGO with CLN (*white arrow*), (**b**) in a 31-year-old woman with Mycoplasma pneumonia shows left upper lobe GGO with CLN (*white arrow*) (**c**) in a 77-year-old man with influenza pneumonia shows tree-in bud (*white arrow*) with bronchial wall thickening (**d**) in a 43-year-old man with COVID-19 pneumonia shows peripheral GGO (*white arrow*). (CLN, centrilobular nodules; GGO, ground-glass opacities).

Table 1. Demographic and clinical characteristics of the patients.

	COVID-19 (n = 120)	Non-COVID (n = 83)	*p* value
	Mean ± SD / n (%)		
Gender			
Female	49 (40.8%)	39 (47%)	0.384
Male	71 (59.2%)	44 (53%)	
Age	47.9 ± 15.7	45.4 ± 18.2	0.204
Comorbidity			
Hypertension	19 (15.8%)	14 (16.9%)	0.844
Chronic lung disease	7 (5.8%)	16 (19.3%)	**0.003**
Diabetes Mellitus	12 (10%)	8 (9.6%)	0.932
Coronary Artery Disease	8 (6.7%)	7 (8.4%)	0.636
Chronic Kidney Disease	3 (2.5%)	5 (6%)	0.205
Cerebrovascular Disease	1 (0.8%)	2 (2.4%)	0.360
ICU hospitalization	16 (13.4%)	8 (9.6%)	0.411
Mortality	4 (3.4%)	2 (2.4%)	0.695

ICU: Intensive care unit

Table 2. Distribution of the lesions in the patients with COVID-19 and non-COVID-19.

Characteristics	COVID-19 (n = 120)	Non-COVID (n = 83)	*p* value
Laterality			
Right	25 (21%)	21 (26.3%)	**< 0.001**
Left	8 (6.7%)	26 (32.5%)	
Bilateral	86 (72.3%)	33 (41.3%)	
Frequency of lobe affected			
Right upper lobe	81 (67,5%)	39 (47%)	**0.003**
Right middle lobe	75 (62.5%)	31 (37.3%)	**< 0.001**
Right lower lobe	101 (84.2%)	52 (62.7%)	**< 0.001**
Left upper lobe	79 (65.8%)	36 (43.4%)	**0.002**
Left lower lobe	86 (71.7%)	43 (51.8%)	**0.004**
Distribution			
Peripheral	72 (60.5%)	19 (23.8%)	
Central	3 (2.5%)	10 (12.5%)	**< 0.001**
Diffuse	42 (35.3%)	14 (17.5%)	
Random	2 (1.7%)	37 (46.3%)	
Lesion number			
Single Lesion	24 (20.2%)	11 (13.8%)	0.244
Multiple lesions	95 (79.8%)	69 (86.3%)	

Table 3. Chest CT findings in the patients with COVID-19 and Non-COVID-19 patients.

Computed Tomography Findings	COVID-19 (n = 120)	Non-COVID (n = 83)	*p* value
Ground glass opacity	113 (94.2%)	69 (83.1%)	**0.011**
Patchy Consolidation	54 (45%)	24 (28.9%)	**0.021**
Multifocal consolidations	9 (7.5%)	18 (21.7%)	**0.003**
Bronchial wall thickening	117 (97.5%)	62 (74.7%)	**< 0.001**
Centrilobular Nodules	18 (15%)	52 (62.7%)	**< 0.001**
Interlobular Septal Thickening	89 (74.2%)	43 (51.8%)	**0.001**
Normal Appearance	1 (0.8%)	2 (2.4%)	0.360
Air Bronchogram	60 (50%)	33 (39.8%)	0.150
Pleural Effusion	4 (3.3%)	9 (10.8%)	**0.032**
Crazy paving	66 (55%)	26 (31.3%)	**0.001**
Halo sign	11 (9.2%)	4 (4.8%)	0.244
Pericardial effusion	3 (2.5%)	3 (3.6%)	0.645
Atelectasis	29 (24.2%)	9 (10.8%)	**0.017**
Lymphadenopathy	1 (0.8%)	4 (4.8%)	0.072
Tree-in bud sign	15 (12.5%)	49 (59%)	**< 0.001**
Vascular thickening	29 (24.2%)	8 (9.6%)	**0.008**
Cavitation	-	2 (2.4%)	0.087
Combinations			
GGO (+), CLN(-)	99 (82.5%)	26 (31.3%)	**< 0.001**
GGO (+), PC (+),CLN(-), PE(-)	42 (35%)	11 (13.3%)	0.001
Periferal distrubiton (+), bilateral (+), Lower lober (+), CLN(-)	37 (30.8%)	7 (8.4%)	**< 0.001**

CLN: centrilobular nodules; GGO: ground glass opacity; PC: patchy consolidation; *PE*: *pleural effusion.*

Random (n = 37, 46.3%) and central (n = 10, 12.5%) distribution of the lesions were significantly higher in the non-COVID-19 group ($p < 0.001$). There was no statistically significant difference between the groups in terms of the multiplicity of the lesions, which tended to be multiple in both groups.

While consolidations were more likely to be patchy in the COVID-19 group ($p = 0.021$), it was more likely to be multifocal in the non-COVID-19 group ($p = 0.003$). Bronchial wall thickening (n = 117; 97.5%), GGO (n = 113, 94.2%), patchy consolidation (n = 54, 45%), crazy paving (n = 66, 55%), interlobular septal thickening (n = 89, 74.2%), atelectasis (n = 29, 24.2%), vascular thickening (n = 29, 24.2%) was statistically higher in COVID-19 group ($p < 0.001$, $p = 0.011$, $p = 0.021$, $p = 0.001$, $p = 0.017$, $p = 0.008$; respectively), whereas CLN (n = 52, 62.7%), tree-in bud sign (n = 49, 59%), pleural effusion (n = 9, 10.8%) were statistically higher in the non-COVID-19 group ($p < 0.001$, $p < 0.001$ and $p = 0.032$ respectively) (Figure 1, 2).

Discussion

Viruses are the most common cause of respiratory tract infections. Numerous viruses can cause several pathologic forms of lower respiratory tract infections including tracheobronchitis, bronchiolitis, and pneumonia in adults [14]. A respiratory tract pathogen needs to be diagnosed due to the requirement of individual antiviral treatment and also SARS-CoV-2 treatment differs from other viral infections in some aspects. Rapid diagnosis can provide early control of potential transmissions and allows the use of appropriate therapeutic agents. Although a definite diagnosis cannot be achieved with CT features, radiologists can refer to whether the pathogen is bacterial, viral, or fungal in conjunction with patients' clinical history on the basis of CT imaging patterns [10]. The imaging findings of viral pneumonia are diverse and overlap with those of other non-viral infections, and inflammatory conditions and can be seen in even healthy asymptomatic patients [10,11].

The typical CT findings of viral pneumonia in adults were poorly defined as CLN (air-space nodules of 4–10 mm in diameter), patchy areas of peribronchial GGO with a lobular distribution, segmental consolidation, or diffuse ground-glass attenuation with thickened interlobular septa [14].

Viruses in the same viridae can have similar imaging characteristics since they utilise similar pathways in the pathogenesis of respiratory tract infections. Imaging features can differ even for the same virus depending on the patient's age, immune system status, and the time course of the infection when the patient is scanned [10]. In this study we only included cases of acute infection with up to 14 days of evolution of infection, to limit this temporal variation of CT findings.

Altmayer *et al.* conducted a meta-analysis issued on the comparison of the chest CT findings between COVID-19 and non-COVID-19 viral pneumonia and revealed that frequent CT features for both COVID-19 and non-COVID-19 viral pneumonia were a mixed pattern of GGO and consolidation, pleural effusion was rare in COVID-19 but more common in other viral pneumonia, and COVID-19 and non-COVID-19 viral pneumonia had overlapping chest CT findings except for a higher prevalence of peripheral distribution, involvement of upper and middle lobes [15]. In our study, besides being more frequent in the COVID-19 group, bronchial wall thickening and GGO were the more common findings in both groups. COVID-19 presented a higher prevalence of crazy paving patterns, peripheral and bilateral distribution than non-COVID-19. Non-COVID-19 demonstrated a higher prevalence of CLN and tree-in bud sign and pleural effusion predominantly unilateral, random distribution than COVID-19. We also found consolidation appearances were different in the two groups, and while predominantly consolidations were patchy rather than multifocal in COVID-19, it is vice versa in non-COVID-19. COVID-19 had a higher prevalence of lobe involvement for each lobe than non-COVID-19. Although more severe in COVID-19, both COVID-19 and non-COVID-19 cases of pneumonia affected the lower lobes more frequently. This was different from this meta-analysis. Altmayer *et al.* reported the lower prevalence of upper and middle zone disease observed in the non-COVID-19 population may be underestimated because many authors in non-COVID-19 did not note which individual lobes were affected while the COVID-19 studies declared the affected lobes individually [15].

Bai *et al.* reported chest CT findings of 424 patients diagnosed with COVID-19 or non-COVID-19. The study demonstrated that peripheral distribution (80% vs. 57%, $p < 0.001$), GGO (91% vs. 68%, $p < 0.001$), vascular thickening (59% vs. 22%, $p < 0.001$), fine reticular opacity (56% vs. 22%, $p < 0.001$) were more common in COVID-19 group than non-COVID-19 group and central + peripheral distribution (14% vs. 35%, $p < 0.001$), pleural effusion (4.1% vs. 39%, $p < 0.001$) and lymphadenopathy (2.7% vs. 10.2%, $p < 0.001$) were less common in COVID-19 group than non-COVID-19 group [16]. We also found peripheral

distribution (60.5% vs. 23.8%, $p < 0.001$), GGO (94.2% vs. 83.1%, $p = 0.011$), interlobular septal thickening (74.2 vs. 51.8%, $p = 0.001$), and vascular thickening (24.2% vs. 9.6%, $p = 0.008$) more common in COVID-19 than non-COVID-19, but diffuse distribution (35.3% vs. 17.5%, $p < 0.001$), pleural effusion (3.3% vs. 10.8 %, $p = 0.032$) was less common in COVID-19 than non-COVID-19. The reason for less frequent pleural effusion in our study may be due to the inclusion criteria of the study population, which consisted of patients admitted to the emergency department with complaints of respiratory and/or covid-like symptoms.

Several studies about the novel swine-origin influenza A (H1N1) virus, one of the causative agents of atypical pneumonia were reported. A common CT finding was GGO with or without consolidations in H1N1 [17-19]. One of these reports states that GGOs had a predominantly peribronchovascular and subpleural distribution [20] while others state a predominantly patchy distribution [20] and bilateral with no axial or craniocaudal predominance in the distribution [18]. In our study, influenza A and B infected 10 patients had a unilateral (%50), peripheral (50%) distribution of GGO (80 %), and CLN (70%).

One of the study, comparing COVID-19 and H1N1 pneumonia patients, revealed that GGO was more common in COVID-19 patients than in H1N1 patients [21]. Liu *et al.* reported that COVID-19 patients were more likely to have rounded opacities (35% vs. 17%, $p = 0.048$) and interlobular septal thickening (66% vs. 43%, $p = 0.014$) than the influenza patients, but less likely to have nodules (28% vs. 71%, $p < 0.001$), tree-in-bud sign (9% vs. 40%, $p < 0.001$), and pleural effusion (6% vs. 31%, $p < 0.001$) [22]. Similarly, we detected tree-in bud sign (12.5% vs 70 %, $p < 0.001$), CLNs (15% vs 70 %, $p < 0.001$), and pleural effusion (3.3% vs. 10%) were less common in COVID-19 than patients infected with influenza A, B.

Our study has a few limitations. First, the non-COVID-19 group suffered from several viruses as well as a bacterium infection (*Mycoplasma pneumonia*), one of the most common causes of atypical pneumonia. We could not compare CT findings of non-COVID-19 group pathogens and with COVID-19 separately due to the small number of each pathogen group. Second, although we included only patients who had a symptom on-set up to 14 days on admission day of the hospital, CT scans of all patients could not be performed on the same symptomatic day, because the admission time of the patients to the hospital was not the same for all patients. Thirdly, we did not compare follow-up CT images, CT findings can be changed in the course of the disease.

Conclusions

Significant differences existed in the CT patterns of patients with COVID-19 and other atypical pneumonia. The presence of patchy consolidations, ground-glass opacities, crazy paving patterns with typical peripheral, bilateral, and predominantly lower lobe distribution and absence of CLN, tree-in bud sign, pleural effusion, multifocal consolidations might help us to differentiate COVID-19 from atypical pneumonia. In conclusion, radiologists may recognize COVID-19 and non-COVID-19 atypical pneumonia based on specific imaging features on chest CT. Further studies with larger sample size and including different subgroups of viruses and patients demographics, symptom duration, follow-ups, and disease severity are needed.

Authors' contributions

EÇ: principal investigator, conceived the overall concept and wrote the first draft of the manuscript and prepared the final version. ISP: Conception, desing, provide revisions to scientific content, approval of final publication. YCG, helped in the collection of the data, literature review and contributed to the first and revised version of the manuscript. GKB helped in the collection of the data and literature review. AK, provided revisions to scientific content, resources.

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