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Note

Early identification of novel coronavirus (COVID-19) pneumonia using clinical and radiographic findings

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ABSTRACT

Introduction: The Japanese Respiratory Society (JRS) scoring system is a useful tool for identifying *Mycoplasma pneumoniae* pneumonia. Most COVID-19 pneumonia in non-elderly patients (aged <60 years) are classified as atypical pneumonia using the JRS scoring system. We evaluated whether physicians could distinguish between COVID-19 pneumonia and *M. pneumoniae* pneumonia using chest computed tomography (CT) findings. In addition, we investigated chest CT findings if there is a difference between the variant and non-variant strain.
Methods: This study was conducted at five institutions and assessed a total of 823 patients with COVID-19 pneumonia (335 had lineage B.1.1.7.) and 100 patients with *M. pneumoniae* pneumonia.
Results: In COVID-19 pneumonia, at the first CT examination, peripheral, bilateral ground-glass opacity (GGO) with or without consolidation or crazy-paving pattern was observed frequently. GGO frequently had a round morphology (39.2%). No differences were observed in the radiological findings between the non-B.1.1.7 groups and B.1.1.7 groups. The frequency of pleural effusion, lymphadenopathy, bronchial wall thickening and nodules (tree-in-bud and centrilobular) was low. In contrast to COVID-19 pneumonia, bronchial wall thickening (84%) was observed most frequently, followed by nodules (81%) in *M. pneumoniae* pneumonia. These findings were significantly higher in *M. pneumoniae* pneumonia than COVID-19 pneumonia.
Conclusions: Our results demonstrated that a combination of the JRS scoring system and chest CT findings is useful for the rapid presumptive diagnosis of COVID-19 pneumonia in patients aged <60 years. However, this clinical and radiographic diagnosis is not adapted to elderly people.

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), follows a biphasic pattern of illness that likely results from the combination of an early viral response phase and an inflammatory second phase [1]. Although most clinical presentations of COVID-19 are mild, approximately 20% of those infected with SARS-CoV-2 are known to develop moderate to severe life-threatening pneumonia with respiratory failure [1]. Many outbreaks of COVID-19 have occurred in families, education facilities, child welfare facilities, welfare facilities for persons with disabilities, long-term care health facilities and medical institutions. To reduces the risk of outbreaks and prevent the infection spread, early identification of COVID-19 is important.

The term 'atypical pneumonia' was first applied to viral community-acquired pneumonia (CAP), which is clinically and radiologically distinct from bacterial CAPs. One feature of the Japanese Respiratory Society (JRS) guidelines is that it tries to differentiate atypical pneumonia, mainly *Mycoplasma pneumoniae* pneumonia and bacterial pneumonia, to select an appropriate antibiotic for managing mild to moderate CAP [2]. The JRS extracted six parameters from patients with *M. pneumoniae* pneumonia using multiple regression analysis [2]. In a recent study, we evaluated whether the JRS scoring system could be used to differentiate COVID-19 pneumonia from bacterial pneumonia. The diagnostic sensitivity for COVID-19 pneumonia was 95.5% for non-elderly patients (aged <60 years) and 32.5% for elderly patients (age ≥60 years) [3]. After the start of vaccination against SARS-CoV-2, infection is centred on non-elderly people, just like *M. pneumoniae* infection. Thus, physicians can clinically diagnose COVID-19 pneumonia using the JRS scoring system if physicians can distinguish

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List of abbreviations

CAP	Community-acquired pneumonia
COVID-19	Coronavirus disease
CT	Computed tomography
GGO	Ground-glass opacity
JRS	Japanese Respiratory Society
PCR	Polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

M. pneumoniae pneumonia from COVID-19 pneumonia. In the clinical setting, physicians usually add chest computed tomography (CT) as an auxiliary diagnostic modality, and the CT findings of *M. pneumoniae* pneumonia are clearly different from those of bacterial pneumonia [4]. However, there is no direct comparison data between COVID-19 pneumonia and *M. pneumoniae* pneumonia. We aimed to clarify the patterns of abnormality with COVID-19 pneumonia on chest CT and investigate whether COVID-19 pneumonia can be distinguished from *M. pneumoniae* pneumonia based on radiographic findings. In addition, we investigated chest CT findings to determine whether there is a difference between the variant and non-variant strain in COVID-19 pneumonia.

The present study was conducted at five institutions (Kansai Medical University Hospital, Kansai Medical University Medical Center, Kansai Medical University Kori Hospital, Kansai Medical University Kuzuha Hospital, and Kansai Medical University Temmabashi General Clinic) between February 2020 and June 2021 [3]. During the study, a new lineage of the SARS-CoV-2, named B.1.1.7, had rapidly spread throughout Japan from March 2021, and there was almost 100% replacement of previous strains by the B.1.1.7 variant in June 2021. We enrolled adult patients diagnosed with mild to moderate CAP, defined according to the JRS guidelines [2]. COVID-19 was diagnosed with positive real-time reverse transcription-polymerase chain reaction (RT-PCR) results from sputum or nasopharyngeal swab specimens according to the protocol recommended by the National Institute of Infectious Diseases, Japan. *M. pneumoniae* was diagnosed with positive real-time PCR results from nasopharyngeal swab specimens and/or a four-fold rise in the antibody titer level between paired sera. During the study period, 823 patients with COVID-19 pneumonia (335 had lineage B.1.1.7.) and 32 patients with *M. pneumoniae* pneumonia were recorded [3]. Cases of pneumonia mixed with other microorganisms were excluded from the study. We further analyzed 68 patients with *M. pneumoniae* pneumonia observed between January 2018 and January 2020 because the sample size was small. Informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee of Kansai Medical University (approval number 2020319).

High-resolution CT was performed with 1-mm collimation at 10-mm intervals. Images were obtained at the lung (level −700 HU; width, 1500 HU) and mediastinal (level 20–40 HU; width, 400 HU) levels. CT images were independently analyzed by three chest radiologists (with 21, 16, and 15 years of experience) who were blinded to the patients' diagnoses. The time between the clinical onset of pneumonia (fever and/or other symptoms) and CT ranged from 1 to 14 days (mean, 4.7 days) for COVID-19 pneumonia and from 1 to 10 days (mean, 5.1 days) for *M. pneumoniae* pneumonia. No differences were observed in the CT image shooting time and clinical findings between the 32 patients (COVID-19 pandemic period) and 68 patients (non-COVID-19 pandemic period) with *M. pneumoniae*.

The CT images were assessed for the presence of consolidation (homogeneous opacification with obscuration of the underlying vasculature), ground-glass opacity (GGO) (hazy areas of increased attenuation without obscuration of the underlying vasculature), reticular pattern (consisting of either coarse linear or curvilinear opacity or fine subpleural reticulation without substantial GGO), and mixed pattern (a combination of consolidation, GGO, and reticular opacity in the presence of architectural distortion). The intralobular lines in GGO described as crazy-paving appearance were not classified as characteristic of an area of reticular or linear opacity. A centrilobular nodule was defined as a nodule identified around the peripheral pulmonary arterial branches, 3–5 mm away from the pleura, interlobular septa, or pulmonary veins. Bronchial wall thickening was defined as thickening that identified widespread areas not close to GGO and/or consolidation areas. Mediastinal lymphadenopathy was judged to be present when the minimal diameter of the lymph node was >10 mm. Hilar lymphadenopathy was judged to be present only if the maximum diameter of the ipsilateral hilum exceeded that of the contralateral hilum by 1.5-fold or more. The final decisions regarding the presence of each finding and opacity pattern for each case were reached by consensus among the three radiologists.

The kappa value between the readers was 0.612 for consolidation, 0.573 for GGO, 0.738 for nodules, 0.588 for thickening of the bronchial wall, 0.571 for reticular or linear opacity, 0.891 for pleural effusion, and 0.632 for lymphadenopathy. These values indicated fair to good inter-reader agreement.

In COVID-19 pneumonia, at the first CT examination, peripheral, bilateral GGO with or without consolidation or crazy-paving pattern was observed frequently (Fig. 1A). GGO frequently (39.2%) had a round morphology (Fig. 1B). Multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and that was nonrounded or non-peripheral were also observed. No differences were observed in the radiological findings between the non-B.1.1.7 groups and B.1.1.7 groups (Table 1). The frequency of pleural effusion, lymphadenopathy, bronchial wall thickening and nodules (tree-in-bud and centrilobular) was low (Table 1). In contrast to COVID-19 pneumonia, bronchial wall thickening (84%) was observed most frequently, followed by nodules (tree-in-bud and centrilobular) (81%) in *M. pneumoniae* pneumonia, and these findings were significant (Table 1).

The median age was significantly younger in *M. pneumoniae* pneumonia than COVID-19 pneumonia ($p < 0.001$, Table 1). Thus, we further analyzed the patterns of abnormality with COVID-19 pneumonia on chest CT between the non-elderly patients (aged <60 years) and elderly patients (age ≥60 years). The frequency of bronchial wall thickening and nodules (tree-in-bud and centrilobular) was low even in the non-elderly patients (Table 2). No significant differences were observed in the radiological findings between the non-elderly patients and elderly patients (Table 2).

We analyzed serial CT findings over time in 363 patients in COVID-19 pneumonia. Fig. 2 shows the temporal changes in COVID-19 pneumonia. In the first week after symptom onset, the predominant pattern of abnormality was GGO (70.2%), followed by a mixed pattern (15.0%) and consolidation (14.8%) (Fig. 2A). In the second week after symptom onset, as the disease progressed, GGO was still the predominant CT finding (51.7%), followed by a consolidation (28.2%) and mixed pattern (20.1%) (Fig. 2B). In the third week after symptom onset, GGO (42.3%) and mixed pattern (37.3%) were the predominant imaging patterns, followed by consolidation (9.1%), reticular pattern (8.1%), and normal pattern (3.2%) (Fig. 2C).

It is well known that it is difficult to suspect the COVID-19 pneumonia in the clinical findings exception of presence of loss of taste and anosmia in the daily clinical setting [3]. Among the diagnostic methods, RT-PCR assay is thought to be the gold standard for diagnosing COVID-19. However, with oropharyngeal and nasopharyngeal swab specimens, the sensitivity of RT-PCR is not high and depends on the time of collection and the collector [5]. In addition, RT-PCR assay is not a point of care testing in daily clinical situations. Furthermore, some physicians do not carry out the RT-PCR or antigen detection test to avoid the droplet infection or airborne infection in the examination room. Thus, simple, rapid and not dangerous testing for diagnosing COVID-19 is important.

In a recent study, we demonstrated that the JRS scoring system is a

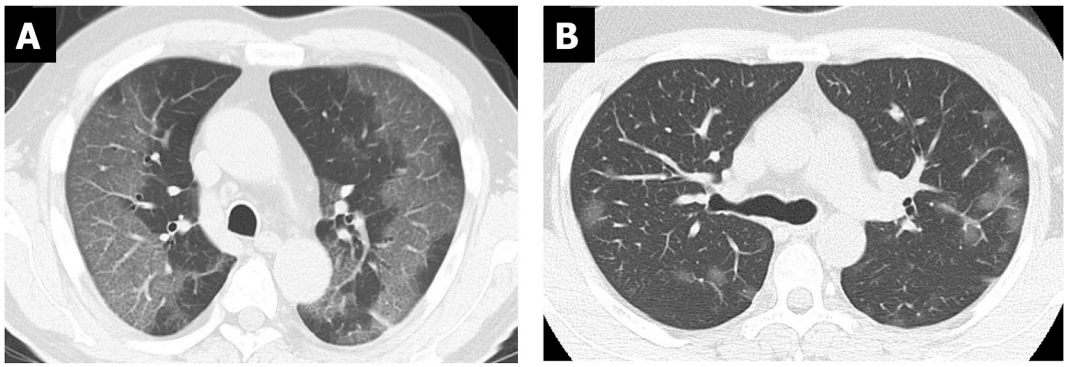

Fig. 1. Non-contrast-enhanced thin-section axial images of the lungs in patients with COVID-19 pneumonia. (A) Chest CT in a 62-year-old man showed bilateral and peripheral GGO with superimposed interlobular septal thickening and crazy-paving appearance. (B) Chest CT scan of a 31-year-old man showed bilateral and multifocal rounded GGO.

Table 1
Underlying conditions and Chest CT findings in patients with COVID-19 pneumonia and *Mycoplasma pneumoniae* pneumonia at the first examination[a].

Variables	COVID-19			*M. pneumoniae*	p-value
	Non-B.1.1.7	B.1.1.7	Total		
No. of patients	488	335	823	100	
Median age (IQR), years	65 (46–76)	64 (51–74)	65 (48–74)	31 (22–43)	<0.001
No. of males/females	302/186	227/108	529/294	51/49	0.011
No. (%) for presumptive diagnosis of atypical pneumonia[b]	287 (58.8)	193 (57.6)	480 (58.3)	87 (87.0)	<0.001
No. (%) of patients with chest CT findings					
Ground-glass opacity	389 (79.7)	275 (82.1)	664 (80.7)	78 (78)	0.507
Consolidation	192 (39.3)	158 (47.2)	350 (42.5)	53 (53)	0.054
Linear opacity	157 (32.2)	122 (36.4)	279 (33.9)	28 (28)	0.262
Cavitation	0	1 (0.3)	1 (0.1)	0	>0.999
Crazy paving	151 (30.9)	121 (36.1)	272 (33.0)	2 (2)	<0.001
Nodules (tree-in-bud and centrilobular)	9 (1.8)	5 (1.5)	14 (1.7)	81 (81)	<0.001
Bronchial wall Thickening	35 (7.2)	31 (9.3)	66 (8.0)	84 (84)	<0.001
Pleural effusion	16 (3.3)	21 (6.3)	37 (4.5)	12 (12)	0.004
Lymphadenopathy	29 (5.9)	24 (7.2)	53 (6.4)	22 (22)	<0.001

[a] Continuous values are presented as medians and interquartile ranges (IQRs) and categorical/binary values as counts and percentages.
[b] Using the six parameters of Japanese Respiratory Society pneumonia guideline [3].

Table 2
Chest CT findings in non-elderly patients and elderly patients with COVID-19 pneumonia at the first examination[a].

Variables	Aged <60 years	Aage ≥60 years	p-value
No. of patients	337	486	
No. (%) of patients with chest CT findings			
Ground-glass opacity	282 (83.7)	382 (78.6)	0.073
Consolidation	130 (38.6)	220 (45.3)	0.062
Linear opacity	101 (30.0)	178 (36.6)	0.051
Cavitation	0	1 (0.2)	>0.999
Crazy paving	100 (29.7)	172 (35.4)	0.097
Nodules (tree-in-bud and centrilobular)	4 (1.2)	10 (2.1)	0.419
Bronchial wall Thickening	21 (6.2)	45 (9.3)	0.120
Pleural effusion	10 (3.0)	27 (5.6)	0.088
Lymphadenopathy	27 (8.0)	26 (5.3)	0.149

[a] Categorical/binary values as counts and percentages.

useful tool for distinguishing between COVID-19 pneumonia and bacterial pneumonia in patients aged <60 years [3]. In addition to the JRS scoring system, physicians often performed chest CT as an auxiliary diagnostic test to differentiate between atypical pneumonia and bacterial pneumonia for the selection of antibiotics. The present results indicate that the diagnosis of *M. pneumoniae* pneumonia would appear reliable when a combination of bronchial wall thickening and tree-in-bud and centrilobular nodules and/or GGO with lobular distribution are found on CT findings. Our findings on chest CT among patients with COVID-19 pneumonia were consistent with those of previous reports with peripheral GGOs with or without consolidation or a crazy-paving pattern and multifocal GGO with rounded morphology [6–12]. Bronchial wall thickening and tree-in-bud and centrilobular nodules are rarely observed in COVID-19 pneumonia. Thus, physicians can differentiate COVID-19 pneumonia from *M. pneumoniae* pneumonia using chest CT findings.

Temporal changes in chest CT findings with COVID-19 pneumonia are consistent with previous reports [13,14]. Although 71.6% of patients had normal chest auscultatory findings at the first examination (Fig. 2A) [3], different adventitious sounds were heard as time progressed (coarse crackles in Fig. 2B and fine crackles in Fig. 2C). Thus, physicians should be aware that chest auscultatory findings depend on the timing of the examination when the JRS scoring system is used.

Our study had several limitations. First, routine screening CT to identify COVID-19 pneumonia is currently not recommended by most radiology societies. However, the sensitivity of PCR assays is not high. Ai et al. investigated the diagnostic value and consistency of chest CT compared to the PCR assay in COVID-19 [15]. Of the 1014 patients, 59% had positive PCR results and 88% had positive chest CT scan findings. The sensitivity of chest CT in predicting COVID-19 was 97% based on the positive PCR results. Thus, we suggest that chest CT may be considered a primary tool for COVID-19 detection in epidemic areas. Second, we excluded patients with extremely severe (A-DROP score 4 or 5) COVID-19 pneumonia. The JRS scoring system applies only to mild-to-moderate pneumonia [3]. Furthermore, some parameters of the

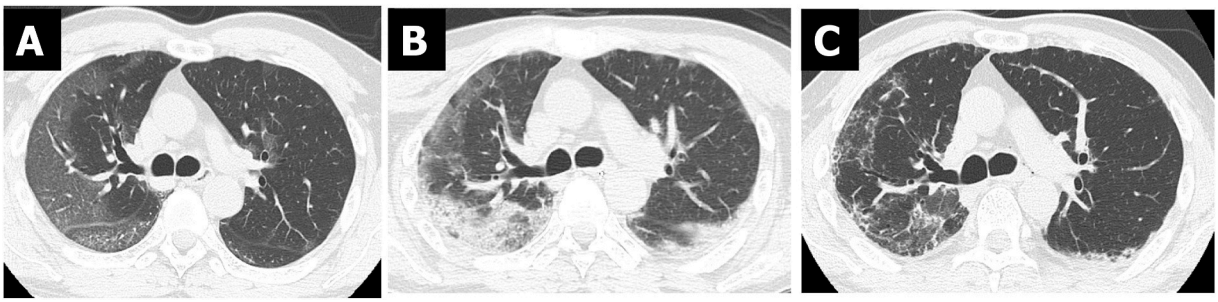

Fig. 2. Chest CT scan of a 51-year-old man with COVID-19 pneumonia. (A) Scan obtained on day 5 of illness showed peripheral GGO mainly in the right upper lobe. (B) Scan obtained on day 13 of illness showed multiple consolidation and GGO with almost the same extent as in image B. (C) Scan obtained on day 21 of illness showed a mixed pattern with reticular pattern, GGO, and consolidation. The perilobular pattern might suggest the presence of organizing pneumonia. The patient was discharged on day 23 of illness. The day of initial symptom onset was defined as day 0 of illness.

JRS scoring system, especially chest auscultatory findings, were subjective. Thus, individual physicians may differ in their judgments about them.

As vaccination against SARS-CoV-2 progresses, infection in elderly people (age ≥60 years) has markedly reduced, and the number of infected people in their 20s–40s has increased. In this situation, combination with the JRS scoring system and chest CT findings are useful tools for the rapid presumptive diagnosis of COVID-19 pneumonia. However, this clinical and radiographic diagnosis is not adapted to elderly people.

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Availability of data and materials

The data will not be shared with participant confidentiality.

Author's contributions

All the authors conceived the study, participated in its design and coordination and collected and managed the data, including quality control. NM, YN and SN drafted the manuscript, and all authors contributed substantially to its revision. All the authors read and approved the final manuscript.

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee at Kansai Medical University and all participating facilities. Informed consent was obtained from all individual participants in the study.

Consent for publication

Not applicable.

Declaration of competing interest

The authors declare that they have no competing interests.

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