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Clinical differences in chest CT characteristics between the progression and remission stages of patients with COVID-19 pneumonia

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Abstract

Introduction: Computed tomography (CT) can be effective for the early screening and diagnosis of COVID-19. This study aimed to investigate the distinctive CT characteristics of two stages of the disease (progression and remission).

Methods: We included all COVID-19 patients admitted to Wenzhou Central Hospital from January to February, 2020. Patients underwent multiple chest CT scans at intervals of 3-10 days. CT features were recorded, such as the lesion lobe, distribution characteristics (subpleural, scattered or diffused), shape of the lesion, maximum size of the lesion, lesion morphology (ground-glass opacity, GGO) and consolidation features. When consolidation was positive, the boundary was identified to determine its clarity.

Results: The ratios of some representative features differed between the remission stage and the progression phase, such as round-shape lesion (8.0% vs 34.4%), GGO (65.0% vs 87.5%), consolidation (62.0% vs 31.3%), large cable sign (59.0% vs 9.4%) and crazy-paving sign (20.0% vs 50.0%). Using these features, we pooled all the CT data (n = 132) and established a logistic regression model to predict the current development stage. The variables consolidation, boundary feature, large cable sign and crazy-paving sign were the most significant factors, based on a variable named "prediction of progression or remission" (PPR) that we constructed. The ROC curve showed that PPR had an AUC of 0.882 (cutoff value = 0.66, sensitivity = 0.75, specificity = 0.875).

Conclusion: CT characteristics, in particular, round shape, GGO, consolidation, large cable sign, and crazy-paving sign, may increase the recognition of the intrapulmonary development of COVID-19.

1 | INTRODUCTION

The highly infectious disease Coronavirus Disease 2019 (COVID-19) has widely spread throughout the world since the beginning of 2020, and is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since emerging in Wuhan, it has rapidly spread to other cities in China, and multiple countries beyond China. On 28 February 2020, the World Health Organization (WHO) declared COVID-19 a global public health emergency (World Health Organization 2020 COVID-19 situation report). As of March 2020, ~800,000 individuals have had a positive diagnosis, and the number is still rising sharply.[1-3]

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Among the limited detection approaches, CT is effective for the early screening and diagnosis of COVID-19. CT features have been used to distinguish community acquired pneumonia and COVID-19 through artificial intelligence algorithms.[4] In addition, CT features may help to indicate severe/critical development, as the incidences of consolidation, linear opacities, crazy-paving pattern and bronchial wall thickening in severe/critical patients were significantly higher than those in ordinary patients.[5] Previous studies have used the total severity score (TSS) according to CT visual quantitative evaluation for diagnosing severe/critical COVID-19, which provides a high area under the curve (AUC) value.[6] Overall, different factors are related to the onset and severity of COVID-19, which contribute to diagnosis and prognosis.[7,8] However, very few studies have focused on the different stages of development of COVID-19, or have accurately distinguished between the progression stage and remission stage using CT data. In the present study, we analysed the CT images from 107 COVID-19 cases, and examined the distinctive characteristics of both the progression and remission stages. Our findings provide a reference for assessing the clinical condition/stage of patients and will help in determining treatment strategies.

What's known

Computed tomography (CT) characteristics, in particular the characteristics of round shape, GGO, consolidation, large cable sign and crazy-paving sign, may help radiologists to distinguish the progression and remission phases of COVID-19. Using CT characteristics, we established a regression model to predict the current development stage of COVID-19.

What's new

Consolidation does not necessarily indicate a worsening of COVID-19 but can be an indicator of a sufficient immune reaction, as well as a sign of improvement.

2 | METHODS

2.1 | Patients

This retrospective study included all COVID-19 patients admitted to our hospital from 10 January 2020 to 20 February 2020. Each patient provided informed consent at admission. The inclusion criteria were as follow: (a) Positive SARS-CoV-2 nucleic acid throat swab test, and a diagnosis consistent with the Diagnostic Standards for COVID-19 Pneumonia Diagnosis and Treatment Program (Trial Version 6). (b) A definite outcome (survival or death). (c) Clear blood routine test results. (d) Chest CT scans were undertaken and the appropriate features were acquired. Almost all patients underwent multiple chest CT scans during the treatment period, at intervals of 3-10 days. Specifically, 32 patients received two scans at two time points (the progression stage and the remission stage), and 100 patients had complete data from a scan at only one stage (the remission stage). Herein, the two stages were defined as follows. If the scan was performed within 3 days before the severity category worsened (from ordinary to severe, or from severe to critical) or the total chest lesion was significantly enlarged, this time point was regarded as the progression stage. If the scan was performed within 3 days before the severity category was alleviated (from mild to cured, from ordinary to mild, from severe to ordinary or from critical to severe), this time point was regarded as the remission stage.

2.2 | CT scanning

A GE OPTIMA 540 16-row multilayer spiral scanner ( ) was used for CT scanning. Patients underwent scanning in the supine position. The continuous scan range was from the apex to the bottom of the lung. Scanning parameters were as follows: voltage, 120 kV; tube current, 200 mA; rotation speed, 27.5 mm/turn; pitch, 1.375; and layer pace and layer thickness, 5 mm. Later, the routine algorithm for thin-layer reconstruction (layer thickness, 1.25 mm) was used to acquire the CT images. Subsequently, chest images were reviewed independently by two senior diagnostic radiologists (one with 15 years and the other with 32 years of experience). The radiologists were blinded to the pathological and clinical status of each patient. When their opinions differed, agreement was reached through discussion.

The lung window and mediastinum window were used to analyse the images, which were grouped according to the dynamic observation and the medical record. We recorded the following CT image characteristics: the lesion lobe, distribution characteristics (subpleural, scattered, or diffused), shape of the lesion (round, nodular or irregular patches), maximum size of the lesion (<3 cm, ≥3 cm and <5 cm, or ≥5 cm), lesion morphology (ground-glass opacity [GGO] and consolidation features, and when consolidation was positive, the boundary was observed to distinguish whether it was clear), large cable sign (a clear large cable sign that usually appears in the late stages and also the similar linear opacities that are usually observed in the early stages; commonly, an early linear opacity can turn to a large cable sign after absorption; when this sign was positive, we further observed whether it was parallel to the pleura or bridged to the pleura. Figure 1C shows some typical large cable signs), crazy-paving sign, air bronchogram signs, septal thickening, pleural effusion and mediastinal lymph node enlargement. Other important features are shown in Figure s1.

2.3 | Statistical analysis

SPSS software (version 25.0) was used for statistical analyses. Categorical data were compared using Fisher's exact test. Continuous data were described as mean ± standard and compared using the Mann-Whitney test or Wilcoxon matched-pairs signed

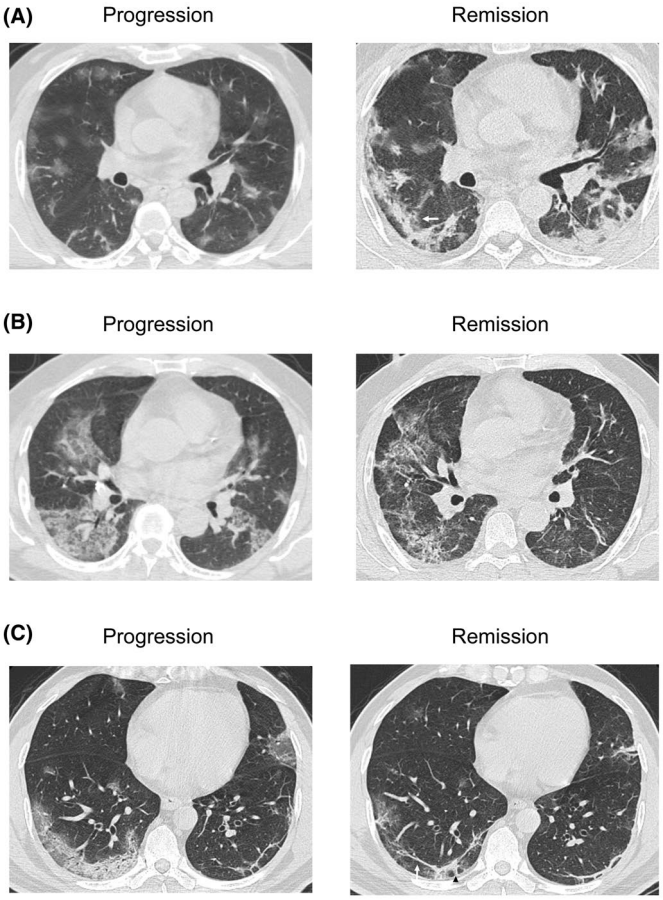

FIGURE 1 Typical chest CT images. (A) A 43-year-old male patient with severe COVID-19. Left: Scan on the third day after onset of symptoms (progression). Multiple patchy ground-glass opacities (GGOs) were observed. Right: Scan on the 13th day after onset of symptoms (remission). Lesion volume was reduced, consolidation was significantly increased, and the linear consolidation sign parallel to the pleura appeared in the subpleural area (white arrow). (B) A 67-year-old male with severe COVID-19. Left: Scan on the seventh day after onset of symptoms. Multiple patchy GGOs and some crazy-paving signs can be seen. Right: Scan on the 25th day after onset of symptoms (remission). Lesions were significantly improved and absorbed, thin sheets of GGO and cable signs can be observed. (C) A 58-year-old male patient with ordinary-type COVID-19. Left: Scan on the eighth day after onset of symptoms (progression). Multiple patchy GGO shadows can be observed, ground glass with consolidation and stripe shadows in multiple areas. Right: Scan on the 15th day after onset of symptoms (remission). Lesion size was reduced, and consolidation and large cable signs can be seen (some cables parallel to the pleura, as indicated by the white arrow and some cables bridged to the pleura, as indicated by black arrow heads)

rank test. Logistic regression was used to predict the development stage. Receiver operating characteristic (ROC) curves were generated using SPSS to assess predictive power. All statistical tests were two-sided, and a value of $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Together, we enrolled 107 cases, including 58 males and 49 females, with an average age of 44.9 ± 12.7 years. Other demographic characteristics are listed in Table 1. Regarding severity levels, 89.7% were of the ordinary type and 10.3% were in severe stages (severe or critical). Baseline symptoms and signs, and laboratory examination results of enrolled patients were as follows. For symptoms and signs (Table 2), fever, dry cough, expectoration, diarrhoea, throat pain, fatigue and muscle aches were commonly seen signs. For laboratory examination results, elevated C-reactive protein, lymphopenia and leukopenia were significant phenotypes (Table 2). After an average period of 22.7 days of treatment (22.7 ± 9.0 days, min = 5 days, max = 60 days), all patients were cured and no deaths occurred.

TABLE 1 Demographic information of enrolled subjects

Index	Value or number	%
Age	44.88 ± 12.68 (2-85)	
Sex		
Male	58	54.2
Female	49	45.8
Nationality		
Han	107	100
Labour type		
NA	54	50.5
Manual	22	20.6
Mental	31	29.0
Marital status		
Unmarried	9	8.4
Married	95	88.8
Divorced	2	1.9
Widowed	1	0.9
Weight (kg)	66.29 ± 13.86 (11.0-125.0)	
Height (cm)	164.45 ± 14.05 (83-1830)	
Severe or not		
No	96	89.7
Yes	11	10.3
Infected through family gathering		
Unknown	67	62.6
Yes	12	11.2
No	28	26.2
From Wuhan		
No	62	57.9
Yes	45	42.1

TABLE 2 The baseline situation and laboratory examination of enrolled patients

Index	Case number	%
Symptoms and signs		
Fever	68	63.6
Dry cough	32	29.9
Expectoration	6	5.6
Diarrhea	5	4.7
Throat pain	2	1.9
Fatigue	2	1.9
Muscle ache	2	1.9
Headache	1	0.9
Chest tightness	1	0.9
Runny	1	0.9
Conjunctival congestion	1	0.9
Constipation	0	0
Chilly	0	0
Dyspnoea	0	0
Laboratory examination		
Total white blood cells		
Normal	79	73.8
Declined	27	25.2
Increased	1	0.9
Lymphocyte absolute value		
Normal	54	50.5
Declined	53	49.5
Increased	0	0.0
C-reactive protein (CRP)		
Normal	48	44.9
Increased	59	55.1

3.2 | CT imaging differences between the two stages

Among all enrolled patients, we found 32 cases with CT images indicating the progression and 100 cases with images indicating the remission stage. Some features were different between the two stages, including round-shape lesion (8.0% vs 34.4%), GGO (65.0% vs 87.5%), consolidation (62.0% vs 31.3%), large cable sign (59.0% vs 9.4%) and crazy-paving sign (20.0% vs 50.0%) (Table 3). Fisher's exact test was performed to analyse these features in the 32 cases with CT scans at two time points. Here, a negative result meant that there was no longer an association between remission and progression, namely that large changes occurred when patients entered the remission stage. Consistently, the round-shape lesion proportion, GGO ratio, consolidation ratio, large cable signs and crazy-paving signs in the remission stage were no longer correlated with the progression stage (Table 4). In particular, consolidation does not necessarily mean a worsening of COVID-19 but can be an indicator of a sufficient immune reaction, as well as a sign of improvement. Finally, remission of crazy-paving sign (which disappeared in 11 individuals) was an obvious indicator of improvement. Some typical cases with consolidation and large cable sign changes are presented in Figure 1, which consistently implied that consolidation and large cable signs are more frequently seen in the remission stage rather than in the progression stage.

3.3 | Features predicting COVID-19 progression and remission

Using the above associated factors, we pooled all the CT data (n = 132) into one dataset and established a model to predict the current developing stage (remission or progression). Using logistic (two-tailed) regression, we found the consolidation, boundary feature, large cable sign and crazy-paving sign variables were the most significant factors distinguishing between progression and remission (Table 5). Next, we constructed a variable that we named "prediction of progression or remission" (PPR) based on the above four parameters (Table 6). The ROC curve showed that PPR had an AUC of 0.882 (cutoff value = 0.66, with a sensitivity of 0.75 and a specificity of 0.875) (Figure 2).

4 | DISCUSSION

To date, this is the first report regarding unique CT features during progression and remission of COVID-19. We revealed that the characteristics of round shape, GGO, consolidation, large cable sign and crazy-paving sign significantly change between the progression and remission stages. Using four features (variable consolidation, boundary feature, large cable sign and crazy-paving sign) can help to distinguish the development stage of COVID-19.

Using CT examinations, the occurrence, development and prognosis of COVID-19 can be comprehensively understood. CT has advantages over histological examination in that it can evaluate the whole lungs. Histological examination may be prone to sampling errors because of sample being obtained from localised regions. Since its emergence, the CT imaging characteristics of COVID-19 have been studied by different research groups. Case reports have shown common trends during development, such as rapidly progressing peripheral consolidations and GGOs in both lungs.[9] In addition, patchy GGOs have been found in both adult and paediatric COVID-19 patients.,[10] Positive CT findings, including consolidation, greater total lung involvement, linear opacities, crazy-paving signs and reversed halo signs, are usually more frequent a long time after the onset of symptoms.[11] After the accumulation of samples, typical manifestations of COVID-19 were reported. Early radiological investigations consistently reported that bilateral GGOs and consolidation with a peripheral and posterior lung distribution were regarded as a cardinal hallmark of COVID-19. Up to 98% of cases have presented GGO as the most common imaging finding.[12] In Zhejiang province of China, it was reported that the imaging pattern of multifocal peripheral ground-glass or mixed opacity

TABLE 3 CT imaging characteristics in progression and remission stages

	Progression	%	Remission	%
Total N	32		100	
Lobe involved				
Right upper lobe	26	81.3%	70	70.0%
Right middle lobe	23	71.9%	66	66.0%
Right lower lobe	30	93.8%	94	94.0%
Left upper lobe	28	87.5%	79	79.0%
Left lower lobe	30	93.8%	94	94.0%
Distribution characteristics				
Subpleural	29	90.6%	92	92.0%
Scattered	23	71.9%	72	72.0%
Diffused	8	25.0%	18	18.0%
Lesion shape				
Round	11	34.4%	8	8.0%
Irregular patches	31	96.9%	91	91.0%
Max lesion size				
<3 cm	7	21.9%	23	23.0%
3-5 cm	5	15.6%	14	14.0%
≥5 cm	20	62.5%	63	63.0%
Lesion morphology				
GGO	28	87.5%	65	65.0%
GGO and consolidation	17	53.1%	56	56.0%
Consolidation	10	31.3%	62	62.0%
Consolidation with clear boundary	9	28.1%	10	10%
Consolidation with blurred boundary	1	3.1%	52	52%
Large cables				
Large cable sign	3	9.4%	59	59.0%
Cables parallel to the pleura	1	3.1%	52	52.0%
Cables bridging the pleura	1	3.1%	49	49.0%
Crazy-paving sign	16	50.0%	20	20.0%
Air bronchogram	25	78.1%	68	68.0%
Septal thickening	25	78.1%	85	85.0%
Pleural effusion	0	0.0%	3	3.0%
Mediastinal lymph node enlargement	0	0.0%	0	0.0%

Note: Abbreviation: GGO, ground-glass opacity.

with predominance in the lower lung is highly indicative of COVID-19 in the first week of symptom onset.[13] In Korea, the observation of pure to mixed GGO lesions with a patchy to confluent or nodular shape is frequent.[14] Some indirect evidence shows that when compared with the initial CT features, a progressive process may exhibit opacities, consolidation, interstitial thickening, fibrous strips and air bronchograms.[15] GGO with a peripheral distribution is the most widely reported manifestation of COVID-19.[16] In summary, early CT findings are generally patchy GGO with or without consolidation involving multiple lobes, mainly in the peripheral zone, accompanied by halo sign, vascular thickening, crazy-paving pattern or air bronchogram sign.[17] However, very few studies have investigated the differences in CT between severity stages, and even fewer studies have reported on the features of progression and remission. In contrast, several reports have described the typical trends of progression. A study published in *Lancet Infectious Diseases* described Wuhan patients grouped on the basis of the interval between symptom onset and the first CT scan. They showed a trend that as the disease developed, the prevalence of GGOs continued to decrease; meanwhile, consolidation and mixed patterns became more frequent.[18]

TABLE 4 CT feature changes at the remission stage (using Fisher's exact test)

Features	Progression No	Progression Yes	*P* value
Round-shape lesion			.111
Remission-No	21	9	
Remission-Yes	0	2	
Ground-glass opacity (GGO)			.620
Remission-No	2	10	
Remission-Yes	2	18	
Consolidation			.141
Remission-No	11	2	
Remission-Yes	11	8	
Large cable sign			.253
Remission-No	13	0	
Remission-Yes	16	3	
Crazy-paving sign			.394
Remission-No	14	11	
Remission-Yes	2	5	

In our study, the 32 progression cases were all included in the 100 remission cases, and as expected, they had some imaging features in common. Overall, the baseline imaging characteristics were as follow: multiple lesions, multiple lobe involvement, mostly subpleural distribution, lesions located in both lungs, irregular patches, air bronchogram and septal thickening, which are largely consistent with published reports.[19-21]

When the disease enters the remission stage, there are no changes in lobe involvement, the distribution of lesions, the maximum lesion size and the shape of the lesion. However, some interesting changes warrant attention. In the remission stage, the frequency of GGO decreases and the frequency of consolidation significantly increases, especially consolidation with blurred boundary. Moreover, increased large cable sign and reduced crazy-paving sign were indicators of remission in our study. As previously suggested, consolidation and cable sign are common signs of viral pneumonia.[22,23] Machine-learning studies have also suggested that consolidation is one of the most discriminative features of COVID-19. Theoretically, consolidation may be associated with the coagulopathy status[24-26] in pneumonia. Some researchers believe that an increase in consolidation indicates disease progression, and the degree of lung consolidation

TABLE 5 Logistics regression in prediction of progression or remission stage

	B	SE	Wald	*P*	OR
Right upper lobe	−20.440	7090.507	0.000	.998	—
Right middle lobe	−23.063	7090.507	0.000	.997	—
Right lower lobe	−18.572	7090.506	0.000	.998	—
Left upper lobe	−21.436	7090.507	0.000	.998	—
Left lower lobe	−16.321	7090.507	0.000	.998	—
Involved lobe number			5.418	.247	—
1	17.236	7090.507	0.000	.998	—
2	36.871	14 181.014	0.000	.998	—
3	57.971	21 271.520	0.000	.998	—
4	80.369	28 362.027	0.000	.998	—
Subpleural distribution	−0.651	1.499	0.188	.664	—
Scattered distribution	−2.685	2.079	1.667	.197	—
Diffused distribution	−2.211	2.068	1.143	.285	—
GGO	−0.025	1.097	0.001	.982	—
Consolidation	2.952	1.416	4.347	.037	19.149
Boundary feature	4.361	1.496	8.502	.004	78.352
Round lesion shape	−1.269	0.805	2.486	.115	—
Irregular patches	−1.201	2.147	0.313	.576	—
Large cable sign	3.420	0.986	12.027	.001	30.565
Crazy-paving sign	−1.486	0.753	3.895	.048	0.226
Air bronchogram	−1.142	0.889	1.650	.199	—
Septal thickening	20.742	18 803.657	0.000	.999	—
Pleural effusion	0.975	0.918	1.129	.288	—
Constant	20.161	7090.507	0.000	.998	—

TABLE 6 Logistics regression in prediction of progression or remission stage using four parameters

	B	SE	Wald	*P*	OR
Consolidation	2.849	1.074	7.037	.008	17.273
Boundary feature	3.697	1.174	9.910	.002	40.326
Large cable sign	2.373	0.692	11.761	.001	10.729
Crazy-paving sign	−1.195	0.538	4.935	.026	0.303
Constant	−3.201	1.221	6.876	.009	0.041

and fibrosis is closely related to the severity of the patient's condition.[27] However, the present study is the first work indicating that consolidation is more closely associated with an improvement rather than worsening, and this feature is diverse in the two stages. In our study, the consolidation feature in progression generally showed nodular consolidation or reversed halo sign changes, while the consolidation in remission frequently showed an increased GGO density but reduced volume, and subsequently many consolidations of the GGO areas were dissipated or absorbed accompanied by large cable signs. This is consistent with the observation from Pan et al's work,[28] which shows that when the disease reaches the peak stage, consolidation usually becomes apparent, and then it enters the absorption phase followed by improvement. In addition, Jin et al claimed that there is a consolidation period after sufficient progression, and the consolidation volume decreases and enters the absorption period.[29] The dynamic observation of all patients showed no increase in consolidation volume. To date, most scholars believe that the consolidation change is an essential part of disease progression, and even a landmark of severe or critical stages.[11,30,31] However, in our study, we found that consolidation differed in the two stages; the remission stage had more frequent consolidation, and the boundary of consolidation in the remission stage was usually blurred, while that in the progression stage was much clearer. Moreover, the possible pathological mechanisms of consolidation in the two stages are different. Progressive consolidation includes the accumulation of a large amount of cell exudate in the alveolar cavity and vasodilation in the interstitial blood vessels, which cause oedema in alveolar and interstitial vessels, and this aggravates symptoms. Remissive consolidation may include the fibrous exudation of the alveolar cavity and the resolution of capillary congestion in the alveoli wall.

Another finding of our study was that the large cable sign was positively correlated with remission, which suggests that large cable sign indicates the gradual absorption of the lesion and that the patient is recovering. Similar changes were also observed in the study by Bernheim *et al*[11] but very few studies have drawn a conclusion about the implication to remission. Out of 53 large cable sign cases, 50 showed cable bridging the pleura, which may be because of the absorption speed in the oedema-thickened interlobular septal being slower than in the exudative lesion. However, the definite mechanism requires further study.

Our study has some limitations. Based on a limited number of cases, we pooled the data of ordinary and severe patients together to form the progression and remission groups, which may have induced intra-group differences. Our future studies will examine features in different subgroups separately. In addition, the follow-up time of absorption was limited, and further recovery of lung function and CT remission features is unclear.

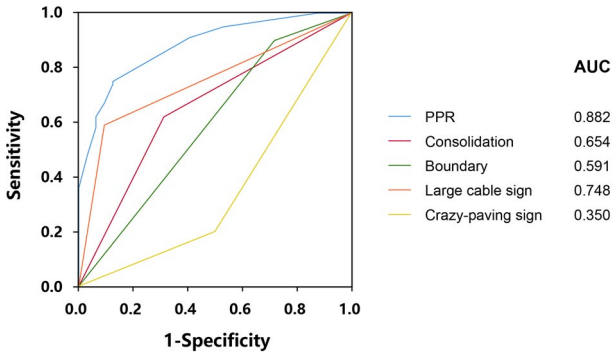

FIGURE 2 A variable named "prediction of progression or remission" (PPR) was constructed to predict the progression and remission stage logistic (two-tailed) regression based on four signs (consolidation, boundary feature, large cable sign and crazy-paving sign). The ROC curve showed that PPR had an AUC of 0.882 (cutoff value = 0.66, with a sensitivity of 0.75 and a specificity of 0.875)

5 | CONCLUSIONS

In conclusion, CT characteristics may strengthen the recognition of the intrapulmonary development of COVID-19 and help radiologists distinguish progression and remission phases more accurately over time. In particular, these characteristics include round shape, GGO, consolidation, large cable sign and crazy-paving sign. Understanding different CT characteristics will help us to better determine the clinical condition and formulate reasonable treatment plans, potentially avoiding over-treatment.

AUTHOR CONTRIBUTIONS

JL collected data, drafted the initial manuscript, and reviewed and revised the manuscript. YC and CH collected data, and reviewed and revised the manuscript. GH reviewed and revised the manuscript. QC conceptualised and designed the study, collected data, carried out the analyses, critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. JD carried out the analyses, critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript.

DISCLOSURE

The authors declare no potential conflicts of interest with respect to authorship, and/or publication of this study.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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