Timely Diagnosis and Treatment Shortens the Time to Resolution of Coronavirus Disease (COVID-19) Pneumonia and Lowers the Highest and Last CT Scores From Sequential Chest CT

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OBJECTIVE. This study aims to assess correlations of the time from symptom onset to diagnosis and treatment with the time to disease resolution and CT scores as based on findings from sequential chest CT examinations.

MATERIALS AND METHODS. Thirty patients with coronavirus disease (COVID-19) confirmed by reverse transcription–polymerase chain reaction analysis underwent chest CT examinations. Five patients who did not have positive CT findings or who had not yet fulfilled criteria for discharge from the hospital were excluded. CT scores were determined according to CT findings and lung involvement. The time from symptom onset to diagnosis and treatment was recorded for each patient, and on the basis of this information, patients with COVID-19 were divided into group 1 (patients for whom this interval was ≤ 3 days) and group 2 (those for whom this interval was > 3 days). The CT scores for each group were fitted using a Lorentzian lineshape curve to show the variation tendency during treatment. The differences in age, sex, and last CT scores determined before discharge between the two groups were analyzed, and correlations of the time from symptom onset to diagnosis and treatment with the time to disease resolution as well as with the highest CT score also underwent statistical analysis.

RESULTS. A total of 25 subjects were enrolled in the study. The fitted tendency curves for group 1 and group 2 were significantly different, with peak points showing that the estimated highest CT score was 10 and 16 for each group, respectively, and the time to disease resolution was 6 and 13 days, respectively. The Mann-Whitney test showed that the last CT scores were lower for group 1 than for group 2 ($p = 0.025$), although the chi-square test found no difference in age and sex between the groups. The time from symptom onset to diagnosis and treatment had a positive correlation with the time to disease resolution ($r = 0.93$; $p = 0.000$) as well as with the highest CT score ($r = 0.83$; $p = 0.006$).

CONCLUSION. Timely diagnosis and treatment are key to providing a better prognosis for patients with COVID-19.

Coronavirus disease (COVID-19), which is an infectious disease caused by a new coronavirus known as severe acute respiratory syndrome coronavirus 2, features lung disease as its main manifestation; an outbreak of COVID-19 began in December 2019 in Wuhan, the capital city of Hubei province in China [1–3]. Severe acute respiratory syndrome coronavirus 2 infection spread across China and to several countries around the world during the first three months of 2020 [4–6]. Patients with COVID-19 either have asymptomatic disease or present with symptoms such as fever, cough, or shortness of breath [7]. Chest CT, which enables early detection of pneumonia and assessment of the course of the disease, has become vital in the early diagnosis of COVID-19, and most patients with COVID-19 have characteristic CT findings [8]. Recent studies showed that the CT features of COVID-19 are related to the duration of infection and can be divided into four stages: early stage, progressive stage, peak stage, and absorption stage [9, 10]. During the treatment of patients with COVID-19, chest CT findings are usually observed to change from ground-glass opacities (GGO) to a crazing-paving pattern and then to consolidation. After the peak stage of the disease, the pneumonia will begin to resolve, and the consolidation will gradually be absorbed in the following days.

Sequential chest CT examinations enable qualitative investigation of alterations in COVID-19 infection during the course of treatment. In a previous study, Pan et al. [9]

proposed CT scoring criteria that took into account lobe involvement, with CT scores ranging from 0 (denoting no involvement) to 25 (denoting maximum involvement), but gave no consideration to changes in CT features (i.e., the change from observation of GGO to a crazy-paving pattern and then consolidation). Therefore, the CT scoring criteria proposed by Pan and colleagues may not be sufficiently accurate to assess the progression of pneumonia. In the present study, we propose a new version of CT scoring criteria that considers both lobe involvement and changes in CT findings, in an attempt to more comprehensively evaluate COVID-19 pneumonia on sequential chest CT examinations.

The interval from symptom onset to diagnosis and treatment varied among patients with COVID-19 pneumonia, as did patient prognosis. On the basis of findings on sequential CT scans, the time to disease resolution, the highest CT score, and the last CT score (calculated for scans obtained around the time that the patient fulfilled the criteria for discharge from the hospital) were three important values used to evaluate progression and prognosis of COVID-19. The present study aims to investigate correlations of the time from symptom onset to diagnosis and treatment with the time to disease resolution and also with the highest and last CT scores from sequential chest CT examinations. We also sought to further verify that timely treatment could shorten the time to disease resolution and lower the highest CT score for patients with COVID-19 pneumonia.

Materials and Methods

This retrospective study was approved by the ethics board of Wuhu Second People's Hospital, and informed consent was waived.

Patients

Thirty patients were admitted to Wuhu Second People's Hospital with confirmed COVID-19 from January 22, 2020, through February 28, 2020. Patients who did not have positive CT findings or who had not yet met the conditions for discharge from the hospital were excluded from the study.

CT Parameters and Evaluation

Chest CT examinations were performed using two 16-MDCT scanners (the MX-16 Slice scanner [Philips Healthcare] and the Optima MR450w scanner [GE Healthcare]). All patients were instructed in breath-holding, and CT images were acquired during a single breath-hold, with the scanning field covering the entire thorax. The following CT parameters were used: tube voltage, 120 kVp; tube current, 278 or 299 mA; reconstruction matrix size, 512 × 512; and slice thickness, 1.0 mm.

Evaluation of chest CT images was performed as in previous studies [10, 11], using terminology such as "opacities", "crazy-paving pattern," and "consolidation." Figures 1 and 2 show sequential chest CT images obtained from repeat examinations of two patients in whom progression COVID-19 was found to be different. We used an upgraded version of CT scoring criteria that was based on lung involvement [9] but allowed further consideration of different CT findings. The base CT score was assigned according to the extent of GGO involvement in the lobes (with a maximum score of 5 possible for each of the five lobes), with scores defined as follows: 0 denoted no involvement; 1, less than 5% involvement; 2, 5–25% involvement; 3, 26–49% involvement; 4, 50–75% involvement; and 5, more than 75% involvement. Weight assignments were different for the three categories of CT findings (i.e., GGO, crazy-paving pattern, and consolidation). If the crazy-paving pattern appeared in one lobe, the base CT score was increased by 1, and if consolidation appeared (either with or without the crazy-paving pattern), the base CT score was increased by 2. Therefore, a maximum CT score of 7 was possible for each lobe. The total CT score was defined as the sum of the scores for each of the five lobes and ranged from 0 to 35, with the highest possible CT score indicating consolidation in all five lobes. Details regarding evaluation of lobe involvement may be found in a previous study by Ooi et al. [12].

All CT data were transferred to the PACS at our hospital, where the images were analyzed. Image analysis and CT scoring were performed by two radiologists with 15 and 10 years of experience in reading chest CT images, and final CT scores were determined by consensus.

Statistical Analysis

To evaluate the difference in the effects of early and late treatment, the 25 study patients were divided into two groups according to the time from symptom onset to diagnosis and treatment, which was 3 days or less for group 1 and more than 3 days for group 2. The sequential CT scores for each patient were interpolated in the time domain with cubic spline interpolation using homemade

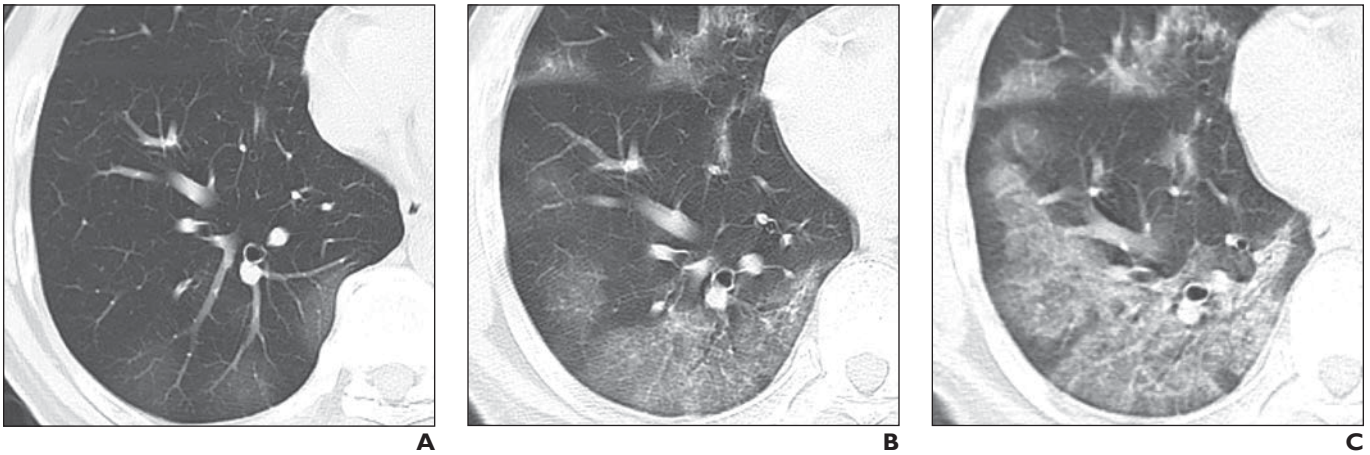

Fig. 1—58-year-old man with coronavirus disease pneumonia with typical disease evolution. CT scoring criteria were applied to images from sequential chest CT examinations.
A, Initial chest CT image obtained 8 days after onset of symptoms shows three small regions of subpleural ground-glass opacities (GGO) involving approximately 20% of right lower lobe (CT score, 2).
B, Chest CT image obtained on day 3 of treatment shows enlarged region of subpleural GGO involving no more than 50% of right lower lobe (CT score, 3) and partial crazy-paving pattern (CT score, 1), for total CT score of 4.
C, Chest CT image obtained on day 5 of treatment shows further enlarged region (< 75% of right lower lobe; CT score, 4) of consolidation (CT score, 2), for total CT score of 6.
(Fig. 1 continues on next page)

Fig. 1 (continued)—58-year-old man with coronavirus disease pneumonia with typical disease evolution. CT scoring criteria were applied to images from sequential chest CT examinations.
D, Chest CT image obtained on day 7 of treatment shows CT findings almost same as those in **C**, for CT score of 6.
E, Chest CT image obtained on day 9 of treatment shows partial resolution of consolidation, for CT score of 5.
F, Chest CT image obtained on day 21 of treatment shows continued resolution of consolidation with minimal residual GGO and parenchymal bands involving less than 25% of right lower lobe, for CT score of 2.

software based on Matlab software (version 2016b, MathWorks), and the time to disease resolution was estimated using the time point of the highest value on the interpolated curve (Figs. 3A and 3B). The variation tendency of CT scores for each group during treatment was investigated using Lorentzian lineshape fitting to the mean CT score for all subjects (Fig. 3C). A chi-square test was performed to determine differences in age and sex between groups 1 and 2, and the last CT scores of the two groups were analyzed using the Mann-Whitney test. Pearson correlation coefficients were used to assess the presence of linear associations of the time from symptom onset to diagnosis and treatment with the highest CT score and also with the time to disease resolution for all patients in both group 1 and group 2 (i.e., the mean highest CT score and the mean time to disease resolution were calculated for patients for whom the time from symptom onset to diagnosis and treatment was either ≤ 3 days or > 3 days, respectively). Statistical significance was denoted by $p < 0.05$. Statistical analyses were conducted using SPSS software (version 22.0, SPSS).

Results

Thirty patients were confirmed to have COVID-19 on the basis of results of RT-PCR analysis and were admitted to our single study center. Five patients were excluded, with four excluded because they did not have positive chest CT findings, and with the remaining patient excluded because disease progression was still evident on CT, resulting in the patient not meeting the criteria for discharge from the hospital. Therefore, a total of 25 patients were enrolled in the present study. The characteristics of these patients are presented in Table 1.

The fitted tendency curves show an obvious difference between groups 1 and 2. For groups 1 and 2, the estimated highest CT

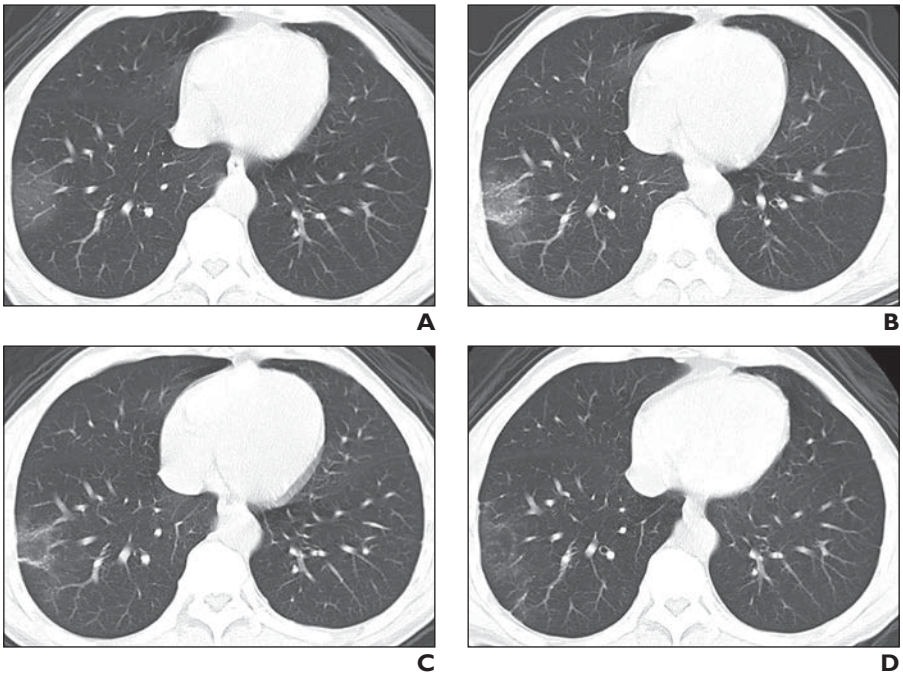

Fig. 2—53-year-old man with coronavirus disease pneumonia. CT scoring criteria were applied to images from sequential chest CT examinations.
A, Initial chest CT image obtained 2 days after onset of symptoms shows small region of subpleural ground-glass opacities in right lower lobe, for CT score of 1.
B, Chest CT image obtained on day 3 of treatment shows slightly enlarged region of subpleural ground-glass opacities with partial crazy-paving pattern and consolidation, for CT score of 3.
C, Chest CT image obtained on day 5 of treatment shows partial resolution of consolidation, for CT score of 2.
D, Chest CT image obtained on day 14 of treatment shows continued resolution of consolidation with minimal residual ground-glass opacities, for CT score of 1.

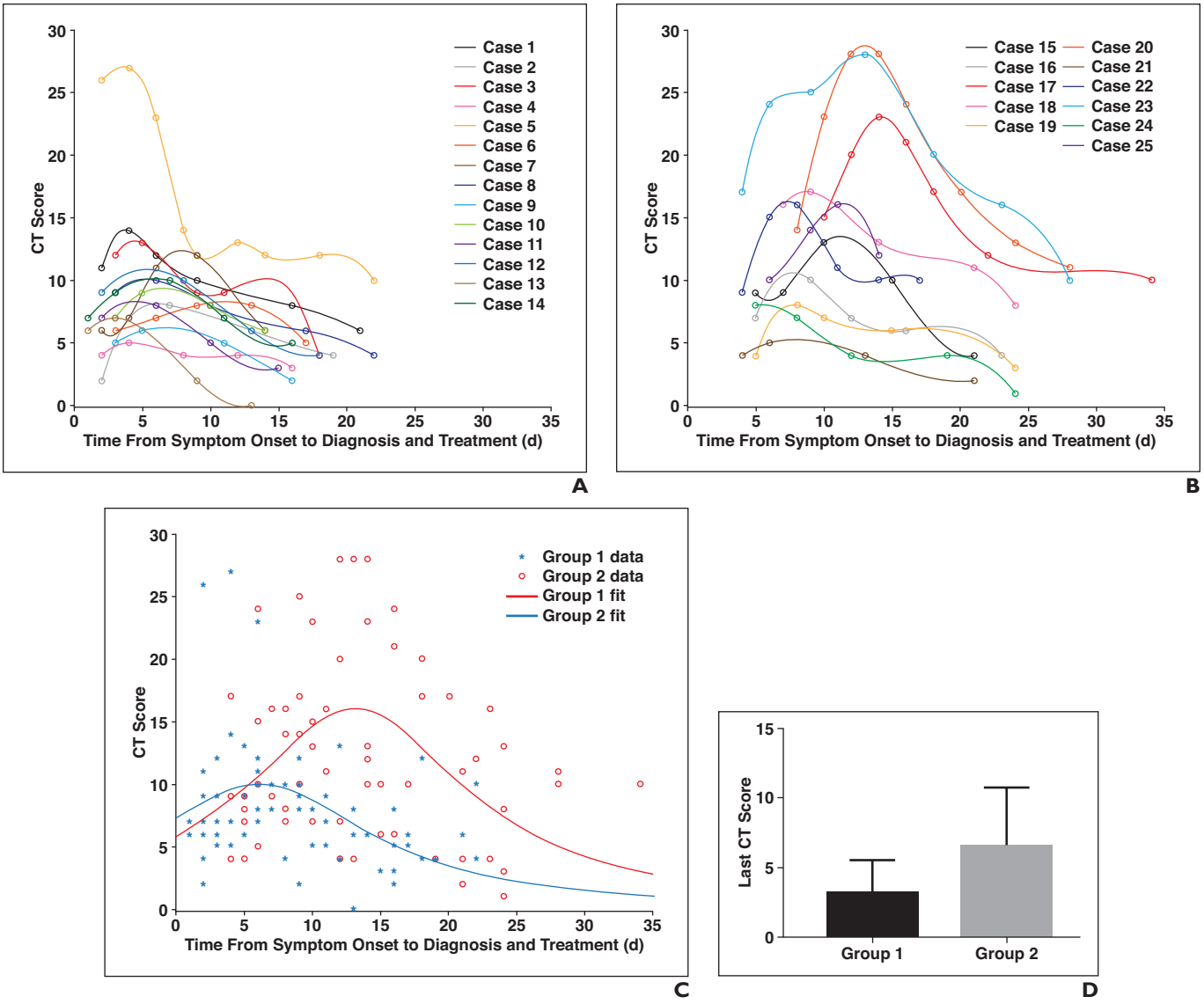

Fig. 3—CT scores.
A and **B,** Fitted tendency curves show changes in CT scores (data were interpolated in time domain with cubic spline interpolation) for each patient in group 1 (those for whom time from symptom onset to diagnosis and treatment was ≤ 3 days) (**A**) and each patient in group 2 (those for whom time from symptom onset to diagnosis and treatment was > 3 days) (**B**) for images from sequential chest CT examinations performed after initiation of treatment. Circles denote data points.
C, Interpolated curves show variation tendency of CT scores for each group as determined by Lorentzian lineshape fitting to mean CT score for all subjects, with curve function for group 1 expressed as $f_1(x) = 1000 / [(x - 6.15)^2 + 10^2]$ and that for group 2 expressed as $f_2(x) = 1600 / [(x - 13.12)^2 + 10^2]$.
D, Bar graph shows last CT scores of groups 1 versus 2 ($p = 0.025$ by t test). Box denotes mean, and whisker denotes SD.

score was 10 and 16, respectively, and the estimated time to disease resolution was 6 and 13 days, respectively. The Mann-Whitney test indicated that the last CT scores in group 1 were significantly lower than those in group 2 ($p = 0.025$) (Fig. 3D), and the duration of hospitalization was much shorter for group 1 than for group 2 ($p = 0.001$ by t test). The chi-square test found no significant differences in age and sex between the two groups (Table 1). For all subjects, the time from symptom onset to diagnosis and treatment had a positive correlation with the time to disease resolution ($r = 0.93$; $p = 0.000$) as well as with the highest CT score ($r = 0.83$; $p = 0.006$), as shown in Figure 4.

Discussion

We propose a new version of CT scoring criteria that takes into account lobe involvement and changes in CT findings (including GGO, crazy-paving pattern, and consolidation) and provides more comprehensive assessment of COVID-19 pneumonia than the criteria previously proposed by Pan et al. [9]. The present study has shown that sequential chest CT examinations and upgraded CT scoring criteria can be used to quantitatively evaluate changes in pneumonia in patients with COVID-19. Fitted tendency curves show an obvious difference between patients for whom the time from symptom onset to diagnosis and treatment was 3 days or less

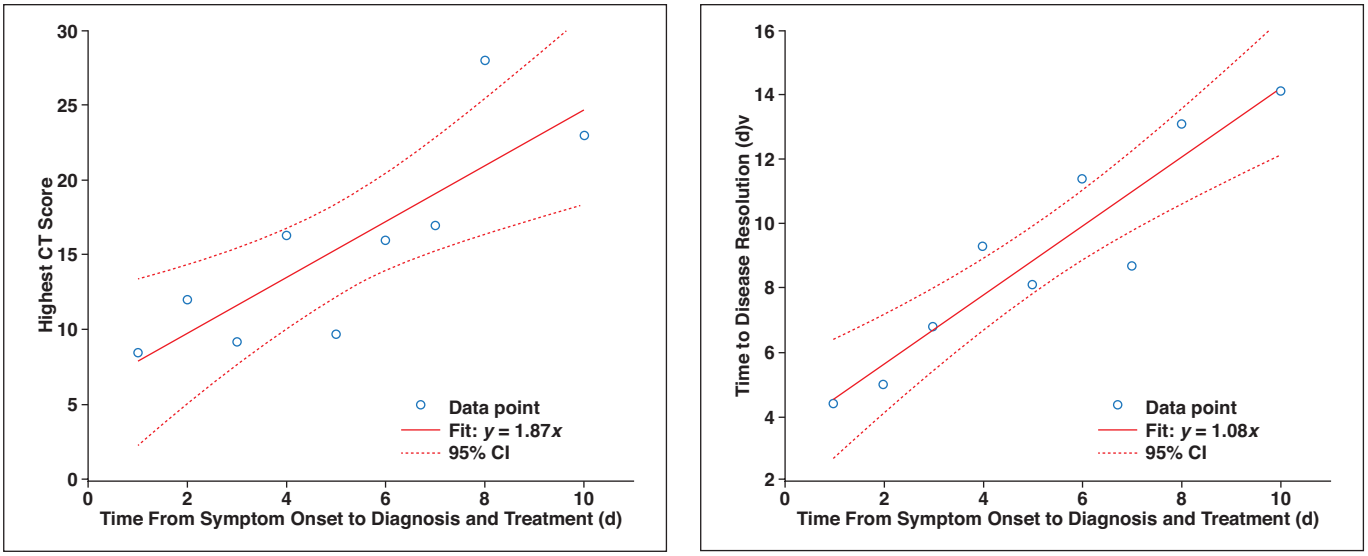

Fig. 4—Correlations of time from onset of symptoms to diagnosis and treatment with highest CT score as well as with time to disease resolution for all patients. Mean highest CT score and mean time to disease resolution for patients for whom time from symptom onset to diagnosis and treatment was either 3 days or less or more than 3 days was calculated for further analysis.
A, Graph shows correlation of time from symptom onset to diagnosis and treatment with highest CT score ($p = 0.006$).
B, Graph shows correlation of time from symptom onset to diagnosis and treatment with time to disease resolution ($p = 0.000$).

versus those for whom it was more than 3 days, and the peak points show that the highest CT score was significantly lower and the time to disease resolution significantly shorter in group 1 than in group 2. The last CT score tends to be lower and the duration of hospitalization shorter for patients for whom the time from symptom onset to diagnosis and treatment was 3 days or less versus those for whom it was more than 3 days, and these differences were statistically significant. For all patients with COVID-19, the present study also found positive correlations of the time from symptom onset to diagnosis and treatment with the time to disease resolution as well as with the highest CT score.

Chest CT is vital in the early diagnosis of COVID-19 pneumonia because most patients (26 of 30 patients [86.7%] at our hospital) have characteristic CT findings. Consistent with the present study (Figs. 1–2), previous studies have shown that three main categories of CT findings are seen in association with the progression of COVID-19: GGO, crazy-paving pattern, and consolidation [9–11, 13–17]. In the early stage of the disease, GGO was the main finding seen in the lower lobes on CT

TABLE 1: Characteristics of Patient Cohort and Comparison of Results in Group 1 and Group 2

Characteristic	All Patients ($n = 25$)	Group 1 ($n = 14$)	Group 2 ($n = 11$)	p[a]
Age (y)				
Mean ± SD	46.9 ± 15.8	47.93 ± 18.01	45.63 ± 12.89	0.756[b]
Range	20–81	20–81	24–71	
Sex, no. of patients				0.607[b]
Male	14	8	6	
Female	11	6	5	
Initial symptom, no. (%) of patients				
Fever[c]	21 (84.0)	11 (78.6)	10 (90.9)	
Cough	18 (72.0)	9 (64.3)	9 (81.8)	
Throat pain	2 (8.0)	0 (0.0)	2 (18.2)	
Expectoration	5 (20.0)	1 (7.1)	4 (36.4)	
Chills	6 (24.0)	2 (14.3)	4 (36.4)	
Fatigue	10 (40.0)	4 (28.6)	6 (54.5)	
Loss of appetite	10 (40.0)	5 (35.7)	5 (45.5)	
Myalgia	3 (12.0)	1 (7.1)	2 (18.2)	
Chest pain	2 (8.0)	0 (0.0)	2 (18.2)	

(Table 1 continues on next page)

TABLE 1: Characteristics of Patient Cohort and Comparison of Results in Group 1 and Group 2 (continued)

Characteristic	All Patients (*n* = 25)	Group 1 (*n* = 14)	Group 2 (*n* = 11)	*p*[a]
Laboratory value				
WBC count (G/L ratio)				
Mean ± SD	5.0 ± 1.9	4.47 ± 1.78	5.69 ± 2.06	0.130[d]
Range	2.3–11.29			
Neutrophil count (G/L ratio)				
Mean ± SD	4.8 ± 3.1	4.12 ± 2.40	5.77 ± 3.80	0.197[d]
Range	0.7–14.3			
Lymphocyte count (G/L ratio)				
Mean ± SD	1. 2 ± 0.6	1.30 ± 0.79	1.02 ± 0.30	0.438[d]
Range	0.5–3.1			
Lymphocyte percentage				
Mean ± SD	25.0 ± 11.1	27.89 ± 10.74	21.40 ± 10.81	0.148[d]
Range	4.7–42.6			
CRP level (mg/L)				
Mean ± SD	36.8 ± 44.9	36.14 ± 45.39	37.40 ± 46.51	0.946[d]
Range	0.3–150.0			
Fitted tendency curve peak point finding				
Time to disease resolution (d)	11	6	13	—
Highest CT score	13	10	16	—
Symptom onset to crazy-paving pattern onset (d)				0.000[d]
Mean ± SD	4.72 ± 2.96	2.85 ± 1.70	7.09 ± 2.50	
Range	0–10			
Symptom onset to crazy-paving and consolidation ending (d)				0.001[d]
Mean ± SD	11.96 ± 5.29	8.78 ± 4.5	16.00 ± 4.71	
Range	0–23			
Last CT score				0.025[e]
Mean ± SD	4.64 ± 3.69	3.14 ± 2.41	5.54 ± 1.20	
Range	0–13			
No. of scans obtained				0.268[d]
Mean ± SD	5.2 ± 1.2	5 ± 1.10	5.54 ± 1.2	
Range	4–8			
Duration of hospitalization (d)				0.001[d]
Mean ± SD	19.7 ± 4.6	17.07 ± 2.73	21 ± 2.52	
Range	13–31			

Note—Group 1 included patients for whom the time from symptom onset to diagnosis and treatment was 3 days or less, and group 2 included patients for whom the time from symptom onset to diagnosis and treatment was more than 3 days. Quantitative data were presented as mean ± SD (range), whereas other data were presented as count (percentage of the total). Dash (—) denotes not available. CRP = C-reactive protein, G/L = granulocyte to lymphocyte.

[a]For group 1 versus group 2.

[b]By chi-square text.

[c]For patients with fever, body temperature ranges were as follows: all patients, 37.3–39.1°C; group 1, 37.3–38.8°C; and group 2, 37.5–39.1°C.

[d]By Mann-Whitney test.

[e]By *t* test.

images. As the disease progressed, the crazy-paving pattern appeared together with the diffuse GGO, and then GGO and the crazy-paving pattern progressed to consolidation, especially in patients with a long interval from symptom onset to diagnosis and treatment. Therefore, in the progression of COVID-19, lobe involvement and changes in CT findings can be two major areas of focus in evaluating changes on sequential chest CT scans. On the basis of these findings, we proposed updated CT scoring criteria as described in the Materials and Methods section.

In comparison with the CT scoring criteria previously proposed by Pan et al. [9],

the upgraded criteria proposed in the present study take into account CT manifestations, and thus one can avoid situations such as that encountered when the involved area of the lobe is similar but imaging features show progression on two sequential CT examinations. According to the findings of the present study, the peak stage of disease was different in the two groups, occurring on approximately day 6 for group 1, approximately day 13 for group 2, and approximately day 11 for all patients in the study. This information seems to be more accurate than that previously published in the literature [12].

For the two groups, there was an obvious difference in the score tendency curves obtained using Lorentzian lineshape fitting, especially in terms of the peak points, which indicated that the highest CT score tended to be lower and the time to disease resolution shorter for group 1 compared with findings for group 2. Also, significant positive correlations of time from symptom onset to diagnosis and treatment with time to disease resolution and highest CT score were observed for all subjects. To our knowledge, the present study is the first to focus on the correlation between the time from symptom onset to diagnosis and treatment and the progression of COVID-19 (as based on time to disease resolution and the highest CT score) using sequential CT examinations. Patient with a longer time from symptom onset to diagnosis and treatment tended to have more severe symptoms at the peak stage and a longer period of disease resolution, even though all patients in the present study were eventually discharged from the hospital. The last CT scores before discharge were higher for patients with a time from symptom onset to diagnosis and treatment of more than 3 days, which showed that the residual parenchymal bands, as shown in Figure 1F, were prone to persisting in the lower chest lobes of patients in group 2 with severe COVID-19. However, the influence of the parenchymal bands remains unknown [18]. Our results indicate that among patients with COVID-19 who received early treatment, the disease would reach the absorption stage in a shorter amount of time, and these patients would have highest and last CT scores that were lower than those of patients who received treatment later after onset of symptoms. In other words, timely treatment of COVID-19 is vital if patients are to have a better prognosis, although symptomatic and supportive treatments have been the primary medical approaches used to date [19].

The limitation of this clinical study mainly lies in the selection of patients and the sample size. All data were from a single center, and the data size was rather small, even though our hospital has seen all patients with COVID-19 (30 of 33 cases; 91%) in Wuhu city in the Anhui province of China. However, the tendency derived from this study would be helpful in establishing clinical treatment protocols for cities outside of Wuhan, where the outbreak originated.

Conclusion

A new version of CT scoring criteria that takes into account lobe involvement and changes in CT findings (i.e., GGO, crazy-paving pattern, and consolidation) could quantitatively and accurately evaluate the progression of COVID-19 pneumonia. The earlier that COVID-19 is diagnosed and treated, the shorter the time to disease resolution and the lower the highest and last CT scores are. Timely diagnosis and treatment are key in improving the prognosis for patients with COVID-19.

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