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RESEARCH ARTICLE

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The natural course of COVID-19 patients without clinical intervention

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Abstract

The natural course of coronavirus disease 2019 (COVID-19) patients without clinical intervention has not yet been documented. One hundred and fifty-eight patients from two hospitals were enrolled to identify the indicators of severe COVID-19 and observe the natural course of COVID-19 patients without clinical intervention. The total computed tomography (CT) score, a quantitative score based on assessment of the number, quadrant, and area of the lesions in CT, tended to perform better than assessment based only on the number or area of the lesions ($p = 0.0004$ and $p = 0.0887$, respectively). Multivariate logistic regression showed that the total CT score, chest tightness, lymphocyte, and lactate dehydrogenase (LDH) were independent factors for severe COVID-19. For patients admitted in 2 weeks from onset to hospitalization, the frequency of severe COVID-19 was gradually increased with the delayed hospitalization. The symptoms of fatigue, dry cough, sputum production, chest tightness, and polypnea were gradually more frequent. The levels of C-reactive protein, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, γ-glutamyl transpeptidase, LDH, and D-dimer were also gradually increased, as well as the scores based on CT. Conversely, the lymphocyte count and the albumin level were gradually decreased with the delayed hospitalization. Detail turning points of the above alterations were observed after 10–14 days from onset to hospitalization. Total CT score was a simple and feasible score for identifying severe COVID-19. COVID-19 patients without clinical intervention deteriorated gradually during the initial 10–14 days but gradually improved thereafter.

KEYWORDS

clinical intervention, computed tomography, COVID-19, delayed hospitalization, natural course

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a novel coronavirus isolated by the Chinese Center for Disease Control and Prevention on January 7, 2020.[1,2] Nowadays, COVID-19 is a rapidly evolving situation, which has induced unprecedented ramifications and severely affected the society due to the high prevalence and long incubation time.[3]

The most frequent symptoms of COVID-19 are fever and dry cough, while the most common clinical imaging sign is bilateral ground-glass opacities,[4–6] which suggests that the clinical features of COVID-19 bear similarities to the infections caused by coronavirus of SARS and the Middle East respiratory syndrome (MERS).[5,7–9]

Although most COVID-19 patients experience mild symptoms, some patients deteriorate rapidly into acute respiratory distress syndrome, acute respiratory failure, and multiple organ dysfunction syndrome (MODS).[5] Owing to the sharp distinction between severe and mild infection in patients in terms of the in-hospital mortality rate,[10] identification of predictive indicators for critically ill patients is necessary to effectively prioritize resources for these patients. This is especially true for regions experiencing medical resource shortages.

The natural course involves in the whole process of the disease from occurrence, development to outcome without any clinical intervention. Profile of the natural course of COVID-19 assists clinicians makes an optimal medical decision at different time points. Usually, symptoms were onset after 3–7 days of incubation phase. The estimated time from the first symptom to pneumonia confirmed by radiology was 5 days. Acute respiratory distress syndrome, the peak of infection, was presented at 9.5–10.5 days after symptoms onset, and most patients were admitted in the intensive care unit at this time.[6,11,12] However, the clinical course described above was observed after their hospitalization and effectively clinical intervention. The natural course of COVID-19 patients without clinical intervention has not been demonstrated.

Here, the number, quadrant, and area of lesions in computed tomography (CT) were assessed to determine the severity of COVID-19 and identify the independent risk factors for severe COVID-19. Then, the alterations of the clinical characteristics were investigated based on the time from onset to hospitalization to assess the natural course of COVID-19 patients without clinical intervention.

2 | METHODS

2.1 | Patients

One hundred and fifty-eight COVID-19 patients were recruited, from january 23, 2020 to February 29, 2020 at the First Affiliated Hospital, Nanchang University ($n = 110$) and the Tongji Hospital, Huazhong University of Science and Technology ($n = 48$), to identify the risk factors of severe COVID-19. This study was conducted in compliance with the principles of the 1975 Declaration of Helsinki and was approved by the Ethics Committees of the two above-mentioned hospitals. Written informed consent was obtained from all patients or their legal representatives.

2.2 | Definitions

COVID-19 was confirmed by detectable nucleic acid by real-time reverse transcriptase-polymerase chain reaction assay using nasal and pharyngeal swab specimens. Only confirmed patients were included in the analysis. Patients who taken drugs (antibiotics, antipyretics, etc.) or received nursing care under the guidance of personnel with professional medical background before their admission were excluded. Severe COVID-19 at admission was defined according to the clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America.[13] Patients who did not meet the criteria of severe COVID-19 were defined as mild COVID-19. It was considered as symptom onset when the patient has any one of the symptoms including fever, dry cough, fatigue, sputum production, chills, myalgia, chest tightness, polypnea, headache and dizziness, sore throat, rhinorrhea and rhinobyon, and diarrhea.

Bacterial infection was diagnosed based on the previous study.[14] Briefly, it was considered if the positive bacterial culture of blood, sputum, urine, or other tissues was obtained. Additionally, it was also considered if any one of items (1)–(3) and item (4) were met: (1) purulent sputum and newly occurred respiratory symptoms or aggravation of original respiratory symptoms; (2) white blood cell count > 10×10^9/L; (3) procalcitonin > 0.1 ng/ml; (4) chest radiography showed bacterial pneumonia.

Liver injury was defined as a total bilirubin (TBil) level of ≥21 μmol/L or an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level of ≥50 U/L. Brain and kidney injuries were characterized by a Glasgow coma scale of ≤14 and a serum creatinine level of ≥105 μmol/L, respectively. Coagulation injuries were characterized by a platelet count of ≤100×10^9/L, the prolongation of the prothrombin time (PT) or thrombin time (TT) by ≥3 s, or the prolongation of activated partial thromboplastin time (APTT) by ≥10 s. Circulation injury was characterized by a mean arterial pressure of less than 70 mmHg or vasoactive agents were used. Muscle injury was characterized by creatine kinase levels of ≥200 U/L.

2.3 | Clinical management of COVID-19 patients

All patients received comprehensive medical treatments during hospitalization, including bed rest, water/electrolyte balance, nutritional support, and antiviral therapy with interferon-α, lopinavir and ritonavir, ribavirin, or arbidol. For patients with decreased PaO_2 or SpO_2, oxygen therapy with a nasal catheter or venturi mask was supplied. For patients with bacterial infection, empirical antibiotic therapy was executed immediately and then adjusted based on the results of microbial culture. Glucocorticoid, immunoglobulin, mechanical ventilation, and/or vasoactive drugs were used as necessary for severe patients. COVID-19 patients who met all the following items could be discharged from hospital: (1) normal body temperature persisted more than 3 days; (2) the symptoms, especially respiratory symptoms, improved significantly; (3) the acute exudative lesions in pulmonary imaging were significantly improved; (4) at least two nucleic acid tests for SARS-CoV-2 were negative.

2.4 | Data acquisition

Data on the demography, epidemiology, symptoms, and signs, as well as on laboratory parameters were collected from the patients'

medical records or the hospital database using a predesigned datasheet. Laboratory parameters detected using fasting blood samples at patients' admission were adopted. Detail detected laboratory parameters included C-reactive protein, white blood cell count, lymphocyte count, neutrophils count, red blood cell count, hemoglobin, platelets, albumin, ALT, AST, TBil, direct bilirubin (DBil), γ-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatinine, urea nitrogen, creatine kinase, PT, TT, APTT, and D-dimer. All detections were performed routinely at the Central Clinical Laboratory of the hospital where the patients were enrolled.

2.5 | CT score

The number, quadrant, and area of lesions in CT were scored using a simple method to assess the severity of COVID-19. As shown in Table 1, the lesion number was scored zero for patients without lesion, and scored one, two, and three for patients with one, two, and three lesion(s), respectively. The lesion number was scored four for patients with four or more lesions. The quadrant was scored zero for patients without lesion and scored one, two, three, and four when lesion(s) occupied one, two, three, and four CT quadrants, respectively. The area was scored zero for patients without lesion and scored one, two, and three when the area of maximum lesion was less than 10, 25, and 100 cm^2, respectively. The area was scored four when the area of maximum lesion was 100 cm^2 or more. The total CT score was calculated as the sum of the lesion, quadrant, and area scores.

2.6 | Statistics

Statistical Package for the Social Sciences (SPSS, vers. 25.0; SPSS Inc.) was used to perform statistical analysis. Continuous data are presented as the mean ± standard deviations or medians with percentiles (P25–P75) and compared using Student's *t*-test or the Mann–Whitney *U* test as appropriate. The rank correlation was analyzed using Spearman's method. Categorical data are presented as numbers (%) and compared either by the χ^2 or Fisher's tests. Independent risk factors for severe COVID-19 were identified by multivariate logistic regression according to the forward Wald method, with entry and removal probabilities of 0.05 and 0.10, respectively. The area under the receiver operating characteristic curves (AUROCs) was compared using a *Z*-test with Delong's method.

3 | RESULTS

3.1 | Clinical characteristics of COVID-19

As shown in Table 2, the mean age of COVID-19 patients was 50.84 ± 16.38, and most patients (85.3%) had a clear exposure history. Sixty (38.0%) patients had one or more comorbidities, and the most frequent comorbidities were hypertension (15.2%), diabetes (12.7%), and bacterial infection (10.8%). The most frequent symptom was fever (85.3%), followed by dry cough (43.7%) and chest tightness (34.8%). Rare symptoms included diarrhea (6.3%) and rhinorrhea/rhinobyon (5.7%). The most frequent extrapulmonary organ injury was liver injury (24.1%), followed by the muscle (7.6%), kidney (6.3%), and coagulation (5.7%) injuries. Circulation (3.8%) and cerebral (1.3%) injuries are rare in COVID-19 patients.

3.2 | Clinical characteristics of severe COVID-19 at admission

The age of severe patients was significantly higher than that of mild patients (55.67 ± 18.36 vs. 48.92 ± 15.19; $p = 0.021$). The comorbidities were more frequent in severe patients than mild patients (51.7% vs. 32.7%; $p = 0.033$). Among the comorbidities, the frequency of bacterial infection was higher in severe patients than mild patients (20.0% vs. 7.1%; $p = 0.023$). No significant differences of other comorbidities between severe and mild patients were observed. Symptomatically, sputum production, chest tightness, and polypnea are more common in severe patients than mild patients (all $p < 0.05$). No other symptomatic difference between severe and mild patients was observed. The levels of C-reactive protein, neutrophils count, DBil, GGT, LDH, creatine kinase, PT, and D-dimer were significantly higher, but lymphocyte count and albumin level were significantly lower in severe patients compared to mild patients (Table 2). The frequency of liver, muscle, and circulation injuries in severe patients was significantly higher than those in mild patients. Both two cases with cerebral injury were severe patients.

TABLE 1 The score of CT for patients with COVID-19

Item	CT-score 0	1	2	3	4
Occupying quadrants of lesions	No lesion	1 Quadrant	2 Quadrants	3 Quadrants	4 Quadrants
Number of lesions	No lesion	1	2	3	≥4
Area of the maximum lesion	No lesion	<10 cm^2	<25 cm^2	<100 cm^2	≥100 cm^2

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography.

TABLE 2 Characteristics at the admission of patients with COVID-19

Variable	Total (*n* = 158)	Mild (*n* = 113)	Severe (*n* = 45)	Univariate logistic regression		Multivariate logistic regression	
				HR (95% CI)	*p*	HR (95% CI)	*p*
Epidemiological and clinical characteristics							
Age (years)	50.84 ± 16.38	48.92 ± 15.19	55.67 ± 18.36	1.026 (1.004–1.049)	0.021		
Gender (female/male)	64/94	46/67	18/27	1.030 (0.509–2.084)	0.935		
Time from onset to hospitalization (days)	7 (3–12)	6 (3–12)	7 (3–12)	1.000 (0.960–1.041)	0.985		
Exposure history (Y/N)	135 (85.3%)	95 (84.1%)	40 (88.9%)	1.432 (0.494–4.164)	0.508		
Any comorbidities	60 (38.0%)	37 (32.7%)	23 (51.1%)	2.119 (1.047–4.288)	0.033		
Hypertension	24 (15.2%)	16 (14.2%)	8 (17.8%)	1.297 (0.512–3.287)	0.583		
Diabetes	20 (12.7%)	15 (13.3%)	5 (11.1%)	0.808 (0.275–2.373)	0.699		
Hepatitis B	8 (5.1%)	7 (6.2%)	1 (2.2%)	0.341 (0.041–2.853)	0.321		
Bacterial infection	17 (10.8%)	8 (7.1%)	9 (20.0%)	3.281 (1.177–9.144)	0.023		
Signs and symptoms							
Fever	135 (85.3%)	94 (83.2%)	41 (91.1%)	1.963 (0.625–6.161)	0.248		
Dry cough	69 (43.7%)	48 (42.5%)	21 (46.7%)	1.167 (0.582–2.338)	0.664		
Sputum production	20 (12.7%)	10 (8.8%)	10 (22.2%)	2.914 (1.119–7.588)	0.028		
Chills	29 (18.4%)	23 (20.4%)	6 (13.3%)	0.595 (0.225–1.577)	0.297		
Myalgia	24 (15.2%)	18 (15.9%)	6 (13.3%)	0.803 (0.297–2.176)	0.667		
Chest tightness	55 (34.8%)	28 (24.8%)	27 (60.0%)	4.500 (2.160–9.374)	<0.001	2.779 (1.162–6.646)	0.022
Polypnea	23 (14.6%)	10 (8.8%)	13 (28.9%)	4.144 (1.660–10.347)	0.002		
Fatigue	43 (27.2%)	27 (23.9%)	16 (35.6%)	1.737 (0.822–3.671)	0.148		
Headache/dizziness	18 (11.4%)	16 (14.2%)	2 (4.4%)	0.282 (0.062–1.281)	0.101		
Sore throat	23 (14.6%)	16 (14.2%)	7 (15.6%)	1.105 (0.421–2.899)	0.839		
Rhinorrhea/rhinobyon	9 (5.7%)	7 (6.2%)	2 (4.4%)	0.704 (0.141–3.527)	0.670		
Diarrhea	10 (6.3%)	6 (5.3%)	4 (8.9%)	1.724 (0.463–6.423)	0.417		
Laboratory parameters							
CRP (mg/L)	8.18 (1.60–27.72)	5.75 (1.16–20.42)	21.03 (6.28–65.28)	1.014 (1. 005–1.023)	0.002		
WBC ($\times 10^9$/L)	5.24 (3.79–6.71)	5.20 (3.76–6.60)	5.48 (4.10–7.09)	1.084 (0.976–1.204)	0.131		
Lymphocyte count ($\times 10^9$/L)	1.06 (0.72–1.48)	1.17 (0.89–1.60)	0.75 (0.45–1.06)	0.090 (0.033–0.248)	<0.001	0.194 (0.067–0.564)	0.003

TABLE 2 (Continued)

Variable	Total (*n* = 158)	Mild (*n* = 113)	Severe (*n* = 45)	Univariate logistic regression		Multivariate logistic regression	
				HR (95% CI)	*p*	HR (95% CI)	*p*
Neutrophils count ($\times 10^9$/L)	3.35 (2.36–5.04)	3.07 (2.09–4.58)	3.92 (2.62–6.08)	1.158 (1.023–1.311)	0.02		
RBC ($\times 10^{12}$/L)	4.53 ± 0.54	4.57 ± 0.53	4.42 ± 0.56	0.601 (0.313–1.155)	0.127		
Hemoglobin (g/L)	142.07 ± 16.57	142.87 ± 16.88	140.04 ± 15.77	0.990 (0. 970–1.010)	0.332		
Platelets ($\times 10^9$/L)	189.20 ± 72.18	192.86 ± 69.59	180.02 ± 78.38	0.997 (0. 992–1.002)	0.314		
Albumin (g/L)	41.46 ± 6.84	42.69 ± 6.57	38.40 ± 6.61	0.892 (0.837–0.951)	<0.001		
ALT (U/L)	22.50 (13.00–40.00)	22.50 (13.00–37.25)	27.13 (18.25–45.69)	1.005 (0.994–1.016)	0.385		
AST (U/L)	24.00 (18.75–33.00)	22.00 (18.00–31.00)	28.00 (22.00–37.50)	1.012 (0.996–1.029)	0.153		
Total bilirubin (μmol/L)	9.50 (6.85–13.65)	9.40 (6.73–12.78)	10.20 (7.85–15.90)	1.051 (0.992–1.113)	0.09		
Direct bilirubin (μmol/L)	3.00 (2.20–4.20)	2.80 (2.10–3.68)	3.90 (2.50–5.65)	1.215 (1.064–1.387)	0.004		
GGT (U/L)	28.80 (17.00–49.75)	24.00 (14.48–40.76)	41.52 (23.25–71.50)	1.007 (1.000–1.015)	0.046		
Lactate dehydrogenase	220.50 (183.50–283.75)	205.00 (172.50–241.50)	276.00 (229.50–399.50)	1.010 (1.006–1.014)	<0.001	1.005 (1.000–1.009)	0.057
Creatinine (mmol/L)	67.00 (56.20–80.90)	67.55 (56.20–80.90)	64.60 (55.50–82.00)	1.005 (0.995–1.016)	0.331		
Urea nitrogen (mmol/L)	4.30 (3.40–5.48)	4.10 (3.30–5.30)	4.55 (3.61–5.50)	1.058 (0.960–1.167)	0.253		
Creatine kinase (U/L)	95.00 (61.25–145.75)	93.00 (63.68–138.62)	108.00 (59.52–203.00)	1.003 (1.000–1.007)	0.046		
Prothrombin time (s)	12.50 (12.00–13.10)	12.46 (11.98–12.96)	12.70 (12.20–13.26)	1.476 (1.021–2.134)	0.039		
Thrombin time (s)	16.10 (15.20–17.10)	16.20 (15.20–17.03)	15.90 (14.95–17.30)	1.075 (0.857–1.350)	0.531		
APTT (s)	30.89 (27.80– 33.50)	30.57 (27.70–33.26)	31.25 (28.35–34.50)	1.016 (0.967–1.068)	0.521		
D-dimer (mg/L)	0.32 (0.20–0.69)	0.27 (0.20–0.56)	0.56 (0.27–2.16)	2.117 (1.300–3.445)	0.003		
Imaging parameters							
Total score	9.0 (5.0–11.0)	8.0 (4.5– 10.0)	11.0 (9.0– 12.0)	1.370 (1.188–1.579)	<0.001	1.192 (1.026–6.646)	0.022
Number score	4.0 (2.0–4.0)	3.0 (1.0– 4.0)	4.0 (4.0– 4.0)	1.748 (1.243–2.457)	0.001		
Quadrant score	3.0 (2.0–4.0)	2.0 (1.0– 4.0)	4.0 (4.0– 4.0)	2.328 (1.578–3.436)	<0.001		
Area score	2.0 (1.0–4.0)	2.0 (1.0–3.0)	4.0 (2.0–4.0)	1.950 (1.441–2.639)	<0.001		
Extrapulmonary organ damage							
Liver	38 (24.1%)	22 (19.5%)	16 (35.6%)	2.282 (1.059–4.918)	0.035		
Kidney	10 (6.3%)	7 (6.2%)	3 (6.7%)	1.082 (0.267–4.381)	0.912		
Muscle	12 (7.6%)	5 (4.4%)	7 (15.6%)	3.979 (1.192–13.286)	0.025		

(Continues)

TABLE 2 (Continued)

Variable	Total (n = 158)	Mild (n = 113)	Severe (n = 45)	Univariate logistic regression HR (95% CI)	p	Multivariate logistic regression HR (95% CI)	p
Coagulation	9 (5.7%)	5 (4.4%)	4 (8.9%)	2.207 (0.539–8.236)	0.284		
Circulation	6 (3.8%)	0 (0%)	6 (13.3%)	17.231 (2.011–147.649)	<0.001		

Note: Cerebral injury data is not shown as its frequency was statistically too small.

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; GGT, γ-glutamyl transpeptidase; RBC, red blood cell count; WBC, white blood cell count.

3.3 | Assessment of COVID-19 with scores based on CT

To quantitatively assess the lesions of COVID-19, the number, occupying quadrant, and area of lesions in CT was scored. As shown in Table 2, the number score of lesions of severe patients was significantly higher than that of mild patients (4.0 [4.0–4.0] vs. 3.0 [1.0–4.0]; $p = 0.001$), as well as the quadrant and area scores (4.0 [4.0–4.0] vs. 2.0 [1.0–4.0] and 4.0 [2.0–4.0] vs. 2.0 [1.0–3.0], respectively; both $p < 0.001$). The total CT score was also markedly higher in severe patients (11.0 [9.0–12.0] vs. 8.0 [4.5–10.0]; $p < 0.001$).

The AUROC of the total CT score for identifying severe COVID-19 was 0.764, with a sensitivity of 0.733 and a specificity of 0.717 at an optimal cut-off value of 9 (Table 3). The total CT score performed better than the number score and tended to provide better identification of severe COVID-19 than the area score ($p = 0.0004$ and $p = 0.0887$, respectively; Figure 1).

3.4 | Independent indicators for severe COVID-19

Next, we evaluated the performance of the total CT score in combination with clinical parameters at admission to identify the severe COVID-19. Univariate and multivariate logistic regression analysis showed that the total CT score, together with chest tightness, lymphocyte count, and LDH were independent indicators for severe COVID-19 (Table 2). Among them, lymphocyte count was the only protective factor for severe COVID-19.

3.5 | Alterations of clinical characteristics with delayed hospitalization

The present study first observed the alteration trends of clinical characteristics with delayed hospitalization in 2 weeks, as shown in Table 4, the frequency of severe COVID-19 patients was gradually increased with the prolongation of the time from onset to hospitalization. Patients admitted to hospital with delays have more comorbidities including hypertension, hepatitis B, and bacterial infection. The symptoms of fatigue, dry cough, sputum production, chest tightness, and polypnea were gradually more frequent with the delayed hospitalization. Notably, the frequencies of headache/dizziness and sore throat were tended to gradually increase but the statistical differences were not significant ($p = 0.050$, and $p = 0.077$, respectively).

The levels of C-reactive protein, ALT, AST, TBil, DBil, GGT, LDH, and D-dimer were also gradually increased, as well as the total CT, number CT, quadrant CT, and area CT scores. On the other hand, the count of lymphocytes and the level of albumin were gradually decreased with the prolongation of the time from onset to hospitalization. To profile the dynamic alterations of COVID-19 with the nature course, the present study further investigated the alterations

TABLE 3 Performance of computed tomography scores for distinguishing severe COVID-19

Models	Cut-off	Sensitivity (%)	Specificity (%)	Youden index	AUC (95% CI)	*p* (vs. total score)
Number score	3	80.00	53.98	0.3398	0.672 (0.593–0.744)	0.0004
Quadrant score	3	77.78	68.14	0.4592	0.742 (0.667–0.808)	0.2740
Area score	3	51.11	86.73	0.3784	0.722 (0.645–0.790)	0.0887
Total score	9	73.33	71.68	0.4501	0.764 (0.689–0.827)	

Abbreviations: AUC, area under the ROC curve; CI, confidence interval; COVID-19, coronavirus disease 2019.

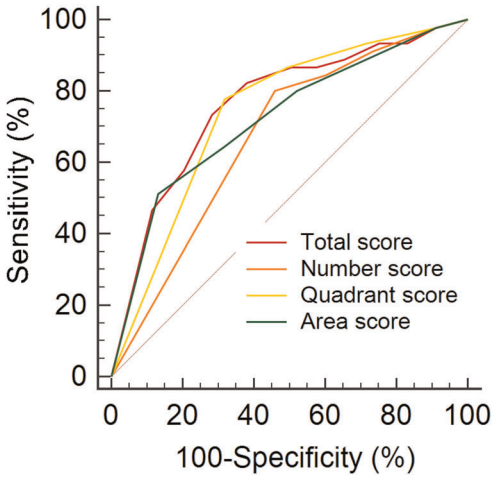

FIGURE 1 Performance of various scores based on computed tomography in identifying severe coronavirus disease 2019

of those parameters with delayed hospitalization more detailly (eight observation time-point named 1–2, 3–4, 5–6, 7–8, 9–10, 10–14, 14–21, >21 days from onset to hospitalization). As shown in Figure 2A–C, the levels of GGT, LDH, and AST were gradually increased in 10 days but gradually decreased after 10 days from onset to hospitalization. The levels of C-reactive protein and D-dimer were gradually increased in 14 days but gradually decreased after 14 days from onset to hospitalization. The levels of ALT and TBil were gradually increased in 14 days and decreased after 14 days, but raised again after 21 days. The count of lymphocytes and the level of albumin were gradually decreased in 14 days and gradually increased after 14 days.

Notably, the total score and area score based on CT were gradually increased in 10 days but gradually decreased after 10 days from onset to hospitalization. The number CT score and quadrant CT score gradually increased in 14 days but gradually decreased after 14 days (Figure 2D).

3.6 | Comparison of clinical characteristics between patients admitted at 7–14 days and admitted after 14 days from onset to hospitalization

As shown in Table 4, the frequency of severe COVID-19 patients admitted after 14 days was significantly lower than those who admitted at 7–14 days. The polypnea was more frequent in patients admitted after 14 days than those admitted at 7–14 days. The levels of C-reactive protein, AST, and LDH were significantly lower in patients admitted after 14 days than those who admitted at 7–14 days, as well as the total CT, number CT, quadrant CT, and area CT scores. The count of lymphocytes of patients admitted after 14 days was significantly higher than that in patients admitted at 7–14 days. Those alterations suggested that 2 weeks after disease onset is a turning point of the clinical course of COVID-19.

4 | DISCUSSION

The clinical manifestations of COVID-19 patients have been found to vary greatly, from asymptomatic carriers to patients with respiratory failure, and even MODS. Consistent with previous reports,[15] the most frequent symptoms of COVID-19 patients were fever, dry cough, and chest tightness, while diarrhea was rare. Toxicosis symptoms, such as fatigue and myalgia, were also common in patients with COVID-19. Upper respiratory tract symptoms, such as rhinorrhea, sneezing, and sore throat, were also found to occur, which were clinical features that were unique from MERS and SARS.[7,8] Additionally, the present study demonstrated that the liver was the most frequently injured extrapulmonary organ, with an incidence rate that was much higher than that of other organs, suggesting that coronavirus may also be a hepatotropic virus. The underlying mechanism of COVID-19 may due to the ubiquitous distribution of angiotensin-converting enzyme 2, which is the main viral entry receptor.[16] However, further experiments using cell and animal models will be required to confirm these findings.

CT plays a very important role in the early diagnosis and efficacy evaluation of COVID-19 due to its high sensitivity.[17] Typical chest CT images present multifocal bilateral ground-glass opacity with patchy consolidations, prominently located in peripheral or subpleural locations. However, at present, the evaluation of COVID-19 patients with CT is mainly qualitative, leading to subjective and imprecise judgments on COVID-19 severity. Hence, a quantitative method for the assessment of CT images is needed. The present study scored the number, quadrant, and area of lesions in CT scans to assess the severity of COVID-19. While the total CT score was simply the sum of these three scores. The results distinguished severe COVID-19 effectively (AUROC = 0.672–0.742), irrespective of

TABLE 4 Characteristics at the admission of the COVID-19 patients according to the time from onset to hospitalization

Variable	Time from onset to hospitalization				*p* (Tendency test in 2 weeks)	*p* (7–14 days vs. >14 days)
	≤3 days (*n* = 46)	4–7 days (*n* = 47)	7–14 days (*n* = 35)	>14 days (*n* = 30)		
Epidemiological and clinical characteristics						
Age (years)	47.78 ± 17.58	50.06 ± 17.79	51.09 ± 13.15	56.47 ± 14.82	0.312	0.098
Gender (female/male)	21/25	21/26	11/24	11/19	0.230	0.656
Severity (mild/severe)	37/9	34/13	18/17	24/6	0.001	0.016
Exposure history (Y/N)	41 (89.1%)	34 (72.3%)	30 (85.7%)	30 (100.0%)	0.516	0.057
Any comorbidities	10 (21.7%)	18 (38.3%)	19 (54.3%)	13 (43.3%)	0.002	0.379
Hypertension	4 (8.7%)	7 (14.9%)	9 (25.7%)	4 (13.3%)	0.040	0.213
Diabetes	5 (10.9%)	7 (14.9%)	4 (11.4%)	4 (13.3%)	0.882	1.000
Hepatitis B	1 (2.2%)	0 (0%)	5 (14.3%)	2 (6.7%)	0.021	0.323
Bacterial infection	1 (2.2%)	7 (14.9%)	6 (17.1%)	3 (10.0%)	0.024	0.406
Signs and symptoms						
Fever	41 (89.1%)	41 (87.2%)	30 (85.7%)	24 (80.0%)	0.645	0.540
Dry cough	16 (34.8%)	20 (42.6%)	20 (57.1%)	13 (43.3%)	0.049	0.267
Sputum production	1 (2.2%)	9 (19.1%)	6 (17.1%)	4 (13.3%)	0.027	0.671
Chills	9 (19.6%)	7 (14.9%)	6 (17.1%)	8 (26.7%)	0.731	0.352
Myalgia	4 (8.7%)	7 (14.9%)	5 (14.3%)	8 (26.7%)	0.414	0.213
Chest tightness	10 (21.7%)	15 (31.9%)	19 (54.3%)	11 (36.7%)	0.003	0.155
Polypnea	2 (4.3%)	7 (14.9%)	11 (31.4%)	3 (10.0%)	0.008	0.036
Fatigue	5 (10.9%)	12 (25.5%)	12 (34.3%)	14 (46.7%)	0.011	0.310
Headache/dizziness	8 (17.4%)	6 (12.8%)	1 (2.9%)	3 (10.0%)	0.050	0.328
Sore throat	12 (26.1%)	7 (14.9%)	4 (11.4%)	1 (3.3%)	0.077	0.363
Rhinorrhea/rhinobyon	4 (8.7%)	2 (4.3%)	1 (2.9%)	1 (3.3%)	0.237	1.000
diarrhea	4 (8.7%)	3 (6.4%)	1 (2.9%)	2 (6.7%)	0.292	0.591
Laboratory parameters						
CRP (mg/L)	6.35 (1.37–29.77)	12.10 (2.81–22.59)	22.99 (6.26–83.00)	2.02 (0.40–9.16)	0.013	<0.001
WBC ($\times 10^9$/L)	5.31 (3.95–6.19)	4.50 (3.39–6.65)	6.06 (3.71–7.27)	5.44 (4.56–9.16)	0.472	0.958
Lymphocyte count ($\times 10^9$/L)	1.11 (0.86–1.50)	1.05 (0.83–1.43)	0.65 (0.40–1.15)	1.34 (1.05–1.65)	<0.001	<0.001
Neutrophils count ($\times 10^9$/L)	3.45 (2.43–4.63)	2.74 (2.01–4.55)	4.47 (2.36–5.95)	3.07 (2.55–4.32)	0.144	0.134
RBC ($\times 10^{12}$/L)	4.60 ± 0.61	4.57 ± 0.59	4.48 ± 0.46	4.41 ± 0.44	0.212	0.001
Hemoglobin (g/L)	143.17 ± 15.72	142.38 ± 20.03	142.34 ± 13.51	139.58 ± 15.62	0.518	0.001
Platelets ($\times 10^9$/L)	166.00 (140.75–206.25)	175.00 (133.00–218.00)	171.00 (134.00–247.00)	196.50 (167.25–243.75)	0.483	0.188
Albumin (g/L)	45.06 ± 6.95	41.35 ± 5.99	39.40 ± 7.04	38.43 ± 5.31	<0.001	0.850
ALT (U/L)	16.50 (10.75–32.00)	18.00 (13.00–39.00)	29.00 (19.00–44.00)	26.25 (22.50–45.31)	0.001	0.248
AST (U/L)	22.00 (17.00–28.00)	24.00 (19.00–34.00)	28.00 (22.00–47.00)	23.00 (17.00–30.50)	0.011	0.023

TABLE 4 (Continued)

Variable	Time from onset to hospitalization				*p* (Tendency test in 2 weeks)	*p* (7–14 days vs. >14 days)
	≤3 days (*n* = 46)	4–7 days (*n* = 47)	7–14 days (*n* = 35)	>14 days (*n* = 30)		
Total bilirubin (μmol/L)	8.15 (6.35–11.30)	8.10 (5.20–14.10)	10.30 (8.90–14.60)	12.20 (9.30–15.05)	0.028	0.462
Direct bilirubin (μmol/L)	2.50 (1.95–3.70)	2.60 (1.90–5.00)	3.60 (2.70–5.60)	3.30 (2.85–3.75)	0.001	0.318
GGT (U/L)	20.00 (12.00–37.02)	24.00 (16.00–45.76)	37.00 (28.00–65.00)	34.32 (22.88–58.60)	<0.001	0.438
Lactate dehydrogenase (U/L)	202.00 (174.25–248.00)	235.00 (200.00–291.00)	281.00 (217.00–382.00)	196.50 (164.25–228.00)	<0.001	<0.001
Creatinine (mmol/L)	62.00 (50.85–75.55)	67.10 (56.20–80.90)	66.90 (56.70–82.30)	73.50 (63.50–81.50)	0.127	0.406
Urea nitrogen (mmol/L)	3.90 (3.25–5.30)	4.40 (3.50–5.60)	4.60 (3.50–5.50)	4.30 (3.15–5.50)	0.113	0.618
Creatine kinase (U/L)	94.00 (60.50–139.50)	85.00 (62.00–135.00)	112.72 (55.95–135.25)	108.48 (71.97–161.76)	0.826	0.672
prothrombin time (s)	12.30 (11.75–12.70)	12.60 (12.10–13.40)	12.60 (12.10–13.00)	12.70 (12.21–13.29)	0.079	0.434
Thrombin time (s)	15.80 (15.05–16.75)	15.80 (15.10–17.00)	16.10 (15.20–17.20)	16.55 (15.90–17.65)	0.289	0.065
APTT (s)	28.50 (27.25–31.90)	31.00 (28.40–34.10)	30.30 (27.68–32.60)	31.65 (30.36–33.59)	0.302	0.077
D-dimer (mg/L)	0.26 (0.15–0.49)	0.27 (0.20–0.70)	0.50 (0.26–1.05)	0.47 (0.20-1.62)	0.001	0.827
Imaging parameters						
Total score	8.00 (4.00–10.00)	9.00 (6.00–12.00)	11.00 (8.00–12.00)	6.00 (4.00–11.00)	<0.001	0.003
Number score	3.00 (1.00–4.00)	4.00 (2.00–4.00)	4.00 (4.00–4.00)	3.00 (2.00–4.00)	0.012	0.011
Quadrant score	3.00 (1.00–4.00)	3.00 (2.00–4.00)	4.00 (3.00–4.00)	2.00 (1.00–4.00)	0.011	0.012
Area score	1.00 (1.00–3.00)	2.00 (1.00–4.00)	3.00 (2.00–4.00)	2.00 (1.00–3.00)	< 0.001	0.017

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; GGT, γ-glutamyl transpeptidase; RBC, red blood cell count; WBC, white blood cell count.

the number score, quadrant score, or area score, and the total CT score performed best in distinguishing severe COVID-19. Thus, this new quantitative CT score represents a simple and feasible score for the identification of severe COVID-19. Moreover, when analyzed together with clinical parameters, the total CT score remained an independent indicator for severe COVID-19 in a multivariate logistic regression analysis.

COVID-19 has spread rapidly, resulting in surges of infected individuals that have brought enormous challenges to the supply of medical resources. As such, there is an urgent need for the accurate identification of severe patients to effectively allocate scarce resources. In agreement with previous studies,[18–20] lymphocyte count was found to be an independent factor for the identification of severe COVID-19. Additionally, the total CT score, chest tightness, and LDH were identified as novel independent indicators for severe COVID-19. Thus, greater attention should be paid to these indicators when evaluating the condition of patients with COVID-19 despite the performance of these indicators still need to be investigated in future studies.

The clinical characteristics of patients admitted at different times from disease onset reflected the natural course of COVID-19 without interventions. In the present study, alterations of the clinical characteristics of COVID-19 patients with the time from onset to hospitalization were evaluated. The level of C-reactive protein was found to increase gradually in the first 14 days from disease onset but gradually decreased thereafter. Hence, it was speculated that the inflammation of COVID-19 was initiated from disease onset and peaked at 14 days, but inhibited at the third week of the clinical course. Conversely, the lymphocyte count decreased gradually in the initial 14 days but began to gradually increase 14 days after disease onset, suggesting that the recovery of the lymphatic system was also initiated after 14 days. Most notably, the total score and area score based on CT were gradually increased in 10 days but gradually decreased after 10 days from onset to hospitalization, as well as the results of LDH, GGT, and AST levels were observed, which suggested that lung lesions began to assimilate and liver function began to recover 10 days after disease onset. These results

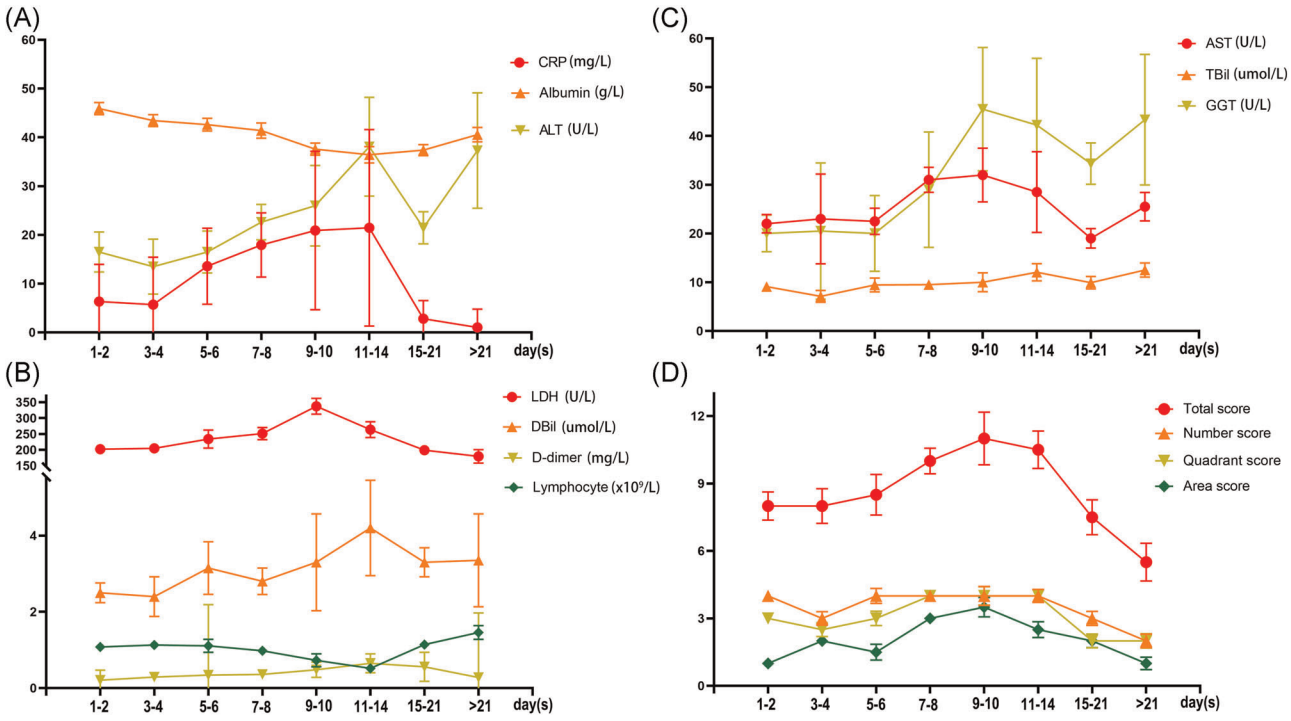

FIGURE 2 Alterations of laboratory parameters and computed tomography scores with the time from onset to hospitalization. The numbers of patients admitted in 1–2, 3–4, 5–6, 7–8, 9–10, 11–14, 15–21, and >21 days after symptom onset were 35, 24, 18, 23, 16, 12,14, and 16, respectively. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; DBil, direct bilirubin; GGT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; TBil, total bilirubin

indicated that the condition of COVID-19 patients without intervention deteriorated gradually during the initial 10–14 days from disease onset, but improved henceforth. Comparing with previous studies[21–23] observed after patients' admission, the turning point of laboratory parameters and CT score observed in our study was slightly delayed, which suggested timely clinical intervention would help to shorten the duration of COVID-19. Anyway, the findings of the present study suggest that more efforts should be focused on the close monitoring of the disease during the first 2 weeks of illness.

This study has several limitations. First, limited by the sample size, the timespan among observation points after 14 days was relatively longer. Hence, a more detailed natural course of COVID-19 after 14 days could not be investigated. Second, the number of critically ill patients was less in this study, therefore, the natural course of those patients should be interpreted carefully and need to further study to clear it.

In conclusion, this study provided a simple and feasible scoring approach based on CT images to assess the severity of COVID-19 and identified four independent indicators for severe COVID-19. Moreover, this study demonstrated COVID-19 patients without clinical intervention deteriorated gradually during the initial 10–14 days, but gradually improved thereafter. We believe that our findings provide an insight into improving the management of COVID-19 and the allocation of limited medical resources.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Wenfeng Zhang was the guarantor of the submission. Daxian Wu and Wenfeng Zhang designed the study. Daxian Wu, Qunfang Rao, and Wenfeng Zhang enrolled the patients and collected the data. Daxian Wu performed the statistical analysis of this study. Daxian Wu and Qunfang Rao analyzed and interpreted the data. Daxian Wu drafted the manuscript and Wenfeng Zhang provided critical revision of the manuscript. All authors approved the final version of the manuscript.

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