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Research Article

A Multivariate Model for Predicting the Progress of COVID-19 Using Clinical Data besides Chest CT Scan

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Objective. Computed tomography (CT) scan is a method to predict the progression and prognosis of COVID-19. It is not sufficient merely to measure the prognosis of COVID-19 without other clinical methods. The purpose of this study was to investigate the association between the CT scan and clinical laboratory indicators as well as clinical manifestations. *Method*. A total of 335 patients were enrolled from January 26, 2020, to February 26, 2020, in Shandong province and Huanggang city. Demographic and clinical characteristics, laboratory variables, and the data from the CT scans were collected for analysis. Scatter plot analysis and correlation analysis were used to calculate the relationship between CT evaluation and other indicators. Multivariable linear regression analysis was used to establish a model for diagnostic and prognostic prediction. Age, CRP, LDH, and lymphocyte counts as independent variables were selected to develop a predictive model, and the results from the CT scans to reflect the degree of lung injury were taken as the dependent variable. *Result*. The median age was 44 years (IQR: 34–56); among them, 188 (56%) were male. Severe patients were older (56 vs. 40, $P < 0.001$). There were statistically significant differences in lymphocyte counts, platelet counts, C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin (PCT), and creatine kinase (CK) between the general patients and severe patients. We found that, without effective antiviral treatment, mild patients had a 6-day interval from symptom onset to CRP elevation, but in severe patients, CRP started to increase from day 2. Lung injury score from a chest CT scan and incidence of acute respiratory distress syndrome (ARDS) were significantly higher in severe patients than in mild patients. Lung injury score from a chest CT scan was closely correlated with CRP ($r_s = 0.704$, $P < 0.01$), and they reflected the severity of the disease. The receiver operating curve (ROC) value of the injury score from the chest CT scan was 0.854 (95% CI: 0.808–0.901), and the area under the curve (AUC) value of CRP was 0.823 (95% CI: 0.769–0.878). *Conclusion*. The results from CRP and chest CT scans were indicators of the severity of COVID-19. Combining patient age, CRP, LDH, and lymphocyte counts, we developed a model that could help to predict lung injury/function of patients with COVID-19.

1. Introduction

COVID-19 was first reported in Wuhan, Hubei Province, China, in December 2019, followed by an outbreak across Hubei province and other parts of the country [1, 2]. On February 11, novel coronavirus pneumonia was declared by the WHO as coronavirus disease 2019 (COVID-19). As of May 14, more than 4,450,000 COVID-19 cases have been confirmed globally, with more than 300,000 deaths, some of them while awaiting diagnosis. In some countries and regions, including Wuhan, China, in the early days of the outbreak, many patients were waiting for beds outside hospitals.

During the course of the disease, a chest CT scan plays an important role in the diagnosis and prognosis of COVID-19 [3, 4]. However, CT requires an appointment and waiting, and COVID-19 is a highly infectious disease. Human-to-human transmission can be exacerbated during CT screening, especially if the patient was not diagnosed [5]. Wang et al. found that 57 (41.3%) were presumed to have been infected in the hospital, including 17 patients (12.3%) who were already hospitalized for other reasons and 40 healthcare workers (29%) in 138 patients [6]. Therefore, protection and disinfection during and after the inspection are critical, but it can take a lot of time. Also, severe patients may be ignored or wait outside the hospital before a chest CT scan. Especially in patients without severe symptoms, such as decreased SPO_2 and increased breathing rate, it will undoubtedly aggravate the further deterioration of the disease. Therefore, we need to find another way to identify which patients may become serious before a chest CT scan [7]. Chest CT scan may also be limited in some countries or regions with severe outbreaks of COVID-19. Based on the current reality, it is very important to find a relatively simple parameter and develop a model to predict the patient's progress besides chest CT scan.

CRP, as a marker of inflammatory response, has been recognized and known in clinical practice for decades [8, 9]. Previous studies show that CRP can discriminate between bacterial and viral infections; also, it has been confirmed that it was closely related to the inflammation reaction [10, 11]. Although CRP was not changed in most virus pneumonia such as H5N1, H7N9, and H1N1 [12], Smith et al. [13] found elevated CRP in patients with COVID-19. They also compared the viral load and the degree of lung injury in 12 severe patients, indicating a positive correlation between CRP and viral load as well as showing a correlation between viral load and the degree of lung injury from the CT scan. At present, no one has reported whether there was a direct correlation between CRP and the results from CT scans among COVID-19 patients. Previous studies also found that the result from the CT scan has relevance with clinical features and related serum indicators [14]. In most patients with COVID-19, the white blood cell counts were reduced, CRP was significantly increased, and LDH was elevated [15, 16]. Based on the above observations, it provides the clue for us to establish the correlation between the chest CT scan and the clinical laboratory indicators.

Firstly, we analyze the effects of these indexes and then select some effective indexes to be used in the model for prediction. In the current study, we retrospectively collected and analyzed detailed clinical data on laboratory-confirmed patients with COVID-19 in Shandong province and Huanggang city, China. The injury score was quantified according to a chest CT scan. Demographic data such as age, sex, white blood cell counts, lymphocyte counts, neutrophil counts, CRP, PCT, LDH, and CK were collected and analyzed to establish a predictive model for patients with COVID-19 and to identify severe lung lesions besides chest CT scan.

1.1. Patient Enrollment and Methods

1.1.1. Patient Enrollment. All adult hospitalized patients ($n = 387$) (admission date from January 26 to February 26, 2020) in eleven designated hospitals of Shandong province and two designated hospitals of Huanggang city were diagnosed as COVID-19 based on RT-PCR of nasopharyngeal swab. The novel coronavirus pneumonia diagnostic criteria were consistent with the WHO's criteria for the diagnosis of COVID-19. A total of 335 cases were included, containing 6 dead cases. 52 cases were excluded, of which 20 were children and 32 were unable to receive a chest CT scan. This study was approved by the institutional ethics board of Yantai Yuhuangding Hospital, Shandong, China (no. 2020026). Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases and retrospectively observational design.

The severity was determined according to the SARS-CoV-2 guidelines for diagnosis and treatment (6th edition) issued by the National Health Commission of China. The patients were divided into mild and severe groups according to the guidelines.

Severe COVID-19 cases refer to any of the following symptoms at any time during the hospitalization: (1) respiratory distress with respiratory frequency ≥30/min; (2) pulse dosimeter oxygen saturation (SPO_2) ≤ 93% at rest; (3) oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, $PaO_2/FiO_2 \leq 300$ mmHg.

1.2. Data Collection. Leukocyte counts, neutrophil counts, lymphocyte counts, CRP, PCT, LDH, and CK were collected on the day of admission. These indicators are detected by hospital equipment with standard methods. For example, CPR is measured by the immune scattering turbidimetric method, and LDH is measured by the IFCC method.

The time difference for collecting data between the chest CT scan and the above indexes was no more than 24 hours. CT score was measured by 3 senior radiologists with more than 8 years of work experience. The CT score was calculated according to the lesion area (Figure 1).

1.3. Statistical Analysis. Continuous variables were shown as mean and standard deviation (SD) or median and interquartile range (IQR), compared using Student's *t*-test or Wilcoxon rank-sum test as appropriate. Categorical variables were reported as numbers and percentages and were analyzed with chi-square test or Fisher's exact test as appropriate.

A multivariable model was used to predict the CT score. First, a descriptive analysis was performed between mild and severe COVID-19 patients. Second, multivariate linear regression models were built with variables of a P value less than 0.1 identified by the univariate analysis or those which were considered clinically important. Third, a stepwise backward elimination method was used to remove variables with P value over 0.1. Potential multicollinearity was tested using the variance inflation factor. Adjusted R-squared was used to assess the model. Nomogram was used to express the

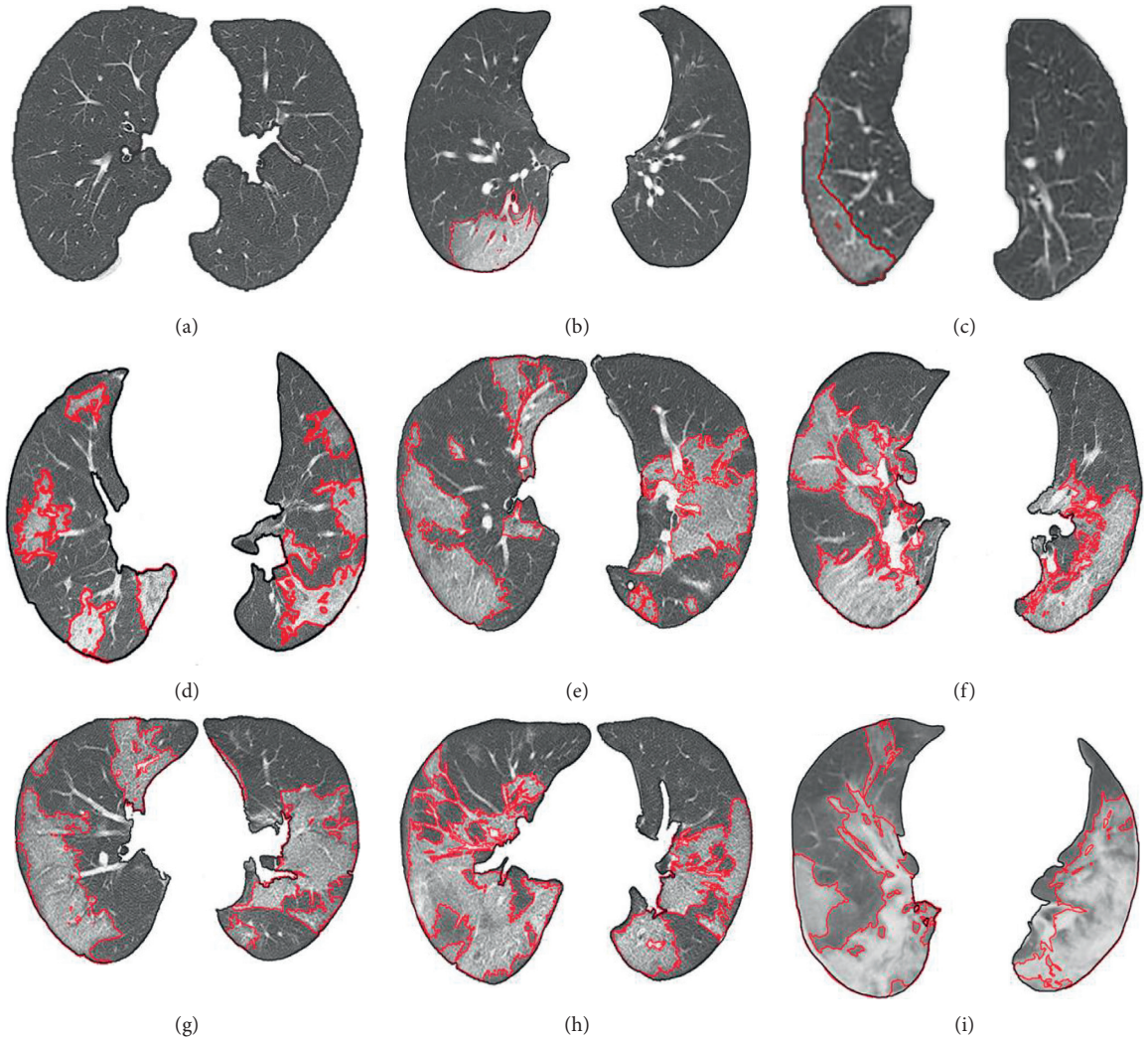

Figure 1: Instruction for the CT score: CT score was conducted according to the percentage of ground-glass opacity (GGO) or patchy shadows in the whole lung. No lesions in the chest CT were assigned 0 points (a); percentage of area range 1–9% was assigned 1 point (b); 1.5 points for 10–19% (c); 2 points for 20–29% (d); 2.5 points for 30–39% (e); 3 points for 40–49% (f); 3.5 points for 50–59% (g); 4 points for 60–69% (h); 4.5 points for ≥70% (i). Patients who had pleural effusion, tuberculosis, chronic bronchitis, emphysema, or bronchiectasis caused by basic lung diseases were assigned another 0.5 points for each condition.

final model. A two-sided P value of less than 0.05 was considered statistically significant. All statistical analyses were performed using R software (version 3.5.1, https://www.r-project.org).

2. Result

387 patients diagnosed as COVID-19 were investigated. A total of 335 patients were analyzed after exclusion (20 children and 32 unable to receive chest CT scan). The median age was 44 years (IQR; 34–56), and 188 (56%) were male patients. Among them, 12 (4%) had diabetes, 15 (4%) had hypertension, and 4 (1%) had cancer. As expected, patients with severe illness were older (56 vs. 40, $P < 0.001$) (Table 1).

Dry cough (78% vs. 50%, $P < 0.001$), expectoration (39% vs. 16%, $P < 0.001$), and fatigue (33% vs. 11%, $P < 0.001$) were higher in severe patients. Severe patients also had higher temperature (38.1 vs. 37.7, $P < 0.001$), respiratory rate (21 vs. 19, $P < 0.001$), and low SpO_2 (93 vs. 98%, $P < 0.001$). Laboratory tests on admission, lymphocyte counts, and platelet counts were all lower in the severe patients' group who showed higher CRP, LDH, PCT, and CK (Table 1). The injury score from the chest CT scan and the incidence of ARDS were higher in severe patients. There was no doubt that the severe patients had more need for respiratory support (i.e., more proportion of HFNC, mechanical ventilation, and intubation). Nevertheless, mild and severe patients received similar antivirus drug treatment (Table 2). We also found that the interval from symptom to elevated CRP was about 6 days in mild patients if they did not receive the effective antivirus treatment, but for severe patients, CRP started to increase from day 2 (Figure 2(a)). There was no significant change in lymphocyte counts at day 6 in mild patients (Figure 2(b)).

Table 1: Demographics and baseline characteristics of patients with COVID-19.

	Total ($N = 335$)	Mild ($N = 242$)	Severe (N =dsl 93)	P value
Age, years	44 (34, 56)	40 (32, 51)	56 (41, 66)	<0.001
Gender (male)	188 (56)	134 (55)	54 (58)	0.748
Comorbidities				0.153
Diabetes mellitus	12 (4)	8 (3)	4 (4)	0.744
Hypertension	15 (4)	8 (3)	7 (8)	0.136
Cancer	4 (1)	2 (1)	2 (2)	0.309
Signs or symptoms				
Dry cough	194 (58)	121 (50)	73 (78)	<0.001
Expectoration	74 (22)	38 (16)	36 (39)	<0.001
Chest distress	39 (12)	30 (12)	9 (10)	0.614
Diarrhea	7 (2)	6 (2)	1 (1)	0.678
Fatigue	57 (17)	26 (11)	31 (33)	<0.001
Onset of symptom to the hospital (days)	5 (4, 6)	4 (3, 5)	6 (5, 7)	<0.0001
Admission vital signs				
Temperature,°C	37.8 (37.4, 38.3)	37.7 (37, 38)	38.1 (37.8, 38.5)	<0.001
Respiratory rate	19 (18, 22)	19 (18, 20)	21 (19, 25)	<0.001
SpO_2, %	98 (96, 99)	98 (98, 99)	93 (92, 97)	<0.001
Laboratory findings on admission				
WBC, $\times 10^9$/L	4.9 (3.9, 6.4)	4.9 (3.9, 6.3)	4.7 (3.8, 6.9)	0.89
Neutrophils, $\times 10^9$/L	3.1 (2.3, 4.4)	3.1 (2.3, 4.0)	3.1 (2.4, 5.6)	0.127
Lymphocytes, $\times 10^9$/L	1.2 (0.82, 1.62)	1.36 (0.98, 1.76)	0.96 (0.55, 1.28)	<0.001
Hemoglobin, g/L	138 (126, 150)	139 (126, 150)	136 (126, 146)	0.549
Platelets, $\times 10^9$/L	184 (155, 227)	193 (163, 240)	163 (134, 194)	<0.001
C-reactive protein, mg/L	8 (3.4, 20.57)	5.2 (2.4, 12.8)	28.3 (11.9, 66.7)	<0.001
Procalcitonin, ng/ml	0.05 (0.04, 0.1)	0.05 (0.04, 0.1)	0.08 (0.04, 0.14)	0.045
Lactate dehydrogenase, U/L	209 (176, 260)	194 (168, 232)	276 (211, 357)	<0.001
Creatine kinase, U/L	65 (42, 97)	61 (40, 92)	73 (52, 129)	0.012
Chest CT images				
Abnormal	315 (94)	197 (91)	78 (89)	0.713
Bilateral lung	156 (47)	78 (36)	78 (89)	<0.001
Single lung	149 (45)	119 (55)	10 (11)	<0.001
Normal	20 (6)	20 (9)	0 (0)	<0.001
Chest CT score				<0.001
0 points	20 (6)	20 (8)	0 (0)	
1 point	51 (15)	49 (20)	2 (2)	
1.5 points	28 (8)	25 (10)	3 (3)	
2 points	80 (24)	70 (29)	10 (11)	
2.5 points	55 (16)	40 (17)	15 (16)	
3 points	51 (15)	31 (13)	20 (22)	
3.5 points	22 (7)	6 (2)	16 (17)	
4 points	22 (7)	1 (0)	21 (23)	
4.5 points	6 (2)	0 (0)	6 (6)	

Data are median (interquartile range) or no./total (%). SpO_2: saturation of peripheral oxygen; CT: computed tomography.

In the present study, the chest CT score was closely associated with CRP. The Spearman correlation coefficient was 0.704 ($P < 0.001$) (Figure 3(b)). They were also significantly associated with disease severity. The ROC of the chest CT score was 0.854 (95% CI: 0.808–0.901), and the AUC of C-reactive protein was 0.823 (95% CI: 0.769–0.878) for disease severity (Figure 3(a)).

For multivariable linear regression analysis, we analyzed the relationship between the chest CT score and several related factors. Age, CRP, LDH, and lymphocyte counts were included in the final model (Table 3). We built a prediction model for the chest CT score with the four variables, which was shown as a nomogram and very practical (Figure 4). When we obtain the information including age, CRP, LDH, and lymphocyte counts, we could predict patient progress and prognosis, rather than using a chest CT scan. For example, in one patient aged 65 years, laboratory tests showed CRP was 66.3 mg/L, LDH was 288 U/L, and lymphocyte count was 0.24×10^9/L, the corresponding points were 49, 72, 38, and 42, respectively, and the total points were 199. According to the prediction model, the predicted chest CT score was 3.679 (Figure 4).

3. Discussion

Our study included 335 patients who had laboratory tests on admission; compared with mild COVID-19 patients, the severe group had higher CRP, LDH, PCT, and CK, whereas

Table 2: Complications and treatment of patients with COVID-19.

	Total ($N = 335$)	Mild ($N = 242$)	Severe ($N = 93$)	P value
ARDS	42 (13)	0 (0)	42 (45)	<0.001
HFNC	11 (3)	0 (0)	11 (12)	<0.001
Mechanical ventilation	24 (7)	0 (0)	24 (26)	<0.001
Intubation	17 (5)	0 (0)	17 (18)	<0.001
Drug treatment	15 (4)	8 (3)	7 (8)	0.136
Arbidol	57 (17)	37 (15)	20 (22)	0.233
Oseltamivir	32 (10)	23 (10)	9 (10)	1
Interferon	146 (44)	114 (47)	32 (34)	0.048
Ribavirin	20 (6)	16 (7)	4 (4)	0.588
Lopinavir	171 (51)	130 (54)	41 (44)	0.145
Chloroquine	8 (2)	7 (3)	1 (1)	0.452

Data are median (interquartile range) or no./total (%). ARDS: acute respiratory distress syndrome; HFNC: high-flow nasal cannula oxygenation.

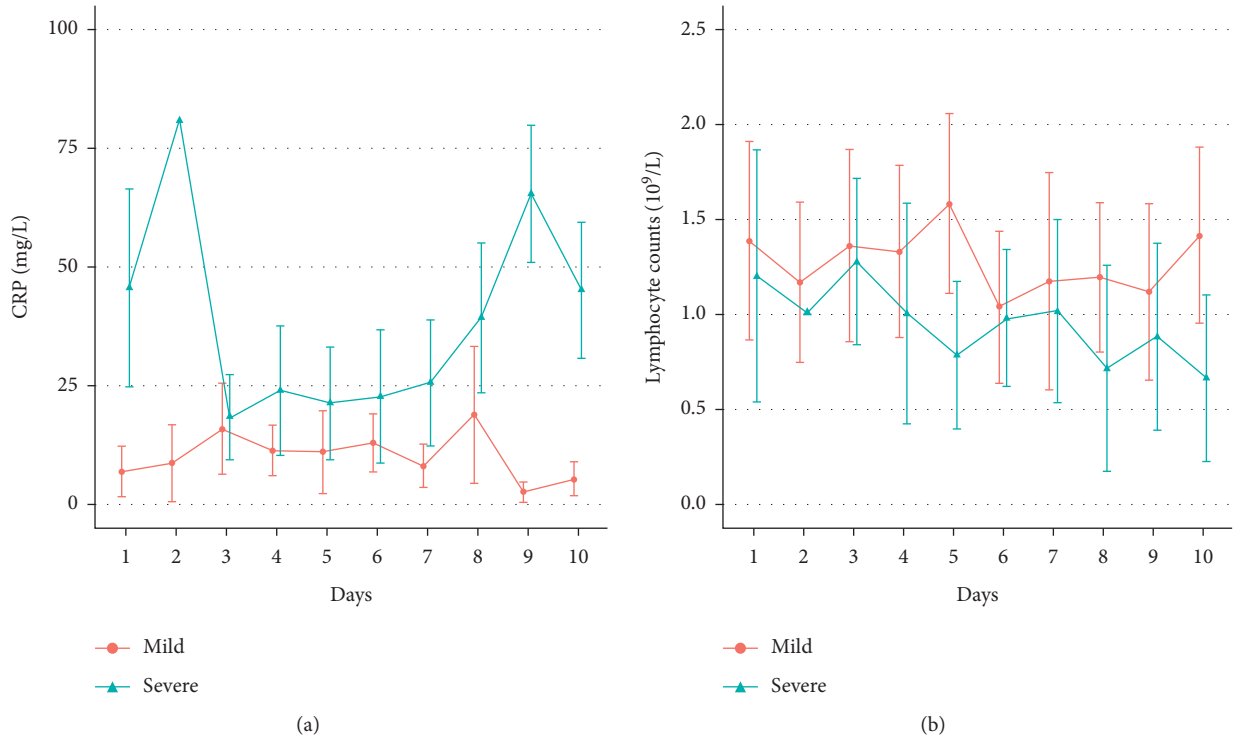

Figure 2: The tendency of CRP and lymphocyte counts on the days from symptom onset to hospital admission.

lower lymphocyte counts and platelet counts. Severe patients had higher chest CT scores and a higher proportion of ARDS. In severe patients, the demand for respiratory support increased significantly, such as increased HFNC ratio, mechanical ventilation, and intubation. Mild and severe patients treated with antiviral drugs were similar. The clinical characteristics of these COVID-19-infected patients were similar to those previously reported [17–19].

First, we found that, in the laboratory tests on admission, lower lymphocyte counts and platelet counts and higher CRP, LDH, PCT, and CK were observed in severe patients, which was consistent with other studies [20, 21]. The severe group also had a higher CT score, suggesting more severe lung injury [22]. These results were consistent with those of other studies, so we can conclude that these parameters were related to the severity of COVID-19. We also found that, without effective antiviral treatment, mild patients had a 6-day interval from symptom to CRP elevation, but in severe patients, CRP increased from day 2. There was no significant change in lymphocyte counts at day 6 in mild patients. Our findings demonstrate that severe patients may have higher and earlier inflammatory reaction to COVID-19 infection corresponding to the tendency of CRP.

In addition, a previous study also found high CRP in severe patients with COVID-19 infection, but it did not make a comparison with mild patients during admission [14]. And it also did not explore the relationship between CRP and chest CT manifestation. In the present study, the

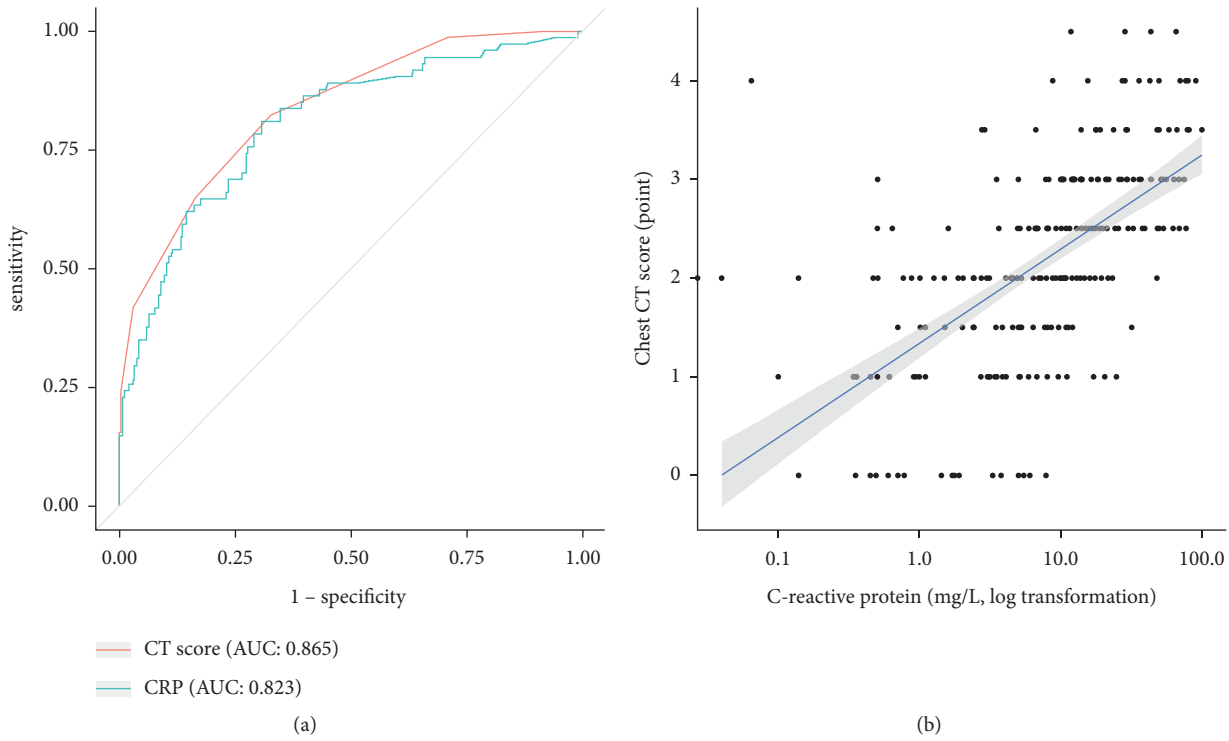

Figure 3: (a) Scatter diagram and correlation between C-reactive protein and chest CT score (Spearman's correlation coefficient: 0.704, $P < 0.001$). (b) AUCs of the chest CT score and C-reactive protein for predicting the severity of COVID-19. The AUC of the chest CT score: 0.854 (95% CI: 0.808–0.901); the AUC of C-reactive protein: 0.823 (95% CI: 769–0.878).

Table 3: Univariate and multivariate linear model for predicting the chest CT score.

Variables	Unadjusted			Adjusted		
	Variable beta estimate (95% CI)		P value	Variable beta estimate (95% CI)		P value
Age, years	0.032	(0.026, 0.038)	<0.001	0.019	(0.012, 0.025)	<0.001
C-reactive protein, mg/L	0.027	(0.023, 0.031)	<0.001	0.017	(0.013, 0.022)	<0.001
Lymphocytes, $\times 10^9$/L	−0.634	(−0.813, 0.456)	0.003	−0.208	(−0.408, −0.009)	0.003
Lactate dehydrogenase, U/L	0.004	(0.003, 0.006)	<0.001	0.002	(0.001, 0.003)	<0.001

chest CT score was closely associated with CRP, and they were both significantly associated with disease severity. CRP was not elevated in most cases of viral pneumonia [11] in the early stage. In our study, we noticed that the patients with COVID-19 infection had higher CRP levels; particularly, this elevation occurred before the identification of COVID-19. There is no doubt that severe patients have a larger lesion area in chest CT scan, which was confirmed by the previous study. So, we can conclude that patients with higher CRP should be noticed or should be hospitalized.

At last, we found that the CT score was associated with age, CRP, LDH, and lymphocyte count. So, we built a prediction model to estimate the status, progress, and prognosis of the patients with COVID-19 infection instead of using a chest CT scan. In fact, this established model could be used as an assessment tool to help doctors identify the severity of a patient before or without a chest CT scan. All of these parameters are off the shelf and easily acquired, so it is easier to perform by any country or region where CT scans are not immediately available or difficult to obtain. Especially during the epidemic period, the lower frequency of chest CT scans, the less the risk of COVID-19 infection for others. It can also save manpower and material resources. Finally, it provides a reference for clinicians to identify severe patients as soon as possible without a chest CT scan.

This study has several limitations. First, we only focused on the correlation between CT severity and CRP at the time of admission. Whether CRP is correlated with CT in the course of disease development still needs further investigation. Second, this study only establishes the model through data, but we did not verify the accuracy of the model through other data. So, further study will be needed to verify the model. Finally, this study is retrospective, so there are memory bias and incomplete test results, which lead to

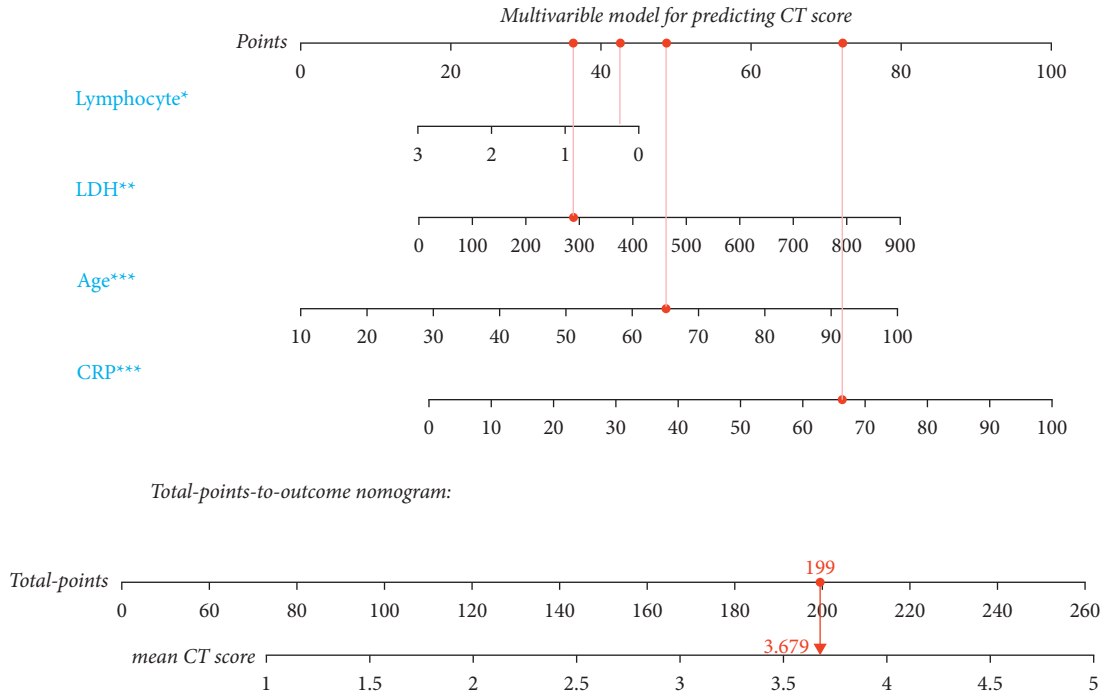

Figure 4: Nomogram of the multivariable linear model for predicting the chest CT score. Four variables were used in the model: age, CRP (C-reactive protein), LDH (lactate dehydrogenase), and lymphocyte count. For example, in one patient aged 65 years, laboratory tests showed CRP was 66.3 mg/L, LDH was 288 U/L, and lymphocyte count was 0.24×10^9/L (red dots on each line of the variables), the corresponding points were 49, 72, 38, and 42 (top line), respectively, the total points were 199, and the predicting chest CT score was 3.679 (the bottom line).

incomplete data of some cases and exclude some people, resulting in selective bias.

4. Conclusion

CRP and chest CT manifestation both are predictors of severity in COVID-19 patients. Combined with the patients' age, CRP, LDH, and lymphocyte counts, we built a model that played a beneficial role to help predict lung function. As a result, it can help physicians to identify patients with severe COVID-19 besides chest CT scan.

Data Availability

The data used to support the findings of this study are available from the corresponding authors upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Yingying Zhu and Haiyan Wu contributed equally to this work.

Acknowledgments

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