Received: 22 March 2020 | Accepted: 9 April 2020

DOI: 10.1002/jmv.25871

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early

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Funding information
Novel Coronavirus Pneumonia Emergency Project of Hunan Provincial Science and Technology Department,
Grant/Award Number: 2020SK3018

Abstract

COVID-19 has developed into a worldwide pandemic; early identification of severe illness is critical for controlling it and improving the prognosis of patients with limited medical resources. The present study aimed to analyze the characteristics of severe COVID-19 and identify biomarkers for differential diagnosis and prognosis prediction. In total, 27 consecutive patients with COVID-19 and 75 patients with flu were retrospectively enrolled. Clinical parameters were collected from electronic medical records. The disease course was divided into four stages: initial, progression, peak, and recovery stages, according to computed tomography (CT) progress. to mild COVID-19, the lymphocytes in the severe COVID-19 progressively decreased at the progression and the peak stages, but rebound in the recovery stage. The levels of C-reactive protein (CRP) in the severe group at the initial and progression stages were higher than those in the mild group. Correlation analysis showed that CRP ($R = .62$; $P < .01$), erythrocyte sedimentation rate ($R = .55$; $P < .01$) and granulocyte/lymphocyte ratio ($R = .49$; $P < .01$) were positively associated with the CT severity scores. In contrast, the number of lymphocytes ($R = -.37$; $P < .01$) was negatively correlated with the CT severity scores. The receiver-operating characteristic analysis demonstrated that area under the curve of CRP on the first visit for predicting severe COVID-19 was 0.87 (95% CI 0.10–1.00) at 20.42 mg/L cut-off, with sensitivity and specificity 83% and 91%, respectively. CRP in severe COVID-19 patients increased significantly at the initial stage, before CT findings. Importantly, CRP, which was associated with disease development, predicted early severe COVID-19.

KEYWORDS
COVID-19, C-reactive protein, SARS-COVID-2

1 | INTRODUCTION

Since the SARS-COVID-2 outbreak in China, a large number of cases have also been reported worldwide and the disease has become a global epidemic. Although the majority of patients show mild symptoms, COVID-19 causes mass casualty and poses great challenges to the global healthcare system.[1,2] Early diagnosis of serious illness is critical to early classification and improvement of patients' prognosis. Additionally, the early identification of patients who will become severely ill could facilitate the allocation of the limited

Abbreviations: AUC, area under the receiver-operating curve; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NLR, granulocyte/lymphocyte ratio; ROC, receiver operating characteristic; WBC, white blood cell.

medical resources to patients in need of aggressive treatment. Therefore, further research is urgently needed on early diagnosis and prognosis. In addition, due to the similarity in the early stages of COVID-19 with the flu, it is not easy to distinguish between them, especially in the winter and spring. Any misdiagnosis will have disastrous consequences in controlling the epidemic. Changes in the number of lymphocytes, C-reactive protein (CRP), and erythrocyte sedimentation rates (ESR) have been previously reported in COVID-19 patients, but little is known about their correlation with disease severity.[3,4]

Therefore, it is necessary to determine the clinical laboratory biomarkers that will allow early and differential diagnosis of SARS-COV-2 infection and predict the severity of the disease. In this study, we aimed to compare clinical laboratory biomarkers between SARS-COV-2 and influenza infection, and also between mild and severe COVID-19 patients, to explore the most useful prognostic factors for early, accurate, and individualized assessment of COVID-19 patients.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The ethics board of the Hunan Provincial People's Hospital approved the present retrospective study (No. 202005; Changsha, China) and informed consent was waived. In the Hunan Provincial People's Hospital, a total of 27 consecutive patients were retrospectively enrolled between 18 January and 10 February 2020, who were identified as patients infected with SARS-COV-2. The diagnosis and treatment of SARS-COV-2 infection followed the *Guidelines and Management of COVID-19 of the National Health Commission of China*.[5] According to clinical records, 6 patients (22%) who had progressed into severe illness were classified as the severity group and the other 21 patients as the mild group. Meanwhile, 75 patients with Influenza A or influenza B infections were enrolled from 18 December 2019 to 10 February 2020. To match the characteristics of COVID-19 infected patients, the following exclusion criteria were applied: (a) <12 years; (b) no history of tumor, severe kidney and liver diseases; (c) no presence of other known infection; (d) no leukemia or other serious blood disease; (e) no pregnancy; (f) no medication before the initial visit.

2.2 | Clinical parameters and data collection

The exposure history, demographic data, clinical symptoms, comorbidities, laboratory findings, chest computed tomographic (CT) scans and clinical outcomes were collected. The radiographic scores for COVID-19 patients were blindly evaluated by two radiologist doctors. CT scores were recorded following previous research with some modifications.[6] In particular, 5 scores were assigned according to visual assessment of the involvement of each of the five lung lobes independently: 0 point, no involvement; 1 point, less than 5% involvement; 2 points, 25% involvement; 3 points, 26%-49% involvement; 4 points, 50% to 75% involvement; 5 points, more than 75% involvement (Figure 1). The total CT score was the sum of the scores of the individual lobes ranging from

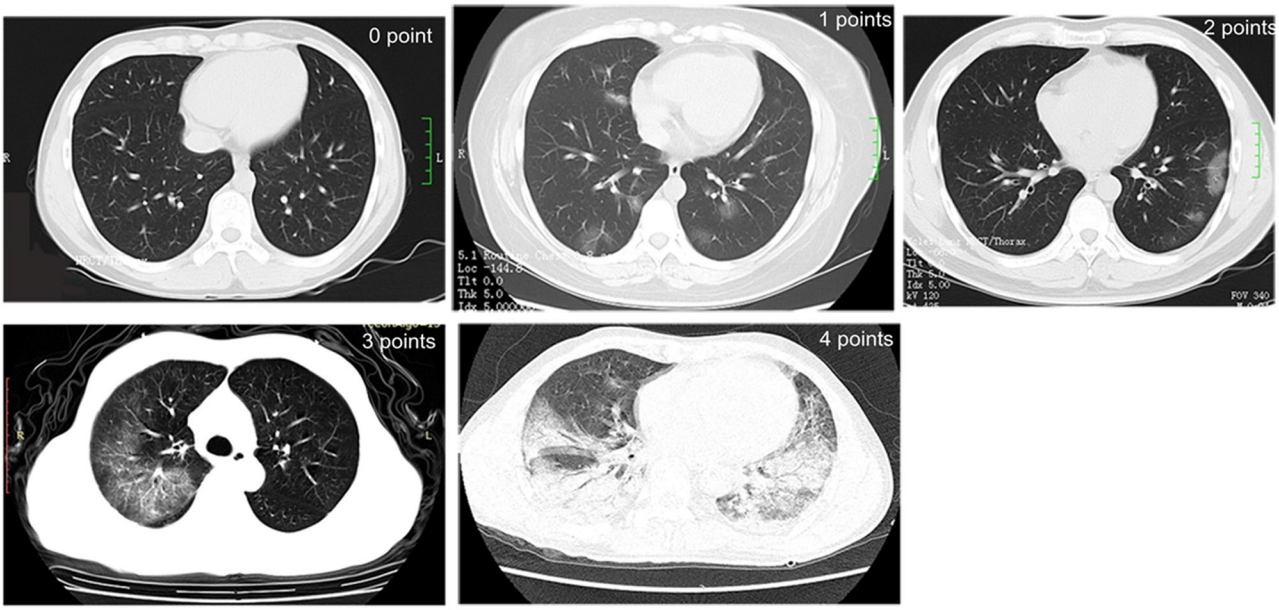

FIGURE 1 CT Score example: 0 point, Five lobes of lungs are not involved, 0 point for every lobe; 1 point, Minimal involvement (<25%) in right middle lobe, right lower lobe, left upper lobe and left lower lobe, 1 point for each lung lobe, 4 points in total; 2 points, Mild involvement (26-50%) in the left lower lobe, 2 points in the left lower lobe; 3 points, Moderate involvement (51-75%) in the right upper lobe, and 3 points in the right upper lobe; 4 points, Severe involvement (>75%) in right lower lobe, left upper lobe and left lower lobe, 4 points for each lung lobe, 12 points in total

0 to 25. At the same time, according to the CT progress and score of every single patient, the course of the disease was divided into four stages: stage 1 (initial stage), stage 2 (progression stage), stage 3 (peak stage), and stage 4 (absorption stage). Furthermore, the corresponding laboratory parameters per stage including blood count, CRP, ESR, if any, were retrieved from the clinical database. The last date of follow-up of clinical outcomes including severity and discharges was 20 February 2020.

2.3 | Statistical analysis

Categorical variables were analyzed by Pearson's the χ^2 test or Fisher's exact test as appropriate and are presented by frequencies and percentages. Continuous variables were described as means and standard deviations or medians and interquartile ranges, depending on variable distributions. Continuous variables were analyzed by Student's *t* test or the Mann-Whitney U test as appropriate. The receiver-operating characteristic (ROC) curves were generated to evaluate the sensitivity and specificity for the prediction of COVID-19 severity. A two-sided $P < .05$ was considered statistically significant. All statistical analyses were performed using SPSS version 19.0 software package (Chicago, IL).

3 | RESULTS

3.1 | Demographics and laboratory characteristics of SARS-COV-2 and influenza

Twenty-seven patients infected by SARS-COV-2 were retrospectively enrolled in our study. As shown in Table 1, 11 (41%) patients had visited Wuhan, 12 (44%) patients had close contact with COVID-19 patients, and 4 patients (15%) denied any obvious history of exposure. There were two patients (7.4%) with no symptoms of pneumonia and six patients (22%) with severe symptoms. The average age of patients was 48.89 ± 18.47. The most common symptoms were fever (88%), cough (44%), and fatigue (33%). Twenty-six patients infected by SARS-COV-2 have been discharged from the hospital, and the remaining ones were still in the hospital. Meanwhile, 75 patients infected by influenza were retrospectively enrolled in our study. Compared to the SARS-COV-2 group, there were higher levels of WBC and granulocytes in influenza patients. There was no difference in the levels of lymphocytes and other biomarkers between the two groups (Table 1).

TABLE 1 Demographics and laboratory characteristics of patients with SARS-COV2 and with flu

Variables	SARS-COV-2	Influenza A or B	*P*
N	N = 27	N = 75	
Median age, y	48.89 ± 18.47	29.40 ± 13.70	<.01
Male sex, N (%)	11 (41%)	27 (36%)	.631
Exposure			
Close contact with infected patients, N (%)	12 (44%)	NA	
Visit to Wuhan, N (%)	11 (41%)	NA	
None, N (%)	4 (15%)	NA	
Comorbidities			
Hypertension, N (%)	6 (22%)	5 (7%)	<.01
Cardiovascular disease, N (%)	3 (11%)	2 (2.6%)	.034
Diabetes, N (%)	2 (7%)	4 (5.2%)	.653
Symptoms			
Fever, N (%)	24 (88%)	NA	
Fatigue, N (%)	9 (33%)	NA	
Cough, N (%)	12 (44%)	NA	
Headache, N (%)	3 (11%)	NA	
Expectoration, N (%)	2 (7%)	NA	
Muscle soreness, N (%)	4 (15%)	NA	
Hemoptysis, N (%)	1 (4%)	NA	
Diarrhea, N (%)	1 (4%)	NA	
Nausea, N (%)	1 (4%)	NA	
Disease severity			
Hospitalization, N (%)	27 (100%)	15 (20%)	<.01
Clinical outcomes			<.01
Discharge from hospital, N (%)	26 (96%)	14 (100%)	
Death, N (%)	0	0	
Staying in hospital, N (%)	1 (4%)	0	
Clinical laboratory			
WBC, $\times 10^9$/L	5.60 ± 1.81	6.18 ± 2.29	.114
Granulocyte, $\times 10^9$/L	3.75 ± 1.47	4.26 ± 2.14	.024
Lymphocyte, $\times 10^9$/L	1.38 ± 0.56	1.17 ± 0.47	.308
NLR (IQR)	2.58 (1.91-3.82)	3.70 (2.10-6.04)	.034
Monocytes	0.44 ± 0.18	0.69 ± 0.33	.007
RBC, $\times 10^{12}$/L	4.79 ± 0.45	4.58 ± 0.48	.980
Hemoglobin, g/L	146.41 ± 13.07	138.52 ± 15.78	.566
Hematocrit, %	42.86 ± 3.94	41.22 ± 5.68	.433
Platelet, $\times 10^9$/L	206.00 ± 68.77	195.68 ± 59.01	.241

Abbreviations; IQR, interquartile range; NLR, granulocyte/lymphocyte ratio; RBC, red blood cell; WBC, white blood cell.

3.2 | Changes of laboratory biomarkers in the course of mild and severe COVID-19

According to CT findings of previous research, COVID-19 patients can be categorized into four stages: initial stage, progression stage, peak stage, and recovery stage. In general, patients had a CT scan at an interval of 3 to 5 days. The median time was 3 days (range 0-8 day) in the initial stage, 7 days (range 4-12 day) in the progression stage, 12 days (range 8-16 day) in the peak stage, and 16 days (range 11-25 days) in the recovery stage after the onset of initial symptoms. Because of the nonnormal distribution of data,

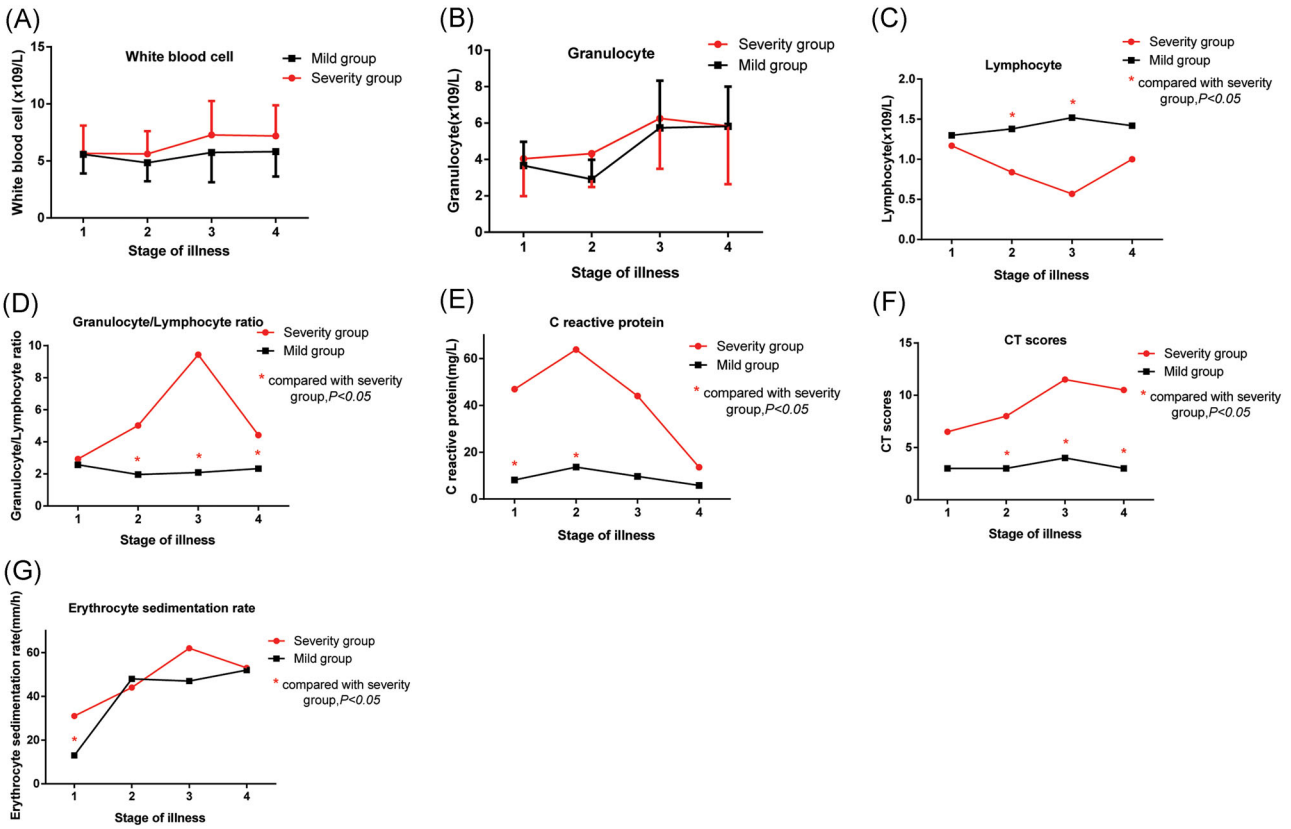

FIGURE 2 The alteration of biomarkers in the disease course

continuous variables such as lymphocyte number, granulocyte/lymphocyte ratio (NLR), CRP, CT scores, and ESR were summarized as medians and interquartile ranges. Compared to the mild group, there were no differences in the levels of WBC and granulocyte numbers among these four stages (Figure 2A, B). Interestingly, these results also showed that compared with the mild group, the lymphocyte number progressively decreased at the progression stage and the peak stage, but increased in the recovery stage (Figure 2C). Moreover, the NLR showed changing trends similar to the lymphocyte numbers, which became significantly higher in the severe group at the recovery stage (Figure 2D). The CRP in the severe group at the progression stage was higher than that in the mild group but was decreased although with no statistically significant differences at the peak and recovery stages (Figure 2E). There were significant increases in the CT scores of the severe group at all four stages (Figure 2F). Also, there were significant differences in the ESR between the two groups at the early stage; however, no significant differences were observed at the three later stages (Figure 2G).

3.3 | Correlation analysis between clinical laboratory biomarkers and CT scores

At present, CT is the main method to evaluate disease severity. Correlation analysis showed that CRP ($R = .62$; $P < .01$), ESR ($R = .55$; $P < .01$), and NLR ($R = .49$; $P < .01$) were all positively correlated with the CT scores. Moreover, our results showed that the lymphocyte number ($R = -.37$; $P < .01$) was negatively associated with the CT scores, and not significantly correlated with CT scores ($R = .14$; $P = .15$) (Figure 3). Our results suggest that a significant increase in CRP is a signal of lung deterioration and progression. Three patients in our study confirmed this point.

3.4 | Receiver operating characteristic analysis of clinical laboratory biomarkers on admission

ROC analysis was performed to evaluate the clinical laboratory biomarkers on first visit for prediction of COVID-19 severity, which demonstrated that areas under the curve (AUC) of CRP and ESR for predicting severe COVID-19 were 0.87 (95% CI, 0.10–1.00) and 0.78 (95% CI, 0.39–1.00), respectively (Table 2, Figure 4). ROC analysis also demonstrated at a cut-off value of 20.42 mg/L, the sensitivity, specificity, positive prediction value (PPV) and negative prediction value (NPV) of CRP were 83%, 91%, 71%, and 95%, respectively. At a cut-off value of 19.50 mm/h, the sensitivity, specificity, PPV, and NPV of ESR were 83%, 81%, 56%, and 94%, respectively. Furthermore, ROC analysis also showed that the AUC of CRP to predict disease severity was higher than CT scores, which demonstrated the excellent predictive power for the severity of COVID-19 patients (Table 2).

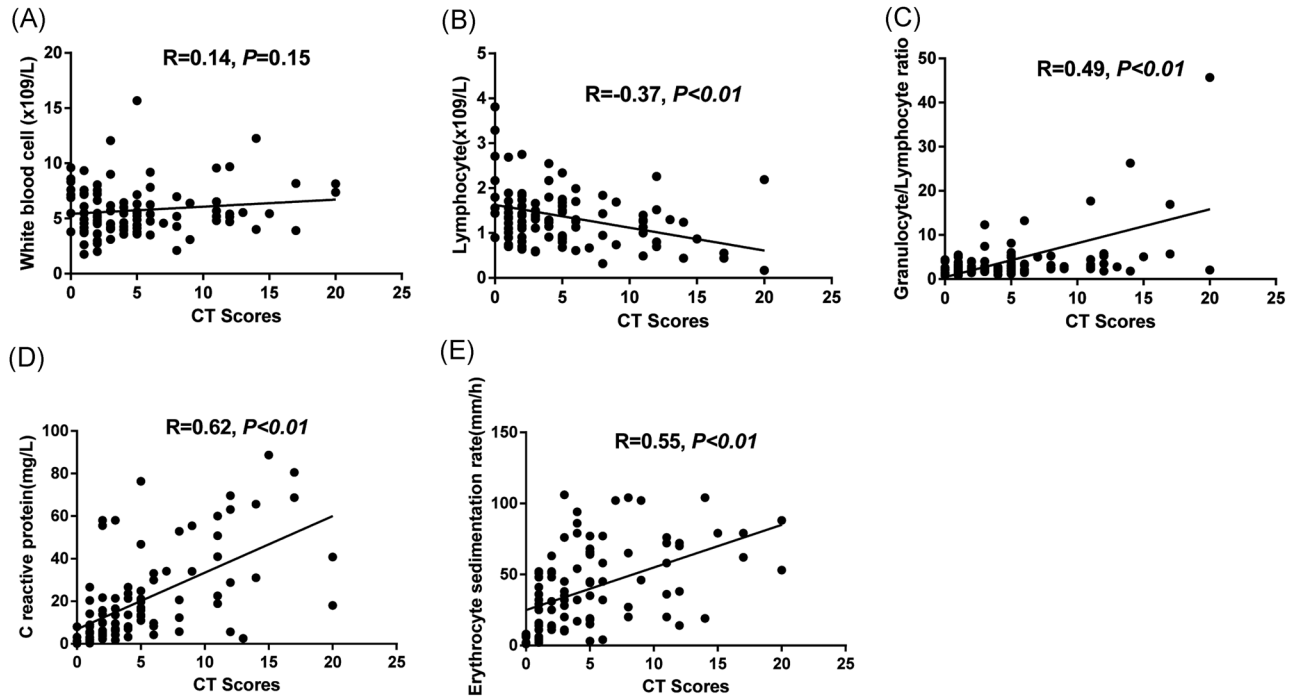

FIGURE 3 Correlation analysis between CT scores and biomarkers. CT, computed tomographic

4 | DISCUSSION

At present, the global outbreak of the SARS-COV-2 epidemic has brought serious burdens to the medical system. It is critical to identify COVID-19 patients who might become severely ill at the early stage, which would greatly facilitate the control of the epidemic and the improvement of the prognosis of patients in light of short and limited medical resources. Reviewing the whole course of COVID-19, we found that CRP increased significantly at the initial stage, further increased at the progression and peak stage l, but recovered dramatically at the recovery stage. Interestingly, we found that CRP increased significantly at the initial stage in severe COVID-19 patients; while still no significant difference in the CT scores were found between the severe and mild groups. Furthermore, ROC further confirmed that CRP was an early biomarker for predicting the severity of COVID-19 with good performance.

In the present cohort of COVID-19 pneumonia, we followed up the patients from the first visit throughout the hospitalization. Their ages ranged from 12 to 84 years. The patients had no history of tumors, severe kidney and liver disease and other serious blood diseases. To match the COVID-19 characteristics, patients with flu were screened under the same conditions and enrolled. Although flu is more common in young people compared with COVID-19 patients, previous research has suggested that both the WBC and granulocyte numbers did not significantly differ with age.[7] The present study showed that patients with flu had higher WBC, granulocyte, and NLR,

TABLE 2 The receiver operating characteristic curves for severity in COVID-19 patients

Variables	Cut-off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Youden index
WBC, $\times 10^9$/L	4.61	0.51 (0.24-0.79)	83%	38%	63%	89%	0.21
N, $\times 10^9$/L	3.15	0.57 (0.30-0.85)	83%	43%	29%	90%	0.26
L, $\times 10^9$/L	1.49	0.40 (0.13-0.67)	33%	67%	22%	78%	0.10
NLR	2.41	0.61 (0.33-0.90)	83%	43%	29%	90%	0.26
CRP, mg/L	20.42	0.87 (0.18-1.00)	83%	91%	71%	95%	0.74
ESR, mm/L	19.50	0.78 (0.39-1.00)	83%	81%	56%	94%	0.64
CT scores	7.00	0.71 (0.44-0.98)	50%	91%	60%	86%	0.41

Note: The 95% confidence interval is shown in parentheses.

Abbreviations: AUC, area under curve; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; L, lymphocyte; N, neutrophils; NLR, granulocyte/lymphocyte ratio; NPV, negative predictive value; PPV, positive predictive value; WBC, white blood cell.

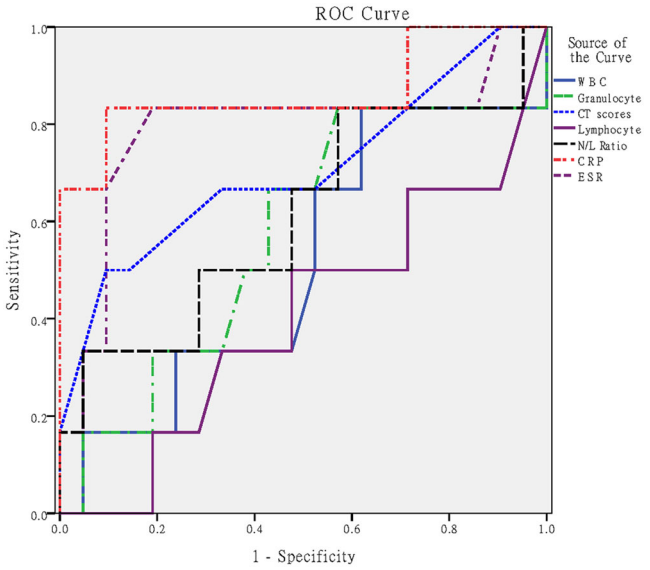

FIGURE 4 The receiver operating characteristic analysis of biomarkers on first visit

which were consistent with previous studies showing that few COVID-19 patients had elevated WBC.[1,8]

During hospitalization, no significant differences in WBC and granulocyte numbers were observed between the mild and the severe COVID-19 groups. Interestingly, we found that lymphocytes progressively decreased and rebound in the recovery stage. Thus, NLR showed similar trends; they progressively increased and decreased at the recovery stage. In the latest diagnosis and treatment guidelines, a progressive decrease of lymphocytes can be regarded as an early warning of critical illness. The pathological results of the latest death cases are consistent with our study. They suggested that a high number of lymphocytes and monocytes infiltrate in the lung, and $CD4^+$ T and $CD8^+$ T cells decrease in the spleen and lymph nodes.[9] Moreover, both the CRP and ESR were significantly elevated in the severe COVID-19 group at the early stage; however, CRP changes were more sensitive to the condition of the disease. CT is the main method to judge the severity of the disease. In the present study, another interesting observation was that CRP and ESR levels were significantly elevated at the early stage in severe COVID-19 patients, while still no significant difference of CT scores could be identified between severe and mild patients. These results suggested that CRP and ESR could be used to early identify patients who might become severely ill and before the CT finding. The latest research about COVID-19 has also suggested that CRP levels differed significantly between the deceased group and the surviving group and may serve as a potential marker for prognosis.[10,11] Furthermore, compared with CT, another important advantage of CRP and ESR as biomarkers for assessing the severity of COVID-19 is the ease with which they can be measured, especially in developing countries.

Most of the previous studies identified and analyzed the data of patients after hospitalization;[3,12,13] however, this usually takes 1 or 2 days from the first visit to admission because of nucleic acid diagnosis. Therefore, to predict the severity of COVID-19 as early as possible, we analyzed the laboratory data of patients' first visit. ROC analysis demonstrated that AUC of CRP for predicting severe COVID-19 was 0.87 (95% CI, 0.10–1.00), with sensitivity and specificity 83% and 91% at a cut-off value of 20.42 mg/L.

The present study is not devoid of limitations. First, only 27 COVID-19 patients were included. Although the small sample size may have resulted in biases, we collected data from multiple stages in the process of disease, which may help to increase the reliability of conclusions. Second, some biomarkers such as renal function and myocardial enzymes were not available in every stage during hospitalization.

In conclusion, we found that patients with flu had higher WBC, granulocyte and granulocyte/lymphocyte ratio, compared with COVID-19 patients. Moreover, CRP and ESR increased significantly at the early stage in severe COVID-19 patients, before identification of any change by the CT scores. Importantly, CRP was associated with disease development and showed good performance in predicting severity in an early stage of COVID-19.

ACKNOWLEDGMENT

This study was funded by the Novel Coronavirus Pneumonia Emergency Project of the Hunan Provincial Science and Technology Department (2020SK3018).

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

CT, YW, FS, and QM were involved in the paper drafting, data acquisition, and analysis; KT, XJ, and YC were responsible for data collection and data analysis; XL involved in the research design and revision of the manuscript.

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How to cite this article: Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol*. 2020;92:856–862. https://doi.org/10.1002/jmv.25871