MAJOR ARTICLE

C-Reactive Protein Level May Predict the Risk of COVID-19 Aggravation

Guyi Wang,[1] Chenfang Wu,[1] Quan Zhang,[2] Fang Wu,[3] Bo Yu,[1] Jianlei Lv,[2] Yiming Li,[4] Tiao Li,[5] Siye Zhang,[1] Chao Wu,[6,7,8] Guobao Wu,[1] and Yanjun Zhong[1]

[1]Critical Care Medicine, The Second Xiangya Hospital, Central South University, Changsha, China, [2]Critical Care Medicine, The First Hospital of Changsha, Changsha, China, [3]Department of Oncology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China, [4]Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China, [5]Department of Respiratory Medicine, The Second Xiangya Hospital, Central-South University, Changsha, Hunan, China, [6]Department of Metabolism & Endocrinology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China, [7]Key Laboratory of Diabetes Immunology (Central South University), Ministry of Education, Changsha, Hunan, China, and [8]National Clinical Research Center for Metabolic Diseases, Changsha, Hunan, China[8]

Background. Clinical findings indicated that a fraction of coronavirus disease 2019 (COVID-19) patients diagnosed as mild early may progress to severe cases. However, it is difficult to distinguish these patients in the early stage. The present study aimed to describe the clinical characteristics of these patients, analyze related factors, and explore predictive markers of the disease aggravation.

Methods. Clinical and laboratory data of nonsevere adult COVID-19 patients in Changsha, China, were collected and analyzed on admission. A logistic regression model was adopted to analyze the association between the disease aggravation and related factors. The receiver operating characteristic curve (ROC) was utilized to analyze the prognostic ability of C-reactive protein (CRP).

Results. About 7.7% (16/209) of nonsevere adult COVID-19 patients progressed to severe cases after admission. Compared with nonsevere patients, the aggravated patients had much higher levels of CRP (median [range], 43.8 [12.3–101.9] mg/L vs 12.1 [0.1–91.4] mg/L; *P* = .000). A regression analysis showed that CRP was significantly associated with aggravation of nonsevere COVID-19 patients, with an area under the curve of 0.844 (95% confidence interval, 0.761–0.926) and an optimal threshold value of 26.9 mg/L.

Conclusions. CRP could be a valuable marker to anticipate the possibility of aggravation of nonsevere adult COVID-19 patients, with an optimal threshold value of 26.9 mg/L.

Keywords. biomarkers; COVID-19; C-reactive protein.

The current outbreak of coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, in December 2019 [1–5]. As of March 6, 2020, at least 80 651 cases and 3070 deaths have been identified across the mainland of China [6]. Outside China, severe acute respiratory coronavirus 2 (SARS-CoV-2) has spread widely around the world, especially in South Korea, Iran, and Italy [7, 8]. The World Health Organization has raised the assessment of the risk of spread and the risk of impact of COVID-19 to very high at a global level on February 28, 2020 [9]. How to reduce the spread of virus and decrease mortality has become a global problem.

Owing to the rapid increase in the number of COVID-19 patients, the hospitals in many regions face huge challenges. Generally, severe patients are treated in the intensive care unit, while mild patients are hospitalized in the usual isolation ward.

However, a small subset of nonsevere patients will develop into severe cases. Therefore, the problem of how to identify this group of patients early and actively monitor and treat them is critical to reducing mortality and improving outcomes of COVID-19 patients. In this study, we found that a few COVID-19 patients diagnosed as nonsevere on admission progressed to severe later in Changsha, China; we analyzed the clinical characteristics of these patients and explored the related factors and predictable markers of aggravation of nonsevere COVID-19 patients as well.

METHODS

Study Design and Participants

This case series was subject to approval by the institutional ethics board of The Second Xiangya Hospital of Central South University (No. 2020001). All laboratory-confirmed adult COVID-19 patients (≥18 years old) admitted to the Public Health Treatment Center of Changsha, China, and diagnosed as nonsevere cases on admission from January 17 to February 20, 2020, were enrolled. Clinical outcomes (severity and mortality) were monitored through February 20, 2020, the final date of follow-up.

Data Collection

Two members of our team carefully collected and reviewed the medical records of patients individually. The detailed information on demographic data, underlying comorbidities, medical

history, symptoms, laboratory parameters, and chest computed tomography (CT) scans on admission were recorded. The date of disease onset was defined as the day when the symptoms were noticed. We used one of the following criteria to determine severe cases of COVID-19: (1) respiratory rate ≥30/min; (2) oxygen saturation ≤93%; (3) PaO2/FiO2 ≤300 mmHg; (4) lung lesions progressed >50% within 24–48 hours; (5) mechanical ventilation was implemented; (6) shock; (7) intensive care unit admission [10].

Statistical Analysis

Because all continuous variables in our study were non–normally distributed, we used median with range and the Mann-Whitney test to depict and analyze them. The χ^2 test or Fisher exact test was utilized to compare differences for categorical variables. Univariate and multivariate analyses were carried out using a logistic regression model to analyze the association between the progression of nonsevere COVID-19 cases and related factors. Demographic variables (gender and age) and variables that were significantly associated ($P < .05$) with disease progression were included in the multivariable analysis. Areas under the curve (AUCs; with 95% confidence intervals) were computed to assess the diagnostic values of C-reactive protein (CRP); AUCs >0.70 were considered clinically relevant [11]. The Kaplan-Meier (KM) curve and the log-rank test were applied to further assess the potential risk factors associated with progression. The Youden index was implemented to set cutoff values. All analyses were performed using IBM SPSS, version 26.

RESULTS

There were 209 adult patients with laboratory-confirmed COVID-19 diagnosed as nonsevere cases on admission by February 20, 2020, in Changsha, and all of them were included in our study; 16 patients (7.7%) progressed to severe cases after admission by February 20, 2020, including 2 patients who eventually developed into critically ill cases.

The clinical characteristics of the 16 aggravated patients are summarized in Table 1. The median age (range) was 54 (35–68) years, and 10 (62.5%) were men. The median duration from the onset of symptoms to disease progression (range) was 9.5 (3–12) days. Of the 16 patients, hypertension (5, 31.3%), cerebrovascular disease (2, 12.5%), and cardiovascular disease (1, 6.3%) were the most common comorbidities. The most common symptoms were fever (14, 87.5%), cough (9, 56.3%), anorexia (9, 56.3%), fatigue (9, 56.3%). All 16 patients showed pulmonary exudative lesions on chest CT scans, of whom 10 (62.5%) showed ground glass opacity in the lungs.

Laboratory findings for the aggravated patients on admission are shown in Table 2. On admission, the median white blood cell count, lymphocyte count, and lymphocyte percentage were all in the normal range. Decreased number of white blood cells,

lymphocytes, and lymphocyte percentage occurred in 25.0%, 37.5%, and 25.0% of patients, respectively. CRP (100.0%) was elevated in all 16 patients, and erythrocyte sedimentation rate (81.3%) increased in most patients on admission. Additionally, median levels of enzymatic indicators of liver, kidney, and myocardial damage were all within the normal range.

Among the 16 aggravated patients, noninvasive ventilation, high-flow oxygen therapy, and invasive mechanical ventilation were adopted in 6.3%, 18.8%, and 6.3% of patients, respectively. One patient (6.3%) received extracorporeal membrane oxygenation as rescue therapy but eventually died.

As shown in Table 1, compared with nonsevere patients, the aggravated patients were significantly older (median age, 54 vs 42 years; $P = .021$). They also showed higher ratios of symptoms than nonsevere cases, including fatigue (56.3% vs 28.0%;

Table 1. Baseline Characteristics of the Aggravated Nonsevere COVID-19 Patients

	Nonsevere to Severe (n = 16)	Nonsevere (n = 193)	P Value[a]
Sex (male/female), No.	10/6	95/98	.307
Age, median (range), y	54 (35–68)	42 (19–84)	.021
Comorbidity			
Hypertension, No. (%)	5 (31.3)	22 (11.4)	.059
Cardiovascular disease, No. (%)	1 (6.3)	4 (2.1)	.331
Diabetes, No. (%)	0 (0.0)	11 (5.7)	.690
Cerebrovascular disease, No. (%)	2 (12.5)	4 (2.0)	.105
No signs and symptoms, No. (%)	0 (0.0)	17 (8.8)	.446
Symptoms			
Fever, No. (%)	14 (87.5)	122 (63.2)	.050
Fatigue, No. (%)	9 (56.3)	54 (28.0)	.037
Cough, No. (%)	9 (56.3)	105 (54.4)	.887
Anorexia, No. (%)	9 (56.3)	60 (31.1)	.040
Chills, No. (%)	5 (31.3)	19 (9.8)	.030
Myalgia, No. (%)	1 (6.3)	16 (8.3)	1.000
Dyspnea, No. (%)	4 (25.0)	9 (4.7)	.007
Expectoration, No. (%)	4 (25.0)	45 (23.3)	1.000
Pharyngalgia, No. (%)	1 (6.3)	29 (15.0)	.554
Diarrhea, No. (%)	1 (6.3)	13 (6.7)	1.000
Nausea, No. (%)	0 (0.0)	5 (2.6)	1.000
Dizziness, No. (%)	2 (12.5)	11 (5.7)	.587
Headache, No. (%)	5 (31.3)	9 (4.7)	.000
Vomiting, No. (%)	1 (6.3)	4 (2.1)	.331
Abdominal pain, No. (%)	0 (0.0)	2 (1.0)	1.000
Chest CT positive rate, No. (%)	16 (100.0)	183 (94.8)	.746
Chest CT with ground glass change, No. (%)	10 (62.5)	81 (42.0)	.111

Abbreviation: CT, computed tomography.

[a]P values indicate differences between nonsevere COVID-19 patients and COVID-19 patients who progressed from nonsevere to severe. $P < .05$ was considered statistically significant. Continuous variables were described as median with range and analyzed by Mann-Whitney test. Categorical variables were described as percentages and analyzed by the χ^2 test or Fisher exact test.

Table 2. Laboratory Findings of Aggravated and Nonsevere COVID-19 Patients

	Normal Range	Nonsevere to Severe (n = 16)	Nonsevere (n = 193)	P Value[a]
White blood cell count, median (range), ×10⁹/L	4–10	4.8 (2.2–7.2)	4.5 (1.9–13.4)	.683
Lymphocyte count, median (range), ×10⁹/L	0.8–4.0	1.0 (0.4–1.9)	1.2 (0.4–3.7)	.110
Lymphocyte, median (range), %	20–40	23.9 (10.4–31.2)	27.7 (6.8–61.1)	**.021**
Alanine aminotransferase, median (range), U/L	0–42	23.9 (13.7–37.1)	19.0 (2.6–87.7)	.068
Aspartate aminotransferase, median (range), U/L	0–37	29.2 (18.3–49.4)	23.2 (2.0–78.8)	**.010**
Total bilirubin, median (range), μmol/L	3.4–20.5	15.0 (5.3–22.9)	10.9 (4.0–40.2)	.653
C-reactive protein, median (range), mg/L	0–8	43.8 (12.3–101.9)	12.1 (0.1–91.4)	**.000**
Erythrocyte sedimentation rate, median (range), mm/h	0–15	49.0 (.0–106.0)	38.0 (1.0–143.0)	.222
Procalcitonin ≥0.05 nmol/L, No. (%)	≤0.05	6 (37.5)	48 (24.9)	.417
Creatinine, median (range), μmol/L	21.5–104	55.4 (27.2–68.1)	51.5 (20.6–124.1)	.783
Creatine kinase, median (range), U/L	10–190	81.2 (19.3–436.3)	68.5 (11.3–365.3)	.594
Creatine kinase-MB, median (range), U/L	0–24	6.5 (1.1–19.4)	9.5 (0.3–221.7)	**.034**

[a]P values indicate differences between nonsevere COVID-19 patients and COVID-19 patients who progressed from nonsevere to severe. $P < .05$ was considered statistically significant. Continuous variables were described as median with range and analyzed by Mann-Whitney test. Categorical variables were described as percentages and analyzed by the χ^2 test.

$P = 0.037$), chills (31.3% vs 9.8%; $P = .030$), anorexia (56.3% vs 31.1%; $P = .040$), dyspnea (25.0% vs 4.7%; $P = .007$), and headache (31.3% vs 4.7%; $P = .000$). Additionally, the aggravated patients had a lower lymphocyte proportion (median, 23.9% vs 27.7%; $P = .021$) and higher levels of CRP (median, 43.8 vs 12.1 mg/L; $P = .000$) and aspartate aminotransferase (median, 29.2 vs 23.2 U/L; $P = .010$) (Table 2).

The associations between the progression of nonsevere COVID-19 patients and their clinical characteristics are presented in Table 3. In the univariate analysis, the progression was associated with hypertension (odds ratio [OR], 3.533; 95% confidence interval [CI], 1.123–11.120; $P = .031$), creatine kinase (OR, 1.006; 95% CI, 1.000–1.012; $P = .047$), lymphocyte proportion (OR, 0.932; 95% CI, 0.876–0.991; $P = .025$), aspartate aminotransferase (OR, 1.044; 95% CI, 1.001–1.088; $P = .044$), and CRP (OR, 1.049; 95% CI, 1.028–1.070; $P = .000$). Only CRP was significantly associated with the progression of nonsevere COVID-19 patients (OR, 1.056; 95% CI, 1.025–1.089; $P = .000$) as determined by multivariate analysis, which suggested that for every 1-unit increase in CRP level, the risk of developing severe events increased by about 5%.

Next, the ROC curve analysis indicated moderate accuracy, with an area under the curve (AUC) of 0.844 (95% CI, 0.761–0.926; $P < .001$) for CRP to predict the possibility of aggravation of nonsevere COVID-19 patients (Figure 1A). Defined by the ROC curve, the optimal threshold value was 26.9 mg/L and was associated with a sensitivity of 81.3% and specificity of 79.3%. Furthermore, the KM curve showed that patients with high levels of CRP (≥26.9 mg/L) had significantly elevated risks of developing into severe cases when compared with patients with low levels (24.5% vs 1.9%; log-rank $P < .001$) (Figure 1B).

DISCUSSION

To our knowledge, this is the first article concerning mild COVID-19 patients who develop into severe cases. We presented the clinical characteristics of those aggravated patients, compared their clinical features with those of nonsevere cases, and analyzed the possible factors associated with progression. Moreover, we further demonstrated the prognostic value of CRP in the progression of mild COVID-19 patients.

Table 3. Analysis of Factors Related to the Progression of Nonsevere COVID-19 Patients

	Univariate		Multivariate	
Variables	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Gender	1.719 (0.601–4.917)	.312	0.757 (0.203–2.818)	.678
Age	1.035 (1.000–1.071)	.050	0.998 (0.953–1.046)	.946
Hypertension	3.533 (1.123–11.120)	**.031***	0.357 (0.078–1.639)	.185
Creatine kinase	1.006 (1.000–1.012)	**.047***	1.005 (0.998–1.013)	.182
Lymphocyte %	0.932 (0.876–0.991)	**.025***	1.015 (0.941–1.093)	.705
Aspartate aminotransferase	1.044 (1.001–1.088)	**.044***	0.982 (0.919–1.050)	.598
C-reactive protein	1.049 (1.028–1.070)	**.000***	1.056 (1.025–1.089)	**.000***

Univariate and multivariate analyses were carried out using a logistic regression model.

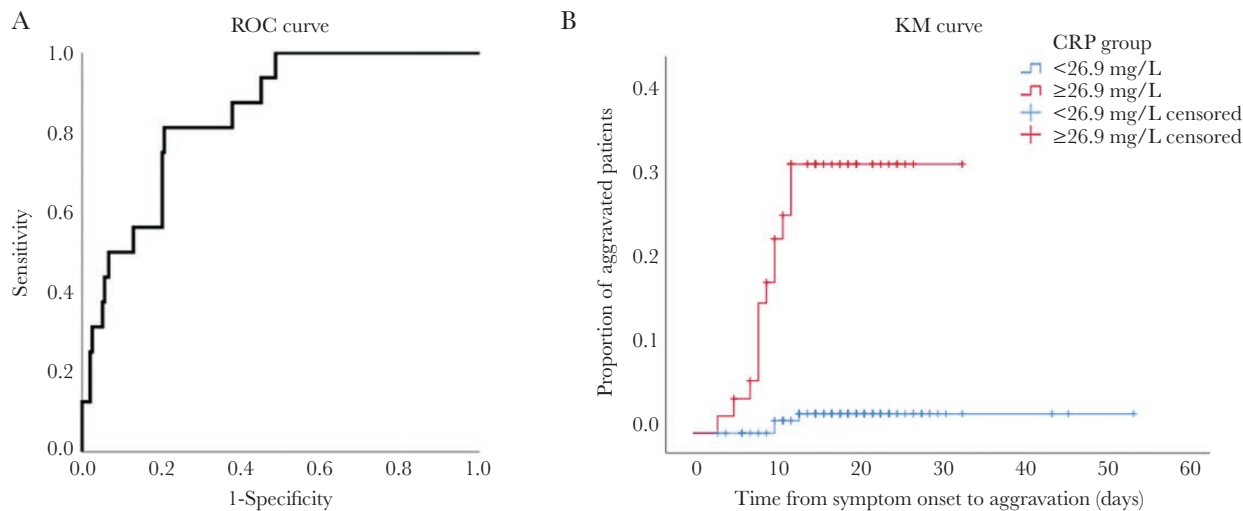Abbreviation: CI, confidence interval.

*Statistically significant.

Figure 1. The relationship between CRP and exacerbations of nonsevere COVID-19 patients and CRP's predictive effect. A, Receiver operating characteristics curve of CRP for the diagnosis of aggravation of nonsevere COVID-19 patients. B, The time-dependent risk of reaching aggravation between nonsevere COVID-19 patients with lower (<26.9 mg/L) and higher (≥26.9 mg/L) levels of CRP. Abbreviations: CRP, C-reactive protein; KM, Kaplan-Meier; ROC, receiver operating characteristics.

In this study, a small fraction of nonsevere patients developed into severe cases in the first 2 weeks after symptom onset. Therefore, health care institutions should also pay close attention to the mild patients, identify progressors early, and provide appropriate treatment to reduce mortality. As reported in a recent article [12], severe COVID-19 patients were older and were more likely to have underlying disease, which is consistent with our study. Nonsevere patients who progressed to severe cases were older and had a higher probability of having underlying diseases. In terms of the symptoms, patients who progressed from nonsevere to severe were more likely to have shortness of breath. Several published articles have also reported a higher rate of shortness of breath in severe COVID-19 patients [5, 12]. Although these exacerbated patients felt dyspnea at an early stage, their blood oxygen saturation did not reach the standard of severe cases, which may be explained by the compensatory effect of faster breathing.

CRP is a type of protein produced by the liver that is elevated in response to inflammation [13–15]. Generally, CRP level is much higher in bacterial infections than in viral infections [16–18]. To our surprise, many COVID-19 patients in this study showed elevated CRP levels, which is in agreement with other studies [12, 19]. Moreover, aggravated cases in this study showed significantly higher levels of CRP than nonsevere patients, which suggested that CRP may be a serum marker of disease aggravation in COVID-19 patients. The logistic regression analysis demonstrated that CRP was indeed related to disease progression, and ROC analysis and a KM curve confirmed that CRP was a valuable predictor of disease progression in nonsevere COVID-19 patients. What's more, the elevated CRP levels occurred before the disease progressed. Therefore,

we believe that COVID-19 patients with high levels of CRP should be adequately monitored and treated even though their respiratory function indicators do not meet the criteria for severe cases.

This study has several limitations. First, the small number of patients limits the conclusions of this study. For example, several indicators may be related to disease progression in univariate regression analysis, while only CRP remains significant in the multivariate analysis. In the future research, these indicators need more attention and analysis. Second, exacerbation of the condition is generally a dynamic process; thus the data at a certain time point may not accurately reflect change in the condition. Third, exacerbation of the remaining mild patients may still occur, because approximately half of the patients were still hospitalized as of February 20, 2020. Thus, the clinical characteristics of COVID-19 patients who may progress from nonsevere to severe still need to be further studied and followed up.

CONCLUSIONS

In summary, we present for the first time the clinical features of COVID-19 patients who progressed from nonsevere to severe cases. Mild patients with an older age and underlying diseases were more likely to exacerbate. Elevated CRP level could be a valuable marker to predict the possibility of aggravation of nonsevere COVID-19 patients, which could help health care workers identify those patients at an early stage for early treatment. However, a large sample size and multicenter studies are needed in order to confirm these results.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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