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Prognostic Value of C-Reactive Protein in Patients With Coronavirus 2019

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Background. An elevated serum C-reactive protein (CRP) level was observed in most patients with coronavirus disease 2019 (COVID-19).

Methods. Data for COVID-19 patients with clinical outcome in a designated hospital in Wuhan, China, were retrospectively collected and analyzed from 30 January 2020 to 20 February 2020. The prognostic value of admission CRP was evaluated in patients with COVID-19.

Results. Of 298 patients enrolled, 84 died and 214 recovered. Most nonsurvivors were male, older, or with chronic diseases. Compared with survivors, nonsurvivors showed significantly elevated white blood cell and neutrophil counts, neutrophil to lymphocyte ratio (NLR), systemic immune inflammation index (defined by platelet count multiplied by NLR), CRP, procalcitonin, and D-dimer and showed decreased red blood cell, lymphocyte, and platelet counts. Age, neutrophil count, platelet count, and CRP were identified as independent predictors of adverse outcome. The area under the receiver operating characteristic (ROC) curve (AUC) of CRP (0.896) was significantly higher than that of age (0.833), neutrophil count (0.820), and platelet count (0.678) in outcome prediction (all $P < .05$). With a cutoff value of 41.4, CRP exhibited sensitivity of 90.5%, specificity of 77.6%, positive predictive value of 61.3%, and negative predictive value of 95.4%. CRP was also an independent discriminator of severe/critical illness on admission with an AUC (0.783) comparable to age (0.828) and neutrophil count (0.729) (both $P > .05$).

Conclusions. In patients with COVID-19, admission CRP correlated with disease severity and tended to be a good predictor of adverse outcome.

Keywords. COVID-2019; SARS-CoV-2; C-reactive protein; prognosis.

Since the first cases of novel coronavirus pneumonia, later named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO), were reported in Wuhan, China, in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected 81 174 patients and caused 3242 deaths in China [1–4]. This newly discovered coronavirus was named severe acute respiratory syndrome coronavirus 2 by the WHO due to its similarity in gene sequence to SARS-CoV [2]. On 30 January 2020, WHO declared the COVID-19 epidemic a public health emergency of international concern [2]. In order to control the SARS-CoV-2 epidemic in a timely manner, multiple active measures have been taken in Wuhan, the worst epidemic area in China, including centralized community quarantine, recruiting designated hospitals, and establishing module hospitals. The SARS-CoV-2 epidemic was preliminarily controlled in Wuhan with the strengthened support from central and local governments. However, confirmed cases worldwide exceeded 200 000 by 19 March 2020. Many other countries, including Italy, Iran, Spain, and the United States, are showing an ongoing outbreak [4] that will inevitably bring a shortage of medical resources. According to Yang et al, the 28-day mortality was 61.5% for a group of critically ill COVID-19 patients [5]. Many patients with mild symptoms have suddenly progressed to severe or critical illness [6]. Hence, identification of a simple and efficient predictor is vital for providing increased attention and treatment to the targeted patients and thus to reduce the mortality from COVID-19.

Similar to SARS, critical patients with COVID-19 presented higher levels of plasma cytokines, suggesting the involvement of an inflammatory storm in the pathogenesis of disease progression [7]. C-reactive protein (CRP), a routinely measured inflammatory marker, was increased in most patients with COVID-19 and was associated with disease severity [7–9]. In a Swedish multicenter study, CRP was suggested to be a simple, early marker for prognosis in intensive care unit (ICU) admissions for sepsis. An admission CRP level >100 mg/L was found to be associated with increased ICU admissions and 30-day mortality [10]. To date, the prognostic value of CRP has not

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been tested in patients with COVID-19. In this retrospective study, we aimed to evaluate the potential of CRP in outcome prediction of patients with COVID-19.

METHODS

Study Design and Participants

This retrospective, single-center study was conducted at Eastern Campus of Renmin Hospital of Wuhan University from 30 January 2020 to 20 February 2020. Eastern Campus was requisitioned as a designated hospital for COVID-19 on 25 January 2020 and began admitting patients on 30 January 2020 after being remodeled. All adult patients who had a clinical outcome (died or recovered) through 20 February 2020 were enrolled. Patients without CRP detection on admission were excluded. The confirmation of patients with COVID-19 was according to guidance issued by National Health Commission of the People's Republic of China (NHC) [11]. This study was approved by the Renmin Hospital of Wuhan University Ethics Committee. Written consent was not required because of the retrospective nature of this study.

Data Collection

Information for each patient was obtained mainly by screening electronic health records and the laboratory information management system provided by DHC Software Co., Ltd (Beijing, China). Nursing records were also reviewed if necessary. Epidemiological information including gender, age, chronic diseases, and history of smoking and drinking was reviewed and assessed, as well as days from illness onset to hospitalization and disease severity on admission. Results of some laboratory tests on admission were collected and evaluated, including complete blood cell count, neutrophil to lymphocyte ratio (NLR), systemic inflammatory index (SII, defined by platelet count multiplied by NLR), CRP, procalcitonin, and D-dimer. Disease severity (ordinary, severe, or critical) was determined according to the guidance issued by NHC [11]. The primary end point was clinical outcome (death or recovery), and the secondary end point was disease severity on admission.

Statistical Analyses

Categorical variables were presented as number (%) and compared using the χ^2 test. Normal distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Normally or nonnormally distributed continuous parameters were described as mean (standard deviation) or as median (interquartile range) and were compared using the independent *t* test or Mann-Whitney test, respectively. Multivariate logistical regression was conducted to identify independent risk factors of study end points. The accuracy of each independent predictor was determined by each area under the receiver operating characteristic (ROC) curve (AUC). The Hosmer and Lemeshow test for goodness-of-fit statistics was used to check model adequacy. The AUCs of independent predictors were compared using the Hanley-McNeil test. All statistical analyses were performed using IBM SPSS Statistics 19.0 and Medcalc software 16.2. A 2-sided test of $P < 0.05$ was considered statistically significant.

RESULTS

Clinical Characteristics of Patients With COVID-19

By 20 February 2020, 359 patients had a clinical outcome, among whom, 61 were excluded due to lack of CRP data on admission. Hence, 298 patients were enrolled, including 141 cases of ordinary illness and 157 cases of severe or critical illness on admission. A total of 84 patients died and 214 recovered. There were 150 males and 148 females, with median age of 57 (40–69) years. A total of 135 (45.2%) patients had chronic diseases. There were 86 cases of hypertension, 32 cases of cerebrovascular diseases, 45 cases of diabetes, 26 cases of coronary heart disease, 23 cases of chronic pulmonary disease, 16 cases of cirrhosis, and 12 cases of anemia. Most patients who died were males, aged >60 years, or with chronic diseases. Twenty-one (7.0%) patients had a history of smoking and 33 (11.1%) had a history of drinking. The median time from onset of symptoms to hospital admission was 9 (6–12) days. No significant difference existed in history of smoking or drinking and days from illness onset to hospitalization between survivors and nonsurvivors. Nonsurvivors showed significantly higher white blood cell and neutrophil counts, NLR, SII, CRP, procalcitonin, and D-dimer and lower red blood cell, lymphocyte, and platelet counts compared with survivors (Table 1).

Independent Predictors for Adverse Clinical Outcome

The independent predictors were identified from risk factors that related to adverse clinical outcome by logistic regression model. As indicated in Table 2, age, neutrophil count, platelet count, and CRP were found to be independent predictors of adverse outcome. The Hosmer and Lemeshow test showed a good model adequacy ($\chi^2 = 6.64$, $P = .576$). To determine and compare the accuracy of these factors in adverse outcome prediction, ROC curve analysis was performed and the difference in AUCs was tested. The AUCs of age, neutrophil count, platelet count, and CRP were 0.833 (95% confidence interval [CI], .782–.884; $z = 12.77$; $P < .001$), 0.820 (95% CI, .761–.880; $z = 10.52$; $P < .001$), 0.678 (95% CI, .609–.747; $z = 5.06$; $P < .001$), and 0.896 (95% CI, .857–.935; $z = 19.76$; $P < .001$), respectively (Table 3, Figure 1). The AUC of CRP was significantly higher than that of age ($z = 2.05$, $P = .041$), neutrophil count ($z = 2.09$, $P = .028$), and platelet count ($z = 5.65$, $P < .001$) for adverse outcome prediction. With a cutoff value of 41.4, CRP exhibited sensitivity of 90.5%, specificity of 77.6%, positive predictive value (PPV) of 61.3%, and negative predictive value (NPV) of 95.4%.

Table 1. Epidemiological and Laboratory Findings of Patients With Coronavirus 2019

Finding	All Patients (N = 298)	Patients Who Died (n = 84)	Patients Who Recovered (n = 214)	*P* Value
Age, y	57 (40–69)	71 (64–80)	51 (37–63)	.000
Gender				.025
Male	150 (50.3%)	51 (60.7%)	99 (46.3%)	
Female	148 (49.7%)	33 (39.3%)	115 (53.7%)	
Smoking	21 (7.0%)	8 (9.5%)	13 (6.1%)	.295
Drinking	33 (11.1%)	10 (11.9%)	23 (10.7%)	.775
With chronic diseases	135 (45.2%)	61 (72.6%)	74 (34.6%)	.000
Hypertension	86 (28.9%)	49 (58.3%)	37 (17.3%)	.000
Cerebrovascular diseases	32 (10.7%)	17 (20.2%)	15 (7.0%)	.001
Coronary heart disease	26 (8.7%)	13 (15.5%)	13 (6.1%)	.010
Diabetes	45 (15.1%)	18 (21.4%)	27 (12.6%)	.056
Chronic pulmonary disease	23 (7.7%)	13 (15.5%)	10 (4.7%)	.002
Cirrhosis	16 (5.4%)	5 (6.0%)	11 (5.1%)	.782
Chronic kidney disease	5 (1.7%)	2 (2.4%)	3 (1.7%)	.928
Anemia	12 (4.0%)	5 (6.0%)	7 (3.3%)	.464
Days from onset to admission	9 (6–12)	9 (7–14)	8 (6–11)	.187
Disease severity				.000
Ordinary illness	141 (47.3%)	4 (4.8%)	137 (64.0%)	
Severe or critical illness	157 (52.7%)	80 (95.2%)	77 (36.0%)	
Laboratory findings				
White blood cell count, × 10^9/L	5.63 (4.12–7.47)	8.58 (5.26–12.70)	5.19 (3.98–6.48)	.000
Neutrophil count, × 10^9/L	3.87 (2.68–5.78)	6.92 (4.33–10.79)	3.20 (2.53–4.56)	.000
Lymphocyte, × 10^9/L	1.03 (0.78–1.44)	0.83 (0.63–1.09)	1.04 (0.83–1.50)	.000
Red blood cell count, × 10^{12}/L	4.14 (0.64)	3.99 (0.71)	4.20 (0.61)	.013
Hemoglobin, g/L	127.3 (18.0)	125.5 (20.0)	128.0 (17.2)	.280
Platelet count, × 10^9/L	190 (143–244)	154 (111–213)	205 (151–252)	.000
Neutrophil to lymphocyte ratio	3.72 (2.42–7.25)	8.17 (6.15–10.90)	2.96 (2.13–4.61)	.000
Systemic inflammatory index	710 (435–1246)	1223 (743–1847)	563 (390–882)	.000
C-reactive protein, mg/L	25.5 (5.0–80.1)	100.0 (60.7–179.4)	9.65 (5.0–37.9)	.000
D-dimer, mg/L	0.75 (0.37–3.42)	4.59 (0.95–17.14)	0.50 (0.29–1.10)	.000
Procalcitonin, ng/mL	0.057 (0.034–0.137)	0.228 (0.119–0.991)	0.043 (0.027–0.065)	.000

Red blood cell count and hemoglobin were presented as mean (standard deviation) and compared with using the independent *t* test between nonsurvivors and survivors. Other continuous variables were presented as median (interquartile range) and compared with the Mann-Whitney test. The χ^2 test was used to compare categorical variables between 2 groups.

Subgroup analysis in adverse outcome prediction was performed for patients according to differences in disease severity on admission. In this case, age, neutrophil count, platelet count, and CRP were still identified as independent risk factors of adverse outcome in patients with severe or critical illness (Table 3). The Hosmer and Lemeshow test showed a good model adequacy ($\chi^2 = 4.99$, $P = .759$). The AUCs of age, neutrophil count, platelet count, and CRP for adverse outcome prediction were 0.726 (95% CI, .646–.806; $z = 5.53$; $P < .001$), 0.787 (95% CI, .716–.859; $z = 7.84$; $P < .001$), 0.697 (95% CI, .618–.767; $z = 4.76$; $P < .001$), and 0.832 (95% CI, .768–.896; $z = 10.23$; $P < .001$), respectively. The AUC of CRP was comparable to that of neutrophil count ($z = 0.98$, $P = .326$), but significantly higher than those of age ($z = 2.06$, $P = .039$) and platelet count ($z = 2.70$, $P = .007$). With a cutoff value of 56.3, CPR showed sensitivity of 81.3%, specificity of 71.4%, PPV of 74.7%, and NPV of 78.6%. For patients with ordinary illness, CRP was identified as the only independent predictor of adverse outcome (Table 3), with AUC 0.989 (95% CI, .967–1.000; $z = 44.04$; $P < .001$). With a cutoff value of 80.9, CRP showed sensitivity of 100.0%, specificity of 95.6%, PPV of 40.0%, and NPV of 100.0%.

Independent Discriminators of Severe/Critical Illness on Admission

Among 150 male patients, 91 were diagnosed with severe/critical illness, while 59 were diagnosed with ordinary illness at

Table 2. Independent Predictors of Adverse Outcome in Patients With Coronavirus 2019

Predictor	Nonstandard Coefficient	Standard Deviation	Odds Ratio (95% Confidence Interval)	*P* Value
Age	0.072	0.017	1.075 (1.040–1.111)	.000
Neutrophil count	0.533	0.111	1.703 (1.369–2.119)	.000
Platelet count	–0.015	0.004	0.985 (.976–.993)	.000
C-reactive protein	0.020	0.005	1.020 (1.010–1.030)	.000

Table 3. Independent Predictors of Adverse Outcome in Subgroup Analysis According to Disease Severity

Predictor		Nonstandard Coefficient	Standard Deviation	Odds Ratio (95% Confidence Interval)	*P* Value
Severe/critical	Age	0.059	0.019	1.060 (1.022–1.100)	.002
	Neutrophil count	0.557	0.126	1.745 (1.364–2.232)	.000
	C-reactive protein	0.015	0.005	1.016 (1.006–1.025)	.001
	Platelet count	–0.017	0.005	0.983 (.974–.992)	.000
Ordinary	C-reactive protein	0.053	0.019	1.055 (1.015–1.096)	.006

admission. A larger percentage of patients with severe/critical illness were male compared with patients with ordinary illness (58% vs 41.8%, $\chi^2 = 7.72$, $P = .005$). A much lower percentage of chronic diseases was observed in patients with ordinary illness (29.1% vs 59.9%, $\chi^2 = 28.43$, $P < .001$). Compared with patients with ordinary illness, patients with severe/critical illness were older (median, 67 [57–75] years vs 42 [32–57] years; $P < .001$) and the time from illness onset to admission was longer (median, 10 [7–13] days vs 8 [5–10] days; $P < .001$). Elevated white blood cell count (median, 6.63 [4.52–9.27] $\times 10^9$/L vs 5.12 [3.92–6.16] $\times 10^9$/L; $P < .001$), neutrophil count (median, 4.99 [3.18–8.14] $\times 10^9$/L vs 3.10 [2.50–4.21] $\times 10^9$/L; $P < .001$), reduced red blood cell count (median, 4.00 [0.68] $\times 10^{12}$/L vs 4.30 [0.57] $\times 10^{12}$/L; $P < .001$), lymphocyte count (median, 0.89 [0.71–1.17] $\times 10^9$/L vs 1.06 [0.86–1.60] $\times 10^9$/L; $P < .001$), platelet count (median, 177 [134–240] $\times 10^9$/L vs 205 [151–250] $\times 10^9$/L; $P = .043$), and hemoglobin level (median, 124 [19] g/L vs 131 [17] g/L; $P = .001$) were observed in patients with severe or critical illness compared with those with ordinary illness. Patients with severe or critical illness tended to exhibit elevated NLR (median, 6.26 [3.49–9.12] vs 2.58 [1.86–3.70]), SII (median, 1053 [581–1612] vs 488 [358–779]), CRP (median, 60.8 [21.0–110.6] mg/L vs 7.7 [5.0–29.3] mg/L), procalcitonin (median, 0.093 [0.047–0.266] ng/mL vs 0.040 [0.021–0.062] ng/mL), and D-dimer (median, 1.21 [0.52–6.86] mg/L vs 0.40 [0.24–0.90] mg/L; all $P < .001$). As indicated in Table 4, age, neutrophil count, and CRP were verified to be independent discriminators of disease severity on admission by multivariate logistic regression analysis. The Hosmer and Lemeshow test showed a good model adequacy ($\chi^2 = 8.31$, $P = .404$). The AUCs of these discriminators were 0.828 (95% CI, .781–.875; $z = 13.69$; $P < .001$), 0.729 (95% CI, .671–.786; $z = 7.79$; $P < .001$), and 0.783 (95% CI, .731–.835; $z = 10.69$; $P < .001$), respectively. The AUC of CRP was comparable to that of age ($z = 0.145$, $P = .147$) and neutrophil count ($z = 1.54$, $P = .124$; Figure 2). With a cutoff value of 41.3, CRP exhibited sensitivity of 65.0%, specificity of 83.7%, PPV of 81.6%, and NPV of 68.2%.

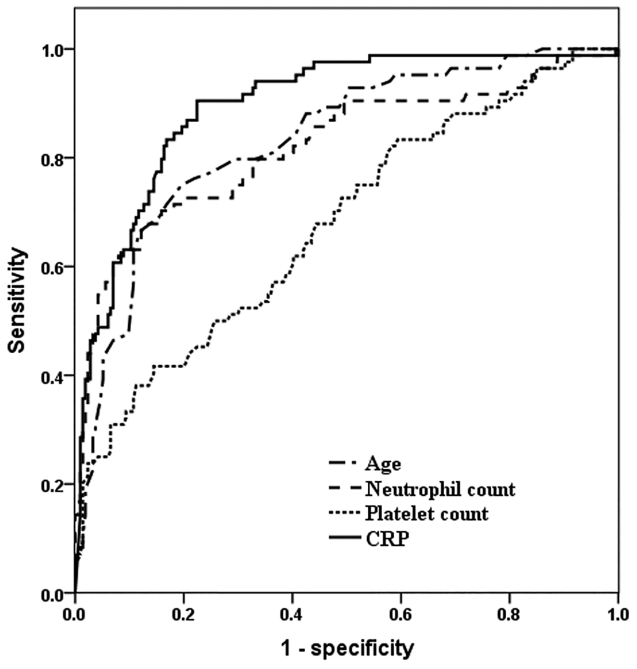

Figure 1. Receiver operating characteristic (ROC) curves of age, neutrophil count, platelet count, and CRP for adverse outcome prediction. The area under the curve (AUC) of age, neutrophil count, platelet count, and CRP for predicting adverse outcome was 0.833, 0.820, 0.678, and 0.896, respectively. The AUC of CRP was significantly higher than that of age ($z = 2.05$, $P = .041$), neutrophil count ($z = 2.09$, $P = .028$), and platelet count ($z = 5.65$, $P < .001$) for adverse outcome prediction. Abbreviation: CRP, C-reactive protein.

DISCUSSION

In this retrospective study, age, neutrophil count, platelet count, and CRP were verified to be independent outcome predictors in patients with COVID-19, and age, neutrophil count, and CRP were identified to be independent discriminators of disease severity on admission. Some important biomarkers of infection or critical illness, including NLR, SII, procalcitonin, and D-dimer, were found to be associated with clinical outcome and disease severity. However, none of them were identified as independent predictors. Our findings in this study suggest that CRP performed better than the other 3 parameters in predicting adverse outcome in patients with COVID-19. In addition, the admission serum CRP level was identified as a moderate discriminator of disease severity. To our knowledge, we are the first to report on the prognostic value of CRP in patients with COVID-19.

The pathological mechanism of COVID-19 is not fully known. In this study, the median age of nonsurvivors was 71 (64–80) years, significantly higher than 51 (37–63) years in survivors. Further, age was an independent predictor of adverse outcome and discriminator of severe/critical illness,

Table 4. Independent Discriminators of Disease Severity on Admission

Discriminator	Nonstandard Coefficient	Standard Deviation	Odds Ratio (95% Confidence Interval)	*P* Value
Age	0.045	0.011	1.047 (1.024–1.070)	.000
Neutrophil count	0.252	0.072	1.286 (1.117–1.481)	.000
C-reactive protein	0.009	0.004	1.009 (1.002–1.017)	.010

which suggested that older people are more vulnerable to SARS-CoV-2 and more likely to develop severe/critical disease [5, 6, 8]. Elevated neutrophil count was observed in patients with severe illness compared with those with nonsevere illness [7]. In this study, admission neutrophil count was a moderate predictor of clinical outcome and disease severity. These results imply that factors that contribute to raised neutrophil count, such as secondary infection, excessive inflammatory stress, or glucocorticoids use, might exacerbate disease progression in patients with COVID-19. Reduction in peripheral lymphocyte count was commonly observed in patients with COVID-19, which was considered a possible critical factor associated with disease severity and mortality [12, 13]. Reduced CD4 and CD8 T-cell counts accompanied by their overactivation might contribute to impaired immunity and disease progression in patients with COVID-19 [12]. In this study, significant discrepancy was observed in lymphocyte count between patients with different outcome or disease severity. NLR, an inflammatory index defined by neutrophil count divided by lymphocyte count, was found to be associated with sepsis and multiple-organ damage [14]. Recently, a prospective study suggested NLR an early predictor of COVID-19 progression to severe illness; however, the power of NLR in outcome prediction was not determined due to no follow-up of the final outcome [15]. In this retrospective study, raised NLR was found in nonsurvivors compared with survivors and was associated with disease severity on admission. However, results of multivariate logistical regression revealed that neither lymphocyte count nor NLR was an independent predictor of adverse outcome or discriminator of severe/critical illness.

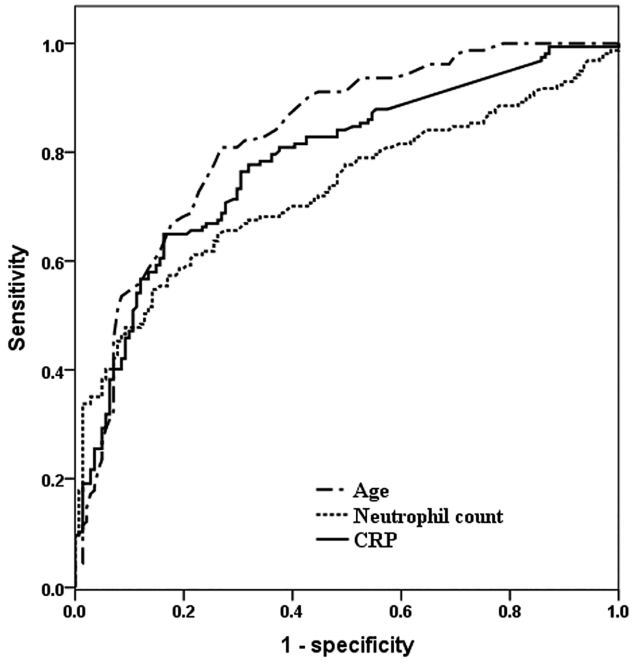

Figure 2. Receiver operating characteristic curves of age, neutrophil count, and CRP for discriminating disease severity on admission. The area under the curve (AUC) of age, neutrophil count, and CRP was 0.828, 0.729, and 0.783, respectively. The AUC of CRP was comparable to that of age ($z = 0.145$, $P = .147$) and neutrophil count ($z = 1.54$, $P = .124$). Abbreviation: CRP, C-reactive protein.

As one of the most distinctive acute phase reactants, CRP can increase rapidly after the onset of inflammation, cell damage, or tissue injury. Pulmonary diseases with inflammatory features usually raise serum CRP level in response to inflammatory cytokines such as interleukin-6 (IL-6), IL-1, or tumor necrosis factor-alpha (TNF-α) [16, 17]. Hence, markedly elevated serum CRP level in nonsurvivors or patients with severe/critical illness in this study indicated excessive inflammatory response, which was consistent with raised serum proinflammatory cytokines observed in COVID-19 patients [18, 19]. The role of CRP in disease pathology may involve host defense and inflammation. In response to inflammatory onset, CRP binds to pathogens and promotes their elimination by phagocytic cells, functioning as the first line of innate host defense. In addition, CRP can exhibit anti-inflammatory effects by inhibiting neutrophil chemotaxis [20]. However, by upregulating expression of adhesion molecules and proinflammatory IL-1, IL-6, IL-8, and TNF-α, CRP can also exert proinflammatory effects [21]. Controversial results of serum CRP levels were observed in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) [22, 23]. The association between high serum CRP level and a favorable outcome was found in adult patients with ALI/ARDS [22]. In elderly patients with ALI, however, a high serum CRP level was correlated with higher mortality [23], which is consistent with our findings in patients with COVID-19. Direct attacks from SARS-CoV-2 and organ damage caused by excessive inflammatory response might be responsible for the pathogenesis of disease progression [20]. Therefore, markedly elevated serum CRP levels in patients with COVID-19 might be an indication of excessive inflammatory stress and contribute to severe/critical illness or even death. Nevertheless, the exact function of CRP in patients with COVID-19 remains unclear. Future research should be focused on involvements of CRP in the pathogenesis of COVID-19.

There are some limitations to our study. First, aging, chronic diseases, and secondary infection in some cases might exert effects on the increased serum CRP level in addition to the SARS-CoV-2 infection itself. Such superimposed effects, however, would better reflect the features of patients with severe COVID-19. Second, some patients with critical illness were not admitted to an ICU due to a shortage of resources, which undoubtedly had a negative impact on the outcomes of those patients. Third, patients were not recruited consecutively due to exclusion of some cases without serum CRP detection on admission, which might bring about selective bias. Fourth, serum CRP level correlates with the degree of inflammatory response [24]; therefore, changes in CRP over time might provide more information about disease prognosis. However, no continuous CRP values over time were included in this study since it was designed to explore the potential of admission CRP in outcome prediction.

In conclusion, our results suggest that admission serum CRP level performed well in discriminating disease severity and predicting adverse outcome in patients with COVID-19. Patients with markedly elevated admission CRP should be provided more attention and stronger treatment. The findings from this single-center study need to be validated by multicenter research with larger samples.

Notes

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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