

Increased pretreatment C-reactive protein-to-albumin ratio predicts severe coronavirus disease 2019

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Abstract

Objective The aim of this study was to identify early warning signs for severe coronavirus disease 2019 (COVID-19). **Methods** We retrospectively analysed the clinical data of 90 patients with COVID-19 from Guanggu District of Hubei Women and Children Medical and Healthcare Center, comprising 60 mild cases and 30 severe cases. The demographic data, underlying diseases, clinical manifestations and laboratory blood test results were compared between the two groups. The cutoff values were determined by receiver operating characteristic curve analysis. Logistic regression analysis was performed to identify the independent risk factors for severe COVID-19. **Results** The patients with mild and severe COVID-19 had significant differences in terms of cancer incidence, age, pretreatment neutrophil-to-lymphocyte ratio (NLR), and pretreatment C-reactive protein-to-albumin ratio (CAR) ($P = 0.000$; $P = 0.008$; $P = 0.000$; $P = 0.000$). The severity of COVID-19 was positively correlated with comorbid cancer, age, NLR, and CAR ($P < 0.005$). Multivariate logistic regression analysis showed that age, the NLR and the CAR were independent risk factors for severe COVID-19 (OR=1.086, $P = 0.008$; OR=1.512, $P = 0.007$; OR=17.652, $P = 0.001$). **Conclusion** An increased CAR can serve as an early warning sign of severe COVID-19 in conjunction with the NLR and age.

1. Introduction

Coronavirus disease 2019 (COVID-19) has spread to more than 200 countries, areas and territories worldwide because of its strong infectivity and tendency to cause familial clusters of infections[1-3]. On 27 April 2020, data reported by the World Health Organization (WHO) showed that there were more than 2.8 million confirmed cases of COVID-19, and approximately 0.2 million individuals had died; 379.4 per million people had contracted COVID-19 worldwide, and the mortality rate had reached 68,000 per million infected persons[4]. COVID-19 is divided into 4 types, namely, mild, moderate, severe and critical, and patients with severe and critical cases have a higher mortality rate and longer hospitalization times. The prompt identification of early warning signs of severe COVID-19 and the timely initiation of interventions may help reduce mortality, improve the cure rate and shorten the hospital stay duration.

It is widely believed that inflammatory cytokine storms may be related to the progression of COVID-19 [5-7]. C-reactive protein (CRP), which is a typical marker of inflammation, is a reliable biomarker used in clinical practice. Furthermore, CRP is an acute reactant protein that is increasingly expressed in the presence of infection, trauma, tissue necrosis, cancer, and several types of inflammatory diseases [8, 9]. Albumin (ALB) reflects the nutritional state and response to inflammation, which is associated with the treatment outcome of cancers and inflammatory diseases. Previous studies also found that the ALB level was significantly lower in patients with severe COVID-19 [10]. The CRP/ALB ratio (CAR) is an independent prognostic factor in patients with cancers [11-13]. Hence, we hypothesized that an elevated CAR is associated with severe COVID-19 and may be an early warning sign of disease progression.

2. Methods

2.1 Study design and patients

A retrospective study of 90 patients in our ward in Guanggu District of Hubei Women and Children Medical and Healthcare Center *who were* diagnosed with COVID-19 between February 10, 2020, and March 20, 2020, was designed and performed. The diagnosis and classification of COVID-19 was performed according to the new coronavirus pneumonia diagnosis and treatment plan (trial version 5) developed by the National Health Committee of the People's Republic of China [14]. COVID-19 is divided into mild, moderate, severe and critical types. In our ward, COVID-19 cases mainly consist of moderate and severe cases, while there are relatively few mild and critical cases. Therefore, in our research, we defined mild and moderate cases as belonging to the mild group and severe and critical cases as belonging to the severe group. This study was approved by the Ethics Committee of Guanggu District of Hubei Women and Children Medical and Healthcare Center and was performed in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent before enrolment in this study. A total of 118 COVID-19 patients were initially enrolled in this retrospective study; 10 patients were excluded because their absolute lymphocyte count before treatment was not available, and 18 patients were excluded because of a lack of pretreatment coagulation marker measurement. Pretreatment data were extracted from the medical records of patients from the hospital computerized databases or from the clinical charts by means of a questionnaire. The following information was included: demographics (age and sex); past medical history and clinical manifestations; pretreatment laboratory blood test results (such as white blood cell count, neutrophil count, lymphocyte count, coagulation marker levels, and renal and liver function tests); vital signs; chest CT; and nucleic acid detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

2.2 Statistical analysis

The NLR was calculated as the neutrophil count divided by the lymphocyte count, and the CAR was calculated as the CRP level divided by the ALB level. Normally distributed data are expressed as the means \pm standard deviations, and nonnormally distributed data are expressed as the medians (interquartile ranges). Differences between two groups were evaluated using t-tests, chi-square tests or Mann-Whitney U tests. Correlations between risk factors and severe COVID-19 were evaluated by Spearman correlation analysis. Logistic regression was used to select the independent risk factors. The cutoff values for the NLR and CAR were determined by receiver operating characteristic (ROC) curve analysis. All data were statistically analysed using a commercially available statistical software package (SPSS 24.0; IBM Corp., Armonk, NY, USA). All tests were bilateral, and a P -value < 0.05 was considered statistically significant. Power analysis was done using G*Power 3.1[15]. A power analysis ($1-\beta = 0.9$, $\alpha = 0.05$) determined that at least 56 patients (28 in each group) had to be enrolled in our study, and finally 90 in total were enrolled.

3. Results

3.1 Clinical characteristics

A total of 90 COVID-19 patients were enrolled in this retrospective study; 60 were diagnosed as having mild or moderate COVID-19 (mild group), and 30 were diagnosed as having severe or critical COVID-19 (severe group) on admission. As shown in Table 1, the median ages of the two groups were significantly different: the median age of the mild group was 63 years old, and the median age of the severe group was 75.5 years old ($P=0.000$). No significant differences were found between the two groups in terms of gender, hypertension, diabetes or coronary heart disease ($P=0.370$; $P=0.511$; $P=0.715$; $P=0.062$). There were more patients with cancer in the severe group than in the mild group ($P=0.008$). The NLR and CAR in the severe group were significantly higher than those in the mild group (Table 2).

The common chest computed tomography features of both groups included ground-glass opacities (88/90, 97.8%) and linear opacities (74/90, 82.2%). Consolidation, lymph node enlargement and pleural effusion were found in some patients with severe COVID-19 (19/30, 63.3%). In addition, the number of involved lung lobes in the severe group was higher than that in the mild group ($P= 0.019$).

3.2 Correlation analysis of risk factors with severe COVID-19

Using Spearman correlation analysis, we found that age, cancer, the NLR and the CAR were significantly correlated with severe COVID-19 ($r = 0.459$, $P = 0.000$; $r = 0.323$, $P = 0.002$; $r = 0.573$, $P = 0.000$; $r = 0.506$, $P = 0.000$). The data also indicated that these factors were positively associated with severe COVID-19 (Table 3).

3.3 ROC curve analysis of independent risk factors

ROC curve analysis established 4.939 as the cutoff point for the NLR for the prediction of severe COVID-19, with an area under the curve (AUC) of 0.851 (CI=0.762-0.940, $P= 0.000$). The results of ROC curve analysis also showed that the AUC of the CAR was 0.812 (CI=0.709-0.914, $P=0.000$), and the optimal cutoff value that maximized the sensitivity and specificity was 0.296 (76.7% sensitivity and 80.4% specificity) (Figure 1).

3.4 Regression analysis of risk factors for severe COVID-19

As shown in Table 4, multivariate logistic regression analysis showed that age, the NLR and the CAR were independent risk factors for severe COVID-19 (OR=1.086, $P=0.008$; OR=1.512, $P=0.007$; OR=17.652, $P=0.001$). To address whether cancer was a confounding factor in our study, we excluded the 7 cancer patients and performed the regression analysis again. The repeated analysis also showed that the NLR and the CAR were independent risk factors for severe COVID-19 (OR=1.557, $P=0.029$; OR=1.494, $P=0.040$).

4. Discussion

COVID-19 is prevalent in many countries worldwide, and the number of deaths is increasing daily. The identification of early warning signs for severe COVID-19 and the timely initiation of interventions are urgent issues [4, 16].

The results of the present study showed that there were significant differences in age, cancer incidence, the NLR, and the CAR between the patients with severe and mild COVID-19, and there were positive correlations between severe COVID-19 and age, cancer, the NLR, and the CAR. In the multivariate analysis logistic regression model, a high CAR ($CAR > 0.296$) was a significant independent predictor for severe COVID-19 ($OR = 17.652$, $P = 0.001$), as well as a high NLR and advanced age, which was in accordance with previous studies [17-19]. An ambispective cohort study by Li et al. indicated that older age, underlying hypertension and high cytokine levels were significantly associated with severe COVID-19 on admission [17]. Compared with patients with non-severe cases, those with severe cases had significantly higher levels of inflammation-related markers, such as CRP, and higher erythrocyte sedimentation rates. Lower ALB levels were observed in critically ill patients than in severely ill patients. Huang et al. reported that ICU patients had higher plasma levels of inflammatory cytokines such as IL-2, IL-7, IL-10, GCSF, IP10, MCP1, MIP1A and TNF- α than non-ICU patients, which reflected the obvious inflammatory reaction in patients with severe and critical cases of COVID-19 and was consistent with our results [20].

CRP, an acute-phase protein, is a sensitive systemic marker of inflammation and tissue damage [8]. It has been speculated that CRP may have significant proinflammatory effects by binding to ligands exposed on cells or other autologous structures as a result of infection, inflammation, and other pathologies and then triggering complement activation, eventually exacerbating tissue damage and leading to more severe disease. Previous studies reported that the CRP level was an independent factor that was predictive of a poor prognosis in patients with cardiovascular disease, non-small-cell lung cancer and gastric cancer [21-23]. A retrospective study by Li et al. recently reported that an increase in the CRP level can be used as an indicator of disease progression in patients with COVID-19 [24]. A recent meta-analysis also showed that concentrations of CRP remained high in patients who died of COVID-19 and that CRP could be a promising biomarker for assessing disease severity [25]. The elevated levels of CRP might be linked to the overproduction of inflammatory cytokines in patients with severe COVID-19. However, CRP levels in COVID-19 patients who may progress from having non-severe cases to having severe cases need to be further studied in large-scale multicentre studies [26].

The ALB concentration is negatively associated with the systemic inflammatory response due to increased catabolism and the downregulation of hepatic synthesis by the cytokine TNF- α [27]. The level of ALB, which is associated with inflammation and nutritional status, was revealed to be significantly related to poor survival in previous studies [28, 29]. Miura et al. concluded that the preoperative ALB level could predict overall survival in patients with non-small-cell lung cancer [28]. A retrospective multicentre study by Gong et al. indicated that a lower ALB level was associated with severe COVID-19 [10]. Patients

with decreased levels of ALB were reported to have a higher risk of mortality due to COVID-19 and should be managed more aggressively [30].

As expected, we observed a strong positive association between the CAR and severe COVID-19. The CAR, which is the ratio of the CRP level to the ALB level, is considered an important marker of the systemic inflammatory response and accurately reflects the balanced relationship between the severity of the inflammatory reaction and the immune state. The CAR is widely used to assess the prognosis of patients with cancers and atherosclerosis. An increased CAR indicates a poor clinical prognosis in patients undergoing percutaneous coronary intervention [31]. Recent studies showed that the CAR was predictive of disease progression and mortality in patients with gastric cancer, pancreatic cancer and non-small-cell lung cancer [13, 22, 32, 33]. The results of the study by Miyamoto et al. showed that the CAR was an independent factor that was predictive of two-week survival; in particular, the CAR is a useful tool for predicting survival times in end-stage patients with or without cancer [34].

To the best of our knowledge, our study is the first to observe a significant positive association between the CAR and the severity of COVID-19. However, there were limitations of the current study. First, our study was an observational study, and further prospective studies are needed to confirm our findings. Second, missing data for some pretreatment variables may have caused bias in the estimations and reduced the representativeness of the sample. Finally, there were statistical limitations of the study due to the small sample size, especially for mild and critical COVID-19. Next, we will conduct a large-scale multicentre study to explore the relationship between the pretreatment CAR and mortality in COVID-19 patients and the prognostic value of the CAR throughout the disease course.

5. Conclusions

In summary, the pretreatment CAR was a simple, inexpensive, and convenient predictor for severe COVID-19 and maybe an early warning sign for severe COVID-19 in conjunction with the NLR and age during our clinical care. Further prospective studies with a large number of participants are necessary to validate the predictive role of the CAR in COVID-19 patients.

Abbreviations

ALB:Albumin; AST: aspartate transaminase; AUC: area under the curve; CAR : C-reactive protein-to-albumin ratio; COVID-19: novel coronavirus-infected pneumonia; CRP: C-reactive protein; Fib: fibrinogen; Hb: hemoglobin; NLR : neutrophil-to-lymphocyte ratio; Plt: platelet; ROC : receiver operating characteristic curve analysis; Scr: serum chlorine; WHO : World Health Organization

Declarations

Availability of data and materials

The datasets used during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the institutional review boards of the two hospitals and was performed in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

H Liao and X Chen developed the idea. X Wang contributed to the literature search and writing the manuscript. D Jiang, H Huang, X Chen, C Zhou, D Jiao, P Fan, B Shi, and Q Cui contributed to data collection. H Huang and Y Xu contributed toward data analysis and revising the paper.

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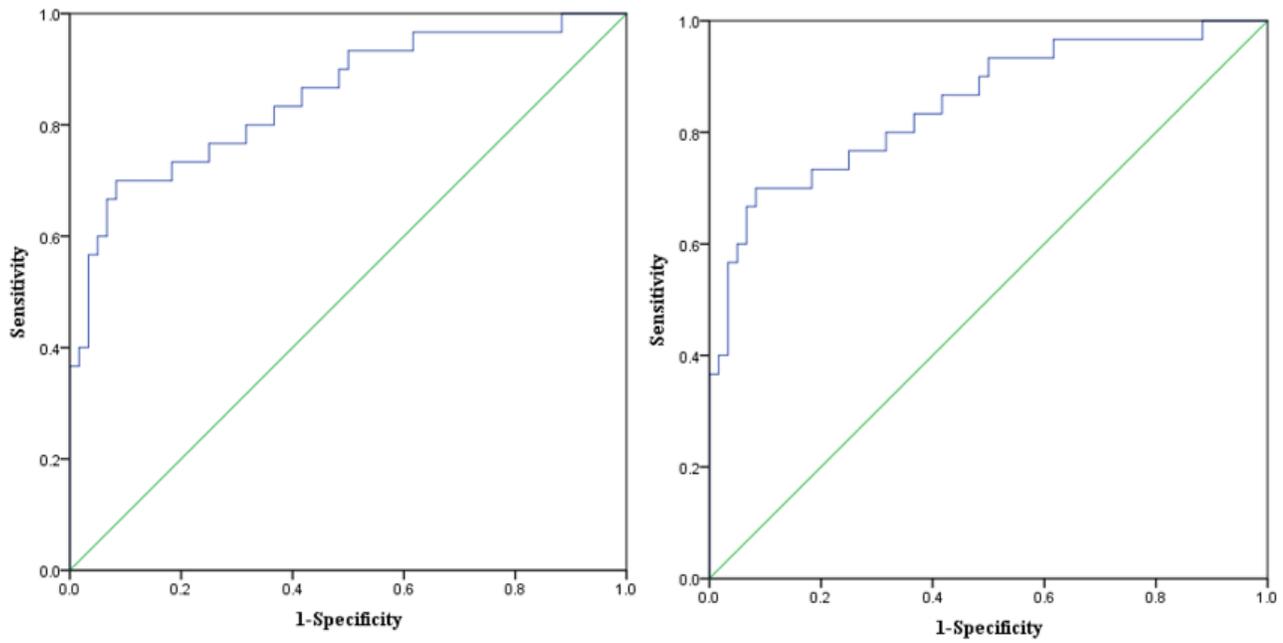
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Figures



Abbreviation: NLR neutrophil-lymphocyte ratio; CAR C-reactive protein-to-albumin ratio.

Figure 1

Receiver operating characteristic curve (ROC) and area under the curve (AUC) for the pretreatment NLR and CAR (AUC=0.851, P=0.000; AUC=0.812, P=0.000) Abbreviation: NLR neutrophil-lymphocyte ratio; CAR C-reactive protein-to-albumin ratio.