An increased pretreatment C-reactive protein-to-albumin ratio predicts severe novel coronavirus-infected pneumonia

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Abstract

Objective

The aim of this study was to identify early warning signs for severe novel coronavirus-infected pneumonia (COVID-19).

Methods

We retrospectively analyzed 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 was determined by receiver operating characteristic curve analysis. Logistic regression analysis was performed to identify the independent risk factor that predicted the severe COVID-19.

Results

The patients with mild and severe COVID-19 showed significant differences in terms of cancer incidence, age, pretreatment neutrophil-to-lymphocyte ratio (NLR), and pretreatment C-reactive protein-to-albumin ratio (CAR) (P < 0.05). The severity of COVID-19 was correlated positively with the comorbidity of cancer, age, NLR, and CAR (P < 0.05). Multivariate logistic regression analysis showed that age, NLR and 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, respectively).

Conclusion

An increased CAR can serve as an early warning sign of severe COVID-19 in conjunction with the NLR and age.

1. Introduction

Novel coronavirus-infected pneumonia (COVID-19) has been prevalent in more than 200 countries, areas or territories of the world because of its strong infectivity and familial aggregation[1–3]. On 27 April 2020, data reported by the World Health Organization (WHO) showed that 2883603 cases were confirmed novel coronavirus infections and 198842 individuals died in total[4]. COVID-19 was divided into 4 types: mild, moderate, severe and critical, among which severe and critical cases have higher mortality and longer hospitalization time. Early identification of early warning signs of severe COVID-19 and timely intervention may help to reduce mortality, improve the cure rate and shorten the hospital stay.
It is widely believed that the inflammatory cytokine storm maybe related to the progression of COVID-19[5, 6]. C-reactive protein (CRP) as a typical marker of inflammation is a reliable biomarker for clinical practice. Furthermore, CRP is an acute reactant protein that is increasingly expression in the presence of infection, trauma, tissue necrosis, cancer, and several types of inflammatory diseases [7, 8]. Albumin (ALB) reflects nutritional state and response to inflammation, which is associated with the treatment outcome of cancers and inflammatory diseases. Previous studies also founded that ALB was significantly lower in severe COVID-19[9]. CRP/ALB ratio (CAR) is an independent prognostic factor in patients with cancers [10–12]. Hence, we hypothesized that elevated CAR is associated with severe COVID-19.

2. Materials And Methods

2.1 Study design and patients

A retrospective study of 90 patients in our ward diagnosed with COVID-19 between February 10, 2020 and March 20, 2020 was designed and performed. 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[13]. COVID-19 is divided into mild, moderate, severe and critical types. In our ward, COVID-19 cases mainly consist of moderate and severe type cases, while mild type and critical type cases are relatively few. Therefore, in our research, we defined mild and moderate as the mild group and severe and critical as 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 Declaration of Helsinki. All patients provided written informed consent before enrollment 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 for lack of pretreatment coagulation markers. Pretreatment data were extracted from the medical records of patients from hospital computerized databases, or from clinical charts by means of a questionnaire. The following information was included: demographics (age and sex); past-history and clinical manifestations; pretreatment laboratory blood test results (such as white blood cell count, neutrophil count, lymphocyte count, coagulation markers, renal and liver function tests); vital signs; chest CT; and nucleic acid detection of novel coronavirus.

2.2 Statistical analysis

The NLR was calculated as the neutrophil count divided by the lymphocyte count, the CAR calculated as the CRP divided by the ALB. Normally distributed data were expressed as the mean ± standard deviation, and nonnormally distributed data as the median (interquartile range). Differences between two groups were evaluated using t-tests, chi-square test or Mann-Whitney U tests. Correlations analysis of risk factors with severe COVID-19 was evaluated by Spearman correlation analysis. Logistic regression was used to select independent risk factors. The selection of cutoff values of NLR and CAR were determined by
receiver operating characteristic (ROC) curve analysis. All data were statistically analyzed 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.

3. Results

3.1 Clinical characteristics

A total of 90 COVID-19 patients were enrolled in this retrospective study, 60 were diagnosed as mild or moderate (mild group) and 30 as severe or critical (severe group) on admission. As shown in Table 1, the median age of the two groups was statistically different, the common group was 63 years old and the severe group was 75.5 years old ($P = 0.000$), while no significant differences were found in gender, clinical symptoms, hypertension, diabetes or coronary heart disease between the two groups ($P > 0.05$). The patients with cancer in the severe group were more than those 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).
Table 1
Baseline characteristics of patients with 2019 novel coronavirus pneumonia

| Variables               | Mild group | Severe group | $\chi^2/Z$ | $P$  |
|-------------------------|------------|--------------|------------|------|
| Age, years              | n = 60     | n = 30       | -4.328     | 0.000|
|                         | 63.000(46.000–71.000) | 75.500(69.000-84.500) |           |      |
| Gender                  |            |              |            |      |
| Male                    | 30         | 18           | 0.804      | 0.370|
| Female                  | 30         | 12           |           |      |
| Comorbidities           |            |              |            |      |
| Hypertension            | 16         | 10           | 0.433      | 0.511|
| Diabetes                | 12         | 7            | 0.133      | 0.715|
| Coronary heart disease  | 3          | 6            | 3.472      | 0.062|
| Cancer                  | 1          | 6            | 6.990      | 0.008|
| Clinical symptoms       | 27         | 16           | 0.557      | 0.456|
| Fever                   | 25         | 14           | 0.204      | 0.652|
| Cough                   | 10         | 10           | 3.214      | 0.073|
| Chest tightness         | 11         | 7            | 0.313      | 0.576|
Table 2
Comparison of blood test results of patients with 2019 novel coronavirus pneumonia

| Blood tests | Mild group | Severe group | t/Z   | P    |
|-------------|------------|--------------|-------|------|
|             | n = 60     | n = 30       |       |      |
| NLR         | 2.322(1.812–3.565) | 7.078(3.499–14.178) | -5.409 | 0.000 |
| Hb, g/L     | 129.000(120.250–137.750) | 124.500(101.250–134.250) | -1.439 | 0.150 |
| Plt, ×10⁹/L | 214.500(150.750–243.750) | 191.500(116.000–224.750) | 1.120  | 0.266 |
| AST, U/L    | 17.800(12.850–32.725)  | 19.500(14.700–41.700)  | -0.693 | 0.490 |
| Scr, µmol/L | 63.700(57.100–78.850)  | 64.150(55.625–97.175)  | -0.417 | 0.677 |
| CAR         | 0.047(0.022–0.191)    | 2.080(0.281–3.481)    | -4.465 | 0.000 |
| Fib, g/L    | 3.420(2.800–4.180)    | 4.305(2.913–5.570)    | -1.907 | 0.067 |
| D-Dimer, mg/L| 0.290(0.208–0.568)  | 1.515(0.925–3.588)  | -1.694 | 0.103 |

Abbreviations: NLR neutrophil-lymphocyte ratio; Hb hemoglobin; Plt platelet; AST aspartate transaminase; Scr serum chlorine; CAR C-reactive protein-to-albumin ratio; Fib fibrinogen.

3.2 Correlation analysis of risk factors with severe COVID-19

The correlation analysis of risk factors showed that age, cancer, NLR and CAR were significantly positively correlated with severe COVID-19 (Table 3).

Table 3
Correlation analysis of risk factors with severe COVID-19

| Statistics | Age | Cancer | NLR | CAR |
|------------|-----|--------|-----|-----|
| r          | 0.459 | 0.323  | 0.573 | 0.506 |
| P-value    | 0.000 | 0.002  | 0.000 | 0.000 |

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

3.3 ROC curve analysis of independent risk factors

ROC curve analysis established 4.939 as the cutoff point of NLR for 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 CAR is 0.812 (CI = 0.709–0.914, \( P = 0.000 \)), the optimal boundary value is 0.296 corresponded to the maximum joint sensitivity and specificity (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 concluded that age, NLR and CAR were independent risk factors for severe COVID-19.

| Factor | \( B \) | \( SE \) | \( Wals \) | \( P \) | \( OR \) | \( OR (95\% CI) \) |
|--------|--------|--------|----------|-------|-------|-----------------|
| Age    | 0.082  | 0.031  | 7.131    | 0.008 | 1.086 | 1.022 – 1.153   |
| Cancer | -2.12  | 1.997  | 1.134    | 0.287 | 0.119 | 0.002 – 5.974   |
| NLR    | 0.413  | 0.154  | 7.166    | 0.007 | 1.512 | 1.117 – 2.046   |
| CAR    | 2.871  | 0.849  | 11.430   | 0.001 | 17.652| 3.342 – 93.245  |

Abbreviations: \( NLR \) neutrophil-lymphocyte ratio; \( CRP \) C-reactive protein; \( CAR \) C-reactive protein-to-albumin ratio.

### 4. Discussion

COVID-19 has been prevalent in many countries in the world, and the number of deaths is rising daily. Identification of early warning signs for severe COVID-19 and timely intervention may become the urgent issues.

The results of the present study showed that there were significant differences in age, cancer incidence, NLR, CRA between the severe COVID-19 patients and mild COVID-19 patients, and there was a positive correlation between age, cancer, NLR, CAR and severe COVID-19 \( (P < 0.05) \). In the multivariate analysis logistic regression model, high CAR \( (CAR > 0.296) \) was a significantly independent predictor for severe COVID-19 \( (OR = 17.652, \ P = 0.001) \), as well as NLR and age, which was in accordance with previous studies \([14, 15]\). 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\[14\]. Compared with non-severe cases, inflammation-related marker levels such as CRP and erythrocyte sedimentation rate were significantly higher in severe cases. Low ALB was observed in critically ill cases compared with severely ill cases. 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-\( \alpha \) than non-ICU patients, which reflected the obvious inflammatory reaction in severe and critical patients and was consistent with our results \([16]\).
CRP, an acute-phase protein, is a sensitive systemic marker of inflammation and tissue damage[7]. It was 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 it may exacerbate tissue damage and lead to more severe disease. Previous studies reported that CRP was a poor independent prognostic factor for patients with cardiovascular disease, non-small cell lung cancer and gastric cancer [17–19]. A retrospective study by Li et al. lately reported that the rising of CRP can be used as indicators of disease progression in patients with COVID-19[20].

ALB concentration is negatively associated with the systemic inflammatory response due to increased catabolism and the down-regulation of hepatic synthesis by cytokines TNF-α[21]. ALB, associated with inflammation and nutritional status, was revealed to be significantly related to poor survival in previous studies [22, 23]. Miura et al. concluded that preoperative ALB could predict overall survival in patients with non-small cell lung cancer [22]. A retrospective multicenters study by Gong et al. indicated that lower albumin was associated with severe COVID-19[9].

As expected, we observed a strong positive association between CAR and severe COVID-19. The CAR, the ratio of CRP to ALB, is considered an important marker of the systemic inflammatory response and more accurately reflects the balanced relationship between the severity of inflammatory reactions and the immune state. The CAR was a widely used marker for the assessment of the prognosis of patients with cancers. The increased CAR indicated poor clinical prognosis. Recent studies revealed that the CAR was predictive of disease progression and mortality in patients with cancers[12, 24, 25]. The result of Miyamoto et al. concluded that CAR was an independent factor to predict short-term survival of within two weeks, in particular, CAR is a useful tool for predicting survival times in end-stage patients with or without cancer [26].

To the best of our knowledge, our study is the first to observe a significantly positive association between CAR and the severity of patients with COVID-19. However, there were limitations to the current study. Firstly, our study was an observational study, further prospective studies are needed to confirm our findings. Secondly, missing data on some pretreatment variables may cause bias in the estimation and reduce the representativeness of the samples. Finally, the statistical limitations of the study due to the small sample size, especially in mild and critically ill patients.

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
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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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.