CRP and L are important indicators of severe coronavirus disease and poor prognosis in elderly patients

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Abstract

**Objective** To explore the value of C-reactive protein (CRP) and lymphocyte (L) in the assessment of disease severity and prognosis of elderly COVID-19 patients.

**Methods:** A total of 150 patients with COVID-19 confirmed by positive pathogen nucleic acid test in a designated hospital of COVID-19 in Wuhan were collected. Their demographic characteristics were analyzed. The dynamic changes of CRP and L in peripheral blood were retrospectively studied.

**Results:** (1) Among the 150 hospitalized patients with severe and critical classification, males were more than females, and patients over 60 were more than patients under 60. Severe, critical, and dying patients were older. There were significant statistical differences between the age, gender and the clinical classification of patients admitted to hospital (P<0.05). In 101 patients over 60 years old, the hospitalized patients with severe or critical types had significantly higher CRP than those with normal type (p<0.01). In the outcome of the elderly patients, the CRP of the patients with the outcomes of discharge, improvement, aggravation and death increased successively (p<0.01). According to the analysis of Logistic regression model, the increase of CRP constitutes a risk factor for death in elderly patients. (3) In the ROC curve analysis to distinguish the death outcome and non-death outcome of COVID-19 patients, the area under the curve (AUC) of CRP and L was 0.732 and 0.648 respectively. CRP and L had good diagnostic accuracy for the death outcome of patients. (4) Changes in CRP were correlated with changes in CT imaging and were consistent with changes in the course of the disease.

**Conclusions:** (1) COVID-19 patients over 60 years old were clinically heavy at admission and had poor prognosis, especially elderly male patients. (2) CRP and L are important monitoring indicators of COVID-19 in elderly patients. Combined with CT examination and observation of their dynamic changes, CRP and L are of important clinical guiding value for the judgment of disease severity and the evaluation of prognosis.

Introduction

Since December 2019, novel coronavirus (SARS-CoV-2) has been identified as the cause of pneumonia in Wuhan, Hubei province, China [1-2]. The World Health Organization has officially named the Disease caused by SARS-CoV-2 as Corona Virus Disease (COVID-19) [3-4]. At present, COVID-19 has been effectively controlled in China, but it is still in the global outbreak, which has become a global public health problem. SARS-CoV-2 spreads rapidly, causing a wide range of lesions with varying degrees of severity. However, the condition of some elderly patients changes rapidly, and inflammatory storms rapidly appear, leading to worsening or even life-threatening conditions [5-8]. Therefore, early diagnosis of the severity of the disease and prognosis of the elderly patients are particularly important. Absolute values of C-reactive protein (CRP) and lymphocyte (L), commonly used laboratory inflammatory indicators in clinical practice, can assist in the diagnosis of infectious inflammation and the judgment of disease severity, but are they also applicable to elderly patients with COVID-19? Can early prognosis be determined? Therefore, we retrospectively analyzed the demographic characteristics of 150 COVID-19 patients in a designated COVID-19 hospital in Wuhan, China, we studied the dynamic changes of inflammatory indicators CRP and L in peripheral blood of 105 patients over 60 years old, and explored the dynamic changes of inflammatory indicators in peripheral blood of elderly patients with COVID-19, so as to determine whether it can be used to determine the severity and prognosis of COVID-19 in elderly patients.

Materials And Methods

1. Case source and inclusion criteria

This study was approved by the Medical Ethics Review Board of Wuhan University of Science and Technology
1) All cases originated from the COVID-19 designated hospital in Wuhan City, Hubei Province, China-Tianyou Hospital affiliated to Wuhan University of Science and Technology from January 18, 2020 to February 26, 2020, tested for SARS-CoV-2 pathogenic nucleic acid Positive hospitalized cases;

2) Completed the laboratory data collection and clinical condition assessment at the three time points required by this study;

3) Study composite endpoint cures discharged patients and deaths before February 26, 2020; cases being treated in hospital on February 26, 2020.

2. Exclusion criteria
Those who failed to collect laboratory data in three times.

3. Criteria for evaluation of clinical conditions
1) Case classification
According to the COVID-19 diagnosis and treatment plan issued by the National Health Commission of China, it is divided into 4 types: light, ordinary, heavy and critical.

Light type: mild clinical symptoms, no pneumonia on imaging

Ordinary type: Symptoms such as fever, respiratory tract, pneumonia can be seen on imaging.

Heavy type: According with any of the following.
(1) Shortness of breath, RR>30 Times / minute.
(2) At rest, Oxygen saturation≤93%.
(3) $\frac{\text{PaO}_2}{\text{FiO}_2} \leq 30 \text{mmHg} 1\text{mmHg}=0.133\text{kPa}$, Pulmonary imaging showed significant progression of > 50% within 24 to 48 hours.

Critical type: One of the following conditions:
(1) Have respiratory failure and require mechanical ventilation;
(2) Shock;
(3) Combining other organ failure requires ICU monitoring treatment.

This study mainly studied the demographic characteristics, disease severity and outcome of COVID-19 patients. To optimize the research program, we mixed light and common types into light and common types according to the research purpose and clinical practice.

2) Outcome of illness
According to the clinical characteristics, the patients were divided into four types: discharge, improvement, aggravation and death. This project was approved by the medical ethics committee of Wuhan University of science and technology.

4. Treatment method
According to the COVID-19 diagnosis and treatment plan issued by the National Health Commission of China, patients generally receive effective oxygen therapy, lopinavir / ritonavir and other drug antiviral treatments, and provide respiratory and circulatory support treatment for patients with severe and critical illness.
5. Composite endpoints of the study

By February 26, 2020, the number of discharge and death cases before February 26, 2020 should be counted, and the length of stay in the hospital should be more than 10 days. The changes of their conditions should be evaluated, and the outcome indicators should be improved, aggravated and stable.

6. Experimental data collection

The experimental data were collected at three time points: admission, 3-5 days of hospitalization, and the composite end point. At the same time, clinical typing, disease severity and outcome were determined, and the corresponding length of hospitalization was collected.

7. Analytical methods

SPSS25.0 software was used for statistical analysis, and chi-square test of independent samples was used to analyze the differences between groups. If the theoretical frequency is less than 1, the Fisher exact probability test method is adopted. The risk degree of admission type and death outcome of each factor was analyzed by binary regression model and multiple regression model. The diagnostic value of CRP, L and other indicators on the death outcome was analyzed by the receiver operating characteristic curve (ROC), and the area under the curve (AUC) and its 95% CI were calculated. The optimal threshold value is determined by the maximum approximate index, providing both sensitivity and specificity. The test level selected for this statistical analysis was α=0.05, and P<0.05 indicated that the difference was statistically significant.

Results

In this study, 150 patients were divided by gender and age on the symmetrical bar chart of population characteristics shown in figure 1, and the corresponding average hospitalization days was calculated. It can be seen intuitively from the figure that the average hospitalization days of patients increases with the increase of age, and the average hospitalization days of patients aged over 60 is longer than that of patients aged under 40. Between the genders, the average hospitalization days were significantly longer for women (see FIG. 1 for details).

Table 1 demographic characteristic of patients

| Gender | Age stratification | Male | Female | Total | <60 | ≥60 | Total |
|--------|--------------------|------|--------|-------|-----|-----|-------|
|        |                    | n=84 | n=66   |       | n=49 | n=101 |       |
| HOD    |                    | 20.27±5.77| 21.11±6.08 | 20.64±5.90 | 20.80±4.578 | 20.56±6.47 | 20.64±5.90 |
| CRP    |                    | 70.00±4.07 | 33.23±3.73 | 53.82±46.65 | 43.52±42.15 | 58.82±4.07 | 53.82±46.65 |
| <3     |                    | 3  | 7  | 10 | 6  | 4  | 10 |
| 3-100  |                    | 54 | 53 | 107 | 35 | 72 | 107 |
| >100   |                    | 27 | 6  | 33 | 8  | 25 | 33 |
| L      |                    | 0.84±0.6 | 1.03±0.4 | 0.92±0.56 | 0.99±0.42 | 0.89±0.62 | 0.92±0.56 |
| <1.1   |                    | 1  | 7  | 109 | 30 | 79 | 109 |
| 1.1-3.2 |                   | 16 | 23 | 39 | 19 | 20 | 39 |
| >3.2   |                    | 2  | 0  | 2  | 0  | 2  | 2  |

We divided the patients into two groups: the < 60 year old group and the ≥ 60 year old group. CRP and L were divided into two groups according to the normal reference value range (CRP: < 3, 3-100, > 100; L: 1.1-3.2, < 1.1, > 3.2). The corresponding mean value of L and CRP and 95% confidence interval were collected and calculated respectively, and error bar graph was drawn. In each group of CRP classification, the mean value of CRP in patients over 60 years old was higher than that in patients under 60 years old (see FIG. 2A for details). In the group with L component of 1.1-3.2 and > 3.2, the mean value of patients over 60 years old is higher than that of
patients under 60 years old. In the group with L > 3.2, the mean value of patients over 60 years old is significantly higher than that of patients under 60 years old (see FIG.2B for details).

At the time of admission, the patients were divided into three clinical types: normal type, severe type and critical type. Based on the differential test analysis of the age, gender and other classification indicators of 150 patients and their clinical classification (classified as common type, severe type and critical type), the relationship between age, gender and admission clinical classification of patients was explored by using the bilateral chi-square test or Fisher's exact probabilistic test according to the data status. The results showed that there were significant statistical differences between the above indexes and clinical typing. The final outcome of the patients was divided into four outcomes: discharge, improvement, aggravation, and death. The difference analysis results showed that there were significant statistical differences between different age groups and outcome, while there were no or no significant differences between gender and outcome (see table 2 for details).

| Characteristic | Clinical typing at admission | Outcome the ending | Total |
|----------------|----------------------------|--------------------|-------|
|                | Common | Severe, critical type | Total | Improvem | Discharge | Aggravation | Death |
| Age a<60       | 30     | 19                 | 49 | 35        | 9     | 1     | 4     | 49 |
| ≥60            | 38     | 63                 | 101 | 49       | 25    | 6     | 21    | 101 |
| Total          | 68     | 82                 | 150 | 84       | 34    | 7     | 25    | 150 |
| c^2            |        |                    |     | c^2=7.415** |      |       |       |     |
| p              |        |                    |     | P=0.009   |       |       |       |     |
| Sex aMale      | 31     | 53                 | 84 | 44        | 18    | 6     | 16    | 84 |
| Female         | 37     | 29                 | 66 | 40        | 16    | 1     | 9     | 66 |
| Total          | 68     | 82                 | 150 | 84       | 34    | 7     | 25    | 150 |
| c^2            |        |                    |     | c^2=5.473* |      |       |       |     |
| p              |        |                    |     | P=0.022   |       |       |       |     |

Note: a Chi-square test (double-tail test)  b Fisher's exact test(double-tail test)
*At level 0.05 (double-tailed), **At level 0.05 (double-tailed), the correlation was significant.

At the time of admission, the first clinical classification was: normal 68 patients (45.3%), severe and critical 82 patients (54.7%). There are more men than women and more patients over 60 than those under 60. The age of severe, critical and dead patients is too old. From the above description and difference analysis, we found that the elderly population (aged over 60 years old) had significant differences in hospitalization time, clinical classification and outcome after admission, and there were significant statistical differences with the clinical classification and outcome after admission. Therefore, this study extracted 101 samples of the elderly population (over 60 years old), and studied the relationship between the demographic and clinical characteristics of the elderly population and the admission classification, outcome, and death outcome. In the analysis of the difference between CRP, L indexes of the elderly and admission clinical typing, we converted CRPL into classification variables according to the range of normal reference values, and explored the relationship between CRP, L and admission clinical typing of the elderly respectively by using the bilateral chi-square test or Fisher's exact probability test according to the data state. The results showed that there was a significant difference between CRP index and clinical typing in the elderly population, while there was no significant statistical difference between index L and clinical typing at admission.
In the binary Logistic regression analysis of elderly patients with or without death outcome, we used univariate Logistic regression analysis to preliminarily determine the factors affecting death outcome and risk degree. The results showed that gender, hospitalization time, CRP, L and other factors had a significant impact on the death outcome of patients. In the gender classification, taking women as the baseline, the risk degree of death of men was 2.750 times that of women, and the 95% interval of OR value was all greater than 1, satisfying the conditions of risk factors. The decrease in the number of days in hospital, relative to the increase in the number of days in hospital, the risk of death was 0.930 times, and the 95% interval of OR value was all less than 1, satisfying the condition of constituting a protective factor. The risk of death increased by 1.022 times for every unit of increase in CRP index, and the 95% interval of OR value was all greater than 1, satisfying the conditions of risk factors. In order to correct the influence of confounder, we included the above variables into the multivariate Logistic regression analysis, and the results showed that the risk of death increased by 1.018 times for every unit of increase in CRP index, and the 95% interval of OR value was all greater than 1, satisfying the conditions constituting risk factors. (see table 4 for details)

Table 4 Logistic regression analysis of influencing factors of admission classification of patients over 60 years old

| Characteristic | Clinical typing at admission | Outcome the ending |
|----------------|------------------------------|--------------------|
|                | Common          | Severe, critical type | Total | Improve | Discharge | Aggravation | Death |
| CRP a          | 33.93 ±32.63   | 73.83 ±49.86       | 58.82 ±48.09 | 42.4 ±1 | 57.8 ±1 | 82.65 ±45.86 | 91.51 ±50.49 | 58.2 ±4 |
| 3-100          | 2               | 2                  | 4      | 4       | 0       | 0            | 0     | 4     |
| >100           | 3               | 22                 | 25     | 5       | 5       | 3            | 12    | 25    |
| Total          | 38              | 63                 | 101    | 49      | 25      | 6            | 21    | 10    |

| L b            | 1.05 ±0.67     | 0.79 ±0.56         | 0.89 ±0.62 | 0.91 ±0.4 | 1.11 ±0.95 | 0.65 ±0.34 | 0.65 ±0.3 | 0.8 ±0.96 |
| 1.1-3.2        | 27              | 52                 | 79       | 36       | 19       | 5            | 19    | 79    |
| >3.2           | 1               | 1                  | 2        | 0        | 2        | 0            | 2     | 10    |
| Total          | 38              | 63                 | 101      | 49       | 25       | 6            | 21    | 10    |

Note: Normal reference values: CRP (<3mg / L); L (1.1× 10^9 / L -3.2 × 10^9 / L)

* Chi-square test (double-tail test)  ** Fisher's exact test(double-tail test)

*At level 0.05 (double-tailed), **At level 0.05 (double-tailed), the correlation was significant.
### Univariate Logistic regression analysis

| Factor | B   | SE  | \( \text{Wald} \, c^2 \) | \( p \) |
|--------|-----|-----|-----------------------|------|
| Sex(male) | 1.012 | 0.424 | 5.405 | 0.017 |
| HOD    | -0.073 | 0.035 | 4.354 | 0.037 |
| CRP    | 0.022  | 0.006 | 13.827 | 0.000 |
| L      | -0.708 | 0.373 | 3.602 | 0.058 |

### Multivariate Logistic regression analysis

| Factor | B     | SE   | \( \text{Wald} \, c^2 \) | \( p \) |
|--------|-------|------|-----------------------|------|
| Sex(male) | 0.480 | 0.488 | 0.969 | 0.325 |
| HOD    | -0.054 | 0.040 | 1.792 | 0.181 |
| CRP    | 0.018  | 0.006 | 8.022 | 0.005 |
| L      | -0.568 | 0.367 | 2.395 | 0.122 |

Note: HOD: Hospitalization days

In the multivariate Logistic regression analysis of hospitalization days, gender, CRP, L and outcome of the elderly patients, compared with the elderly patients who died, the risk of death in discharged patients was 0.985 times for every unit of decrease in CRP, and the 95% interval of OR value was all less than 1. The decline of CRP constituted a condition of protective factors. The outcomes of discharge, improvement and aggravation were compared with those of the elderly patients who died the increase of hospitalization days all constituted the risk factors for death, with the OR values of 1.306, 1.354 and 1.339, respectively (see table 5 for details).

### Table 5 multivariate Logistic regression analysis of the influencing factors of mortality outcome in patients

| Factors     | B     | SE   | \( \text{Wald} \, c^2 \) | \( p \) | \( \text{Exp}(B) \) | 95\%CI |
|-------------|-------|------|-----------------------|------|----------------|-------|
| **Discharged** |       |      |                       |      |                  |       |
| HOD         | 0.267 | 0.069| 14.831                | 0.000| 1.306          | 1.140 | 1.496 |
| CRP         | -0.015| 0.008| 4.132                | 0.042| 0.985          | 0.970 | 0.999 |
| L           | 1.163 | 0.880| 1.746                | 0.186| 3.198          | 0.570 | 17.944 |
| [sex = male]| 0.097 | 0.726| 0.018                | 0.894| 1.102          | 0.265 | 4.574 |
| [sex = female]| 0   |      |                      |      |                |       |       |
| **Improvement** |     |      |                       |      |                  |       |
| HOD         | 0.303 | 0.075| 16.271                | 0.000| 1.354          | 1.169 | 1.570 |
| CRP         | -0.006| 0.008| 0.482                | 0.487| 0.994          | 0.978 | 1.010 |
| L           | 1.719 | 0.904| 3.620                | 0.057| 5.579          | 0.949 | 32.785 |
| [sex = male]| 0.256 | 0.801| 0.102                | 0.749| 1.292          | 0.269 | 6.205 |
| [sex = female]| 0   |      |                      |      |                |       |       |
| **Exacerbation** |      |      |                       |      |                  |       |
| HOD         | 0.292 | 0.103| 7.962                | 0.005| 1.339          | 1.093 | 1.639 |
| CRP         | 0.001 | 0.011| 0.940                | 0.384| 1.001          | 0.979 | 1.023 |
| L           | 0.611 | 1.349| 0.205                | 0.651| 1.842          | 0.131 | 25.931 |
| [sex = male]| 1.125 | 1.292| 0.758                | 0.384| 3.081          | 0.245 | 38.774 |
| [sex = female]| 0   |      |                      |      |                |       |       |

Note: HOD: Hospitalization days
In the diagnostic relationship between CRP, L and death outcome in elderly patients, non-death outcome and death outcome were taken as the positive classification basis. We took AUC=0.5 as the null hypothesis, and the significance of CRP and L in ROC curve analysis was less than 0.05. The area under the CRP curve is greater than 0.7 (AUC=0.732, 95% CI: 0.61-0.86), and the area under the L curve is close to 0.7 (AUC=0.648, 95% CI: 0.51-0.79). It can be seen in the ROC curve that both CRP and L have a good diagnostic value for the outcome of death. The cutoff values of CRP and L diagnosis of death outcome were determined by the maximum Youden index, which were 91.5 and 0.615 respectively (see FIG.3 for details).

Discussion

COVID-19 is an acute infectious disease caused by a novel coronavirus (SARS-CoV-2). When SARS-CoV-2 enters the body through the angiotensin-converting enzyme 2 (ACE2) receptor adsorbed on the surface of mucosal epithelial cells, its pathogen-related molecular pattern (PAMP) can be quickly recognized by immune cells and activate the natural immune system to clear the virus, but over activation can cause inflammatory storms [9-10]. The onset of the disease is mainly fever, most of which are light, and a few are critical [11-13]. Some patients may gradually develop dyspnea. In severe cases, the disease progresses rapidly, and severe inflammatory storms may occur, leading to death, especially in elderly patients.

COVID-19 is a newly discovered human infectious disease [14]. The commonly used clinical inflammatory indicators such as CRP and L are helpful in the diagnosis and evaluation of many inflammatory diseases. CRP is an acute temporal protein synthesized by liver cells in response to inflammatory stimuli, such as microbial invasion or tissue damage, in very low concentrations in serum from healthy people (<5mg/L), and its concentration significantly increased during bacterial infection or tissue damage [15]. L is the core of immune response, which can be divided into three types: T cells, B cells and NK cells. Chaolin H et al. believed that patients with COVID-19 had a large amount of IL-1βIFN-γIP-10MCP-1 and other cytokines release, which may lead to Th1 cell activation [16]. CRP and L can be used as sensitive indicators to reflect the control of infection and inflammation. But can these indicators have the same clinical value for COVID-19 patients, especially elderly patients?

The results of this study showed that there was a significant statistical difference between different age groups and outcome of COVID-19 patients, and elderly patients (over 60 years old) were a highly vulnerable group. From the 150 confirmed cases, we extracted 101 samples from the elderly population (over 60 years old), and made a targeted study on the relationship between the demographic and clinical characteristics of the elderly population and admission classification, outcome, and death outcome. The relationship between CRP and admission clinical typing in elderly patients was explored by using bilateral chi-square test or Fisher's exact probabilistic test. The results showed that there was a significant difference between CRP index and clinical typing in the elderly, suggesting that CRP, a laboratory inflammatory index, could be used to assist in determining the severity of COVID-19 in elderly patients.

Furthermore, binary Logistic regression analysis was carried out to investigate whether the elderly patients died or not. The study found that compared with the elderly patients who died, the risk of death was 0.985 times for each unit of decline in CRP, and the 95% interval of OR value was all less than 1. The decline of CRP met the conditions constituting the protective factor. In the diagnostic relationship between CRP, L and death outcome in elderly patients, we used non-death outcome and death outcome as the basis for positive classification. We took AUC=0.5 as the null hypothesis, and the significance of CRP and L in ROC curve analysis was less than 0.05. It can be seen from the ROC curve that both CRP and L have good diagnostic values for death outcomes, and the optimal thresholds for age and CRP diagnostic death outcomes were determined by the maximum Youden index, which were 91.5 and 0.615, respectively.

CT is very important in the clinical diagnosis and typing of COVID-19. The results of this study showed that CRP was consistent with CT in judging the changes of the disease, and it could be used in combination to judge the
changes of the disease (see FIG.4 for details).

To sum up, the results of this clinical study showed that COVID-19 patients over 60 years old had severe clinical classification and poor prognosis, especially elderly male patients. CRP and L can be used as the key monitoring indicators of COVID-19 in elderly patients. Combined with CT examination and observation of its dynamic changes, CRP and L can play an important clinical guiding value in the assessment of disease severity and prognosis.

Declarations

Ethics approval and consent to participate

Because this study was a retrospective analysis and all the data were anonymous, we did not involve patients' private information. This study was approved by the Medical Ethics Review Board of Wuhan University of Science and Technology (No. 202009).

Consent for publication

After revision and review by all authors, all authors finally agree to publish.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

QH, XFH, XCX, and SYC contributed equally to this article, they are co-first author. The whole experimental design was completed under the guidance of professor QW and professor QMW. QH and XFH were responsible for the arrangement of data, XCX and SYC are responsible for analyzing the data, KWG and XLL participated in the interpretation of the results, QW and WXL wrote the initial draft with all authors providing critical feedback and edits to subsequent revisions. QW, KWG and QMW reviewed and revised the paper before submission, they are co-corresponding authors.

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Patient data

We increased the data sample size on the basis of 132 data samples from another published paper. In another paper, the research point was the judgment value of SAA in the assessment of COVID 19's disease severity and prognosis. In this paper, CRP and L were emphasized as important indicators of severe coronavirus disease and poor prognosis in elderly patients.

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Figure 1
symmetrical bar chart of demographic characteristics

Figure 2
results of lymphocyte and c-reflecting protein in patients of different ages
Figure 3
CRP, L and death outcome

Figure 4
(A male patient aged over 60 years): serial CT scans and CRP dynamic changes
