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# Different characteristics of critical COVID-19 and thinking of treatment strategies in non-elderly and elderly severe adult patients

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ABSTRACT

*Background:* The differences in the characteristics and main causes of critical COVID-19 infection in non-elderly and elderly severe patients remain unknown.
*Methods:* We included 273 adult patients with confirmed severe COVID-19 from Tongji Hospital, Wuhan, China from February 10 to March 8, 2020. Clinical characteristics and risk factors for outcomes were compared between the young and middle-aged and the elderly severe patients.
*Results:* Hemoglobin, neutrophil percentage, inflammatory markers, hepatic, renal, and cardiovascular parameters differed between the non-elderly and elderly severe patients. In young and middle-aged patients, critical patients showed higher high-sensitivity C-reactive protein (hsCRP) during hospitalization than severe patients. However, in the elderly patients, critical patients showed decreased hsCRP during hospitalization and higher proBNP values. The hsCRP fluctuation and proBNP were independent risk factors for intensive care unit (ICU) admission in young and middle-aged severe patients (OR=1.068) and elderly severe patients (OR=1.026), respectively.
*Conclusion:* The study revealed different potential causes of disease and predictive factors for non-elderly and elderly critical patients and treatment recommendations. Deterioration of inflammatory state was the main cause of ICU admission in young and middle-aged severe COVID-19 patients, while a decline in hsCRP was not associated with better outcomes in elderly severe patients, indicating the need for different treatments for non-elderly and elderly severe patients. Anti-inflammatory therapy with corticosteroids should be considered in the early disease stage among non-elderly severe patients, but cardiovascular protection plays a more important role in elderly severe patients.

## 1. Introduction

Coronavirus disease 2019 (COVID-19) was confirmed to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus [1]. According to a recent situation report of the World Health Organization (WHO), there were over 58,000,000 confirmed cases and nearly 1,400,000 deaths caused by COVID-19 as of November 24, 2020 [2]. The clinical spectrum of this disease ranges from asymptomatic infection to severe respiratory tract disease, and viral pneumonia is the main reason for patient hospitalization and death. As the disease progresses further, it induces sepsis, respiratory failure, acute respiratory distress syndrome (ARDS), heart failure, septic shock and other serious complications [3].

Although elderly and young and middle-aged people are likely to develop COVID-19, elderly patients are more susceptible to severe illness with higher mortality [4], while the proportion of young and

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middle-aged critically ill patients is still increasing. Compared to young and middle-aged patients, elderly patients have different clinical features and risk factors affecting the outcome of COVID-19 [4]. These characteristics indicate different underlying mechanisms and main causes of critical COVID-19 in non-elderly and elderly severe patients, indicating the need for different treatments for patients of different ages.

However, the current studies mainly focus on patients of all ages, and there has been a lack of attention on the different prognostic factors for young and middle-aged patients and elderly patients [3,5]. In addition to general supportive treatment, the same treatment strategy of antiviral therapy and anti-inflammatory therapy with corticosteroids is recommended for patients of all ages with severe and critical COVID-19 [6], and these treatments may have different effects in non-elderly and elderly severe patients due to different causes of critical illness. However, there are no differences in the recommendations for treatment strategies according to age.

Thus, the purpose of this study is to explore the different characteristics and causes of intensive care unit (ICU) admission in non-elderly and elderly severe COVID-19 patients, which will lead to further indications for treatment strategies for patients of different ages.

## 2. Methods

### 2.1. Study design and participants

A retrospective study was performed on COVID-19 patients hospitalized from February 10, 2020, to March 8, 2020, at Tongji Hospital in Wuhan, China, as COVID-19 cases in Wuhan showed more typical features in a susceptible population before the following virus mutations. This study was conducted in accordance with the guidelines of the Declaration of Helsinki. Ethical approval for the study was provided by the Clinical Research Ethics Committee of Tongji Hospital, Huazhong University of Science and Technology (No. TJ-IRB20200404). The requirement for written informed consent was waived by the ethics commission for this retrospective study. All patients were diagnosed with severe COVID-19 according to the WHO guidelines. The age of 60 years is regarded as the cutoff point between the elderly population and the young and middle-aged population in China. According to age, patients were divided into 2 groups: elderly (older than 60 years) and young and middle-aged (60 years and younger). Patients who had no clinical outcome observed or were<18 years old were excluded from this study.

According to the diagnosis and treatment guidelines released by the China Health and Medical Commission [7], severe COVID-19 cases were classified by the following conditions: respiratory distress, indicated by a respiratory rate (RR) $\geq$ 30 breaths/min; oxygen saturation<93% on room air at rest; arterial partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) $\leq$ 300 mmHg (1 mmHg = O.133 l < Pa) and lesion progression > 50% within 24 to 48 h on lung imaging. Moreover, critical COVID-19 cases with respiratory failure, shock or other organ failure were monitored and treated in the ICU.

### 2.2. Data collection

Data, including patient demographics, clinical characteristics, past history, and laboratory examinations on admission, were extracted from the hospital's electronic medical record system. Laboratory examination consisted of a complete blood count; blood chemical analysis; assessment of liver, renal and cardiovascular function; and inflammatory biomarkers, including high-sensitivity C reactive protein (hsCRP) and procalcitonin (PCT). As the disease progressed, the maximum values of the laboratory examinations in the hospital were also collected. HsCRP fluctuation was determined by calculating the difference between the maximum hsCRP value in the hospital and the hsCRP value on admission. A positive value indicated an elevation of hsCRP during hospitalization, while a negative value indicated a decline. Clinical outcomes of patients were observed and evaluated according to admission to the ICU or discharge.

### 2.3. Statistical analysis

Categorical variables are represented as frequencies and percentages and were compared using the chi-square and Fisher's exact tests. Continuous variables are represented as medians and interquartile ranges or means and standard deviations (SDs) and were compared using the Mann–Whitney *U* test or *t*-test as appropriate. The association between predictive factors and admission to the ICU was evaluated by multivariable logistic regression. Three models were constructed to adjust for potential confounding factors, including hsCRP fluctuation, glomerular filtration rate (GFR), alanine transaminase (ALT) and pro-B-type natriuretic peptide (proBNP). The receiver operating characteristic (ROC) curve was used to calculate the cutoff value of hsCRP fluctuation. All statistical analyses and graphs were generated by using SPSS 25.0 and GraphPad Prism version 5, and a p value $< 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Demographic, clinical and laboratory characteristics of severe COVID-19 patients

A total of 273 severe COVID-19 patients were included in this study; 188 of the patients were over 60 years old, with an average age of 69.5 years old, and 85 patients were 60 years old or younger, with an average age of 51.0 years old. Approximately half of the patients were male in both the elderly (50.4%) and young and middle-aged group (55.3%). The prevalence of hypertension in elderly patients was 58.5%, which was significantly higher than that in young and middle-aged patients (36.9%) ($P < 0.01$). There was no significant difference in the prevalence of diabetes between the elderly (21.7%) and the young and middle-aged patients (14.9%). The median systolic blood pressure of the elderly patients measured on admission was higher than that of the young and middle-aged patients (133 vs 123 mmHg, $P < 0.01$), which was consistent with the hypertension history (Table 1).

Among all severe COVID-19 patients, 217 (79.5%) were discharged from the hospital and 56 (20.5%) were admitted to the ICU. Admission to the ICU occurred in 21.3% of elderly patients and 18.8% of young and middle-aged patients, and these rates showed no significant difference.

Laboratory examination on admission revealed that compared with the elderly patients, the young and middle-aged severe patients showed higher hemoglobin (HGB) (median, 129 vs 125, $P = 0.04$), and there was no difference in leukocyte count (median, 5.64 vs 5.70, $P = 0.31$) or platelet count (median, 265 vs 234, $P = 0.17$). The young and middle-aged patients showed lower neutrophil percentages (median, 61.3 vs 71.6, $P < 0.01$), higher lymphocyte percentages (median, 27.3 vs 19.0, $P < 0.01$), higher ALT levels (median, 23 vs 20, $P = 0.03$), higher albumin levels (mean, 37.6 vs 34.4, $P < 0.01$), lower total bilirubin levels (median, 7.2 vs 8.0, $P = 0.02$) and lower direct bilirubin levels (median, 3.3 vs 3.7, $P = 0.01$). Blood urea nitrogen (median, 4.3 vs 5.0, $P < 0.01$) and creatinine (median, 64.5 vs 72.0, $P = 0.01$) were lower and GFR (median, 101.5 vs 85.7, $P < 0.01$) was higher in young and middle-aged patients, indicating better renal function reserve. HsCRP in young and middle-aged patients was lower than that in elderly patients on admission (median, 9.4 vs 25.9, $P = 0.02$), but the hsCRP level in both young and middle-aged patients and the elderly patients decreased significantly during hospitalization ($P < 0.01$). The maximum hsCRP value during hospitalization in the young and middle-aged patients was still lower than that in the elderly patients but showed no significant difference (median, 3.4 vs 14.9, $P = 0.02$). Regarding cardiovascular function assessment, the levels of proBNP (median, 70 vs 184, $P < 0.01$) and cTnI (median, 2.6 vs 6.3, $P < 0.01$) in the young and middle-aged patients were lower than those in the elderly patients, indicating a

**Table 1**
Demographic, clinical and laboratory characteristics of severe COVID-19 patients.

| Variables | | Age ≤ 60y (n = 85) | Age > 60y (n = 188) | P value |
|---|---|---|---|---|
| **Demographic and clinical features** | | | | |
| Gender, No(%) | Male | 45 (55.3%) | 95 (50.4%) | |
| | Female | 40 (44.7%) | 93 (49.6%) | |
| Age, years | | 51.0 (43, 57) (n = 85) | 69.5 (66, 75.8) (n = 188) | 0.00 |
| Hypertension history, No(%) | No | 53 (63.1%) | 141 (41.5%) | 0.00 |
| | Yes | 31 (36.9%) | 46 (58.5%) | |
| Diabetes history, No (%) | No | 64 (85.1%) | 101 (78.3%) | 0.89 |
| | Yes | 20 (14.9%) | 28 (21.7%) | |
| Admission to ICU | | | | 0.64 |
| No | | 69 (81.2%) | 148 (78.7%) | |
| Yes | | 16 (18.8%) | 40 (21.3%) | |
| Systolic blood pressure (SBP), mmHg | | 123 (112, 135) (n = 85) | 133 (121, 146) (n = 187) | 0.00 |
| Diastolic blood pressure (DBP) , mmHg | | 77 (68, 86) (n = 85) | 78 (70, 87) (n = 187) | 0.15 |
| **Complete blood count** | | | | |
| Hemoglobin, g/L | | 129 (116, 141) (n = 85) | 125 (114, 134) (n = 186) | 0.04 |
| Leukocytes, $\times 10^9$/L | | 5.64 (4.47, 7.23) (n = 85) | 5.70 (4.62, 7.78) (n = 186) | 0.31 |
| Neutrophil percentage, % | | 61.3 (52.3, 71.9) (n = 85) | 71.6 (60.1, 79.9) (n = 186) | 0.00 |
| Leukocyte percentage, % | | 27.3 (18.1, 34.6) (n = 85) | 19.0 (11.7, 27.4) (n = 187) | 0.00 |
| Platelet, $\times 10^9$/L | | 265 (176, 330) (n = 83) | 234 (168, 309) (n = 184) | 0.17 |
| **Liver and renal function** | | | | |
| ALT, U/L | | 23.0 (16.5, 40.0) (n = 85) | 20.0 (13.0, 32.0) (n = 189) | 0.03 |
| AST, U/L | | 25.0 (18.0, 35.0) (n = 85) | 25.0 (18.3, 36.8) (n = 189) | 0.67 |
| Albumin, g/L | | 37.6 ± 4.6 (n = 85) | 34.4 ± 4.7 (n = 189) | 0.00 |
| Total bilirubin (TBIL), μmol/L | | 7.2 (5, 10.1) (n = 85) | 8.0 (6.2, 11.2) (n = 189) | 0.02 |
| Direct bilirubin (DBIL) , μmol/L | | 3.3 (2.4, 4.5) (n = 83) | 3.7 (2.9, 5.5) (n = 189) | 0.01 |
| ALP, U/L | | 68 (57, 86) (n = 85) | 68 (58, 85) (n = 189) | 0.97 |
| GGT, U/L | | 27 (19, 55) (n = 85) | 25 (17, 51) (n = 189) | 0.35 |
| Blood urea nitrogen (BUN), mmol/L | | 4.3 (3.3, 5.4) (n = 84) | 5.0 (4.1, 6.3) (n = 188) | 0.00 |
| Creatinine, μmol/L | | 64.5 (52.3, 79.8) (n = 84) | 72.0 (60.0, 88.0) (n = 188) | 0.01 |
| GFR, ml/min | | 101.5 (91.8, 112.2) (n = 84) | 85.7 (68.1, 93.2) (n = 187) | 0.00 |
| **Cardiovascular function** | | | | |
| proBNP, ng/L | | 70 (30, 178) (n = 66) | 184 (96, 559) (n = 164) | 0.00 |
| cTnI, ng/L | 2.6 (1.9, 9.2) (n = 75) | 6.3 (3.1, 16.0) (n = 168) | 0.00 | |
| **Inflammatory biomarkers** | | | | |
| Procalcitonin (PCT), ng/mL | | 0.07 (0.06, 0.18) (n = 36) | 0.08 (0.06, 0.17) (n = 97) | 0.86 |
| | Admission | | | 0.02 |
| High-sensitivity C-reactive protein (hsCRP), mg/L | | 9.4 (1.5, 50.6) (n = 85) | 25.9 (2.5, 83.8) (n = 184) | |
| | In hospital[a] | 3.4 (1.0, 84.7) (n = 58) | 14.9 (2.6, 52.6) (n = 129) | 0.20 |

[a] The in hospital value of hsCRP is the maximum value collected during hospitalization.

greater impairment of cardiovascular function in the elderly severe patients (Table 1).

### 3.2. Characteristics of young and middle-aged severe patients

Of the young and middle-aged severe patients, 16 were admitted to ICU and 69 were discharged. Compared with discharged severe patients, the laboratory examinations of critical patients showed higher leukocyte counts on admission (median, 7.4 vs 5.2, $P = 0.01$) and during hospitalization (median, 11.8 vs 5.5, $P < 0.01$), higher neutrophil percentages (median, 82.4 vs 58.1, $P < 0.01$), lower lymphocyte percentages (median, 6.9 vs 30.1, $P < 0.01$), and lower platelet counts (median, 175.5 vs 278, $P < 0.01$). The total number of leukocytes in critical cases increased significantly during hospitalization ($P < 0.01$). The critical patients had higher ALT (median, 38 vs 22, $P = 0.01$), higher aspartate aminotransferase (AST) (median, 53.5 vs 21.0, $P < 0.01$), higher alkaline phosphatase (ALP) (median, 83.5 vs 67, $P = 0.01$), higher gamma-glutamyl transferase (GGT) (median, 54 vs 24, $P < 0.01$), lower levels of albumin (median, 33.5 vs 38.9, $P < 0.01$), higher total bilirubin (median, 9.5 vs 7.1, $P = 0.04$), higher direct bilirubin (median, 4.5 vs 3.1, $P < 0.01$), higher blood urea nitrogen (median, 7.8 vs 4.0, $P < 0.01$) and higher creatinine (median, 72 vs 64.5, $P = 0.01$). ProBNP (median, 408 vs 51, $P = 0.01$) and cTnI (median, 13.0 vs 2.2, $P < 0.01$) were also higher in critical patients than in severe patients (Table 2). Thus the liver, renal and cardiovascular function of young and middle-aged critical patients were all worse than those of severe patients.

Regarding the inflammatory indicators of young and middle-aged critical patients, hsCRP (median, 89.7 vs 5.0, $P < 0.01$) and procalcitonin (PCT) (median, 0.32 vs 0.06, $P < 0.01$) were higher than those of severe patients on admission, revealing that the primary inflammatory state of young and middle-aged critical patients was worse than that of severe patients. Moreover, the hsCRP fluctuation of young and middle-aged critical patients was 67.9 mg/L, indicating that hsCRP increased with the worsening of the inflammatory state during hospitalization among critical patients, while hsCRP fluctuation among severe patients was −2.95 mg/L indicating improvement in the inflammatory state of severe patients during hospitalization. The hsCRP fluctuation in critical patients was significantly higher than that in severe patients ($P < 0.01$), which showed different tendency of change in the inflammatory state during hospitalization between young and middle-aged critical patients and severe patients.

### 3.3. Clinical characteristics of critical patients

The mean age of young and middle-aged critical patients was 50.8 years old and that of the elderly critical patients was 75.7 years old. The comparison of young and middle-aged critical patients with elderly patients indicated that the systolic blood pressure (median, 119 vs 137, $P = 0.01$) and diastolic blood pressure (mean, 73.9 vs 82.4, $P = 0.03$) of young and middle-aged critical patients were significantly lower than those of the elderly patients, which indicated that the presence of underlying cardiovascular disease affected the progression of COVID-19. The young and middle-aged critical patients showed higher ALT (median, 38 vs 20, $P = 0.01$), higher GGT (median, 54 vs 25, $P < 0.01$) and

**Table 2**
Characteristics of young and middle-aged patients.

| Variables | | Severe (n = 69) | Critical (n = 16) | P value |
|---|---|---|---|---|
| **Complete blood count** | | | | |
| Hemoglobin, g/L | | 129 (122, 139) (n = 69) | 133 (115, 134) (n = 16) | 0.51 |
| Leukocytes, ×109/L | Admission | 5.2 (4.4, 6.4) (n = 69) | 7.4 (5.0, 16.2) (n = 16) | 0.01 |
| | In hospital | 5.5 (4.7, 6.9) (n = 50) | 11.8 (6.7, 22.5) (n = 12) | 0.00 |
| Neutrophil percentage, % | | 58.1 (50.5, 65.3) (n = 69) | 82.4 (72.4,88.0) (n = 16) | 0.00 |
| Leukocyte percentage, % | | 30.1 (24.3, 35.4) (n = 69) | 6.9 (3.9, 15.3) (n = 16) | 0.00 |
| Platelet, ×109/L | | 278 (211, 334) (n = 67) | 175.5 (127, 305) (n = 16) | 0.03 |
| **Liver and renal function** | | | | |
| ALT, U/L | | 22 (15, 37) (n = 69) | 38 (24, 52.5) (n = 16) | 0.01 |
| AST, U/L | | 21 (17, 28) (n = 69) | 53.5 (30.5, 67.3) (n = 16) | 0.00 |
| Albumin, g/L | | 38.9 (35.1, 41.4) (n = 69) | 33.5 (30.2, 37.5) (n = 16) | 0.00 |
| Total bilirubin (TBIL), μmol/L | | 7.1 (4.9, 9.7) (n = 69) | 9.5 (6.6, 13.6) (n = 16) | 0.04 |
| Direct bilirubin (DBIL), μmol/L | | 3.1 (2.2, 4.2) (n = 69) | 4.5 (3.3, 7.7) (n = 16) | 0.00 |
| ALP, U/L | | 67 (55, 82) (n = 69) | 83.5 (66, 126) (n = 16) | 0.01 |
| GGT, U/L | | 24 (17.5, 48) (n = 69) | 54.0 (32.5, 92.3) (n = 16) | 0.00 |
| Blood urea nitrogen (BUN), mmol/L | | 4.0 (3.2, 5.0) (n = 69) | 7.8 (5.1, 9.8) (n = 15) | 0.00 |
| Creatinine, μmol/L | | 64.5 (52.3, 79.8) (n = 84) | 72.0 (60.0, 88.0) (n = 188) | 0.01 |
| GFR, ml/min | | 102.5 (97.3, 112.1) (n = 69) | 89.7 (74.9, 113.5) (n = 15) | 0.08 |
| **Cardiovascular function** | | | | |
| proBNP, ng/L | | 51 (28, 113) (n = 55) | 408 (70, 769) (n = 11) | 0.01 |
| cTnI, ng/L | | 2.2 (1.9, 6.1) (n = 61) | 13.0 (4.1, 215.4) (n = 14) | 0.00 |
| **Inflammatory biomarkers** | | | | |
| Procalcitonin (PCT), ng/mL | | 0.06 (0.05, 0.08) (n = 27) | 0.32 (0.21, 0.62) (n = 9) | 0.00 |
| hsCRP, mg/L | Admission | 5.0 (1.05, 19.25) (n = 69) | 89.7 (29.1, 187.8) (n = 16) | 0.00 |
| | In hospital | 1.35 (0.83, 7.6) (n = 44) | 153 (89.2, 229.8) (n = 14) | 0.00 |
| hsCRP fluctuation, mg/L | | −2.95 (-16.25, −0.1) (n = 44) | 67.9 (36.9, 77.1) (n = 14) | 0.00 |

higher GFR (median, 89.7 vs 72.7, P = 0.01). The proBNP level of young and middle-aged critical patients was significantly lower than that of elderly patients (median, 408 vs 999, P < 0.01), reflecting worse cardiovascular function in elderly critical patients. Young and middle-aged patients showed higher PCT than elderly patients (median, 0.32 vs 0.18, P < 0.01), and there was no difference in hsCRP (median, 89.7 vs 103.7, P < 0.01) at the time of admission between the young and middle-aged patients and the elderly critical patients. However, the maximum hsCRP value during hospitalization of young and middle-aged critical patients was significantly higher than that of elderly patients (median, 153 vs 65.2, P < 0.01), resulting in higher hsCRP fluctuation during hospitalization than that of elderly patients (median, 67.9 vs −10.2, P < 0.01) (Table 3), which indicated that the worsening of inflammatory state of young and middle-aged critical patients during hospitalization was significantly more serious than that of elderly critical patients. Even acute inflammation in elderly critical patients exhibited a remission during hospitalization with lower hsCRP than that at the time of admission.

**Table 3**
Characteristics of critical COVID-19 patients.

| Variables | | Age ≤ 60y (n = 16) | Age > 60y (n = 40) | P value |
|---|---|---|---|---|
| **Demographic and clinical features** | | | | |
| Age, y | | 50.8 ± 11 (n = 69) | 75.7 ± 7.6 (n = 16) | 0.00 |
| Systolic blood pressure (SBP), mmHg | | 119 (106, 135) (n = 16) | 137 (127, 151) (n = 38) | 0.01 |
| Diastolic blood pressure (DBP) , mmHg | | 73.9 ± 15.1 (n = 16) | 82.4 ± 12.2 (n = 38) | 0.03 |
| **Liver and renal function** | | | | |
| ALT, U/L | | 38 (24, 52.5) (n = 16) | 20 (15, 33) (n = 38) | 0.01 |
| TBIL, μmol/L | | 9.5 (6.6, 13.6) (n = 16) | 11.2 (7.9, 16.4) (n = 38) | 0.23 |
| ALP, U/L | | 83.5 (66, 126) (n = 16) | 67 (58.5, 88) (n = 38) | 0.09 |
| GGT, U/L | | 54.0 (32.5, 92.3) (n = 16) | 25.0 (16.3, 39.0) (n = 38) | 0.00 |
| Blood urea nitrogen (BUN), mmol/L | | 7.8 (5.1, 9.8)(n = 15) | 6.5 (5.0, 11.6) (n = 37) | 0.96 |
| Creatinine, μmol/L | | 79 (52, 104) (n = 15) | 79 (64, 116.0) (n = 37) | 0.40 |
| GFR, ml/min | | 89.7 (74.9, 113.5) (n = 15) | 72.7 (51.4, 88.8) (n = 37) | 0.01 |
| **Cardiovascular function** | | | | |
| proBNP, ng/L | | 408 (70, 769) (n = 11) | 988 (681, 4285) (n = 27) | 0.01 |
| **Inflammatory biomarkers** | | | | |
| Procalcitonin (PCT), ng/mL | | 0.32 (0.21, 0.62) (n = 9) | 0.18 (0.10, 0.30) (n = 22) | 0.03 |
| hsCRP, mg/L | Admission | 89.7 (29.1, 187.8) (n = 16) | 103.7 (46.9, 142.7) (n = 37) | 0.76 |
| | In hospital | 153 (89.2, 229.8) (n = 14) | 65.2 (43.6, 111.9) (n = 35) | 0.00 |
| hsCRP fluctuation, mg/L | | 67.9 (36.9, 77.1) (n = 14) | −10.2 (-29.6, 12.7) (n = 35) | 0.00 |

### *3.4. Predictive factors for ICU admission in the young and middle-aged and the elderly severe patients*

Table 4 shows the relationship between underlying predictive factors and ICU admission in young and middle-aged and elderly severe patients. After excluding the interference of GFR, ALT and proBNP by multivariate logistic analysis, higher hsCRP fluctuation was significantly correlated with an increased risk of ICU admission and was an independent risk factor for critical COVID-19 (OR = 1.068). Table 4 also shows that the increase in proBNP was correlated with the risk of ICU admission in elderly severe patients (OR = 1.026), while hsCRP fluctuation was not related to the risk of ICU admission in elderly severe patients, which revealed the different mechanisms of critical COVID-19 in young and middle-aged and elderly severe patients. The worsening of the inflammatory state during hospitalization was the main reason for ICU admission in young and middle-aged severe patients, while worse cardiovascular function contributed more to ICU admission in elderly severe patients. The OR values of different variables for ICU admission in

**Table 4**
Association between hsCRP fluctuation and risk of ICU admission in severe patients.

| Age ≤ 60y | | Age > 60y | |
|---|---|---|---|
| Model | Odds Ratio (95% CI) | Model | Odds Ratio (95% CI) |
| **Model 1** | 1.066 (1.032, 1.100) | **Model 1** | 1.009 (1.005, 1.014) |
| **Model 2** | 1.064 (1.029, 1.100) | **Model 2** | 1.028 (1.014, 1.043) |
| **Model 3** | 1.068 (1.025, 1.113) | **Model 3** | 1.026 (1.011, 1.042) |
| Model 1- hsCRP fluctuation | | Model 1- proBNP | |
| Model 2- hsCRP fluctuation, proBNP | | Model 2- hsCRP fluctuation, proBNP | |
| Model 3- hsCRP fluctuation, GFR, ALT, proBNP | | Model 3- hsCRP fluctuation, GFR, ALT, proBNP | |

the young and middle-aged patients and the elderly patients are shown in Fig. 1.

### 3.5. Predictive ability of hsCRP fluctuation for ICU admission in young and middle-aged severe patients

Fig. 2 shows the ROC curve of hsCRP fluctuation for ICU admission in young and middle-aged severe patients. The area under the curve of hsCRP was 0.925 ($P < 0.001$) in young and middle-aged patients, which was statistically significant, indicating that hsCRP fluctuation was significantly predictive of ICU admission in young and middle-aged severe patients. The optimal cutoff value was 13.2 mg/L, with sensitivity of 92.9% and specificity of 95.5%. The AUC in the elderly severe patients was 0.528 ($P = 0.632$), which was not statistically significant. Therefore, hsCRP fluctuation in elderly severe patients had no predictive significance. After comparing the AUC of the two curves, the AUC in young and middle-aged severe patients was greater than that in the elderly patients ($Z = 4.49$, $P < 0.001$), indicating that hsCRP fluctuation reflecting the change in inflammatory state predicted critical COVID-19 progression in young and middle-aged severe patients, but not in elderly severe patients.

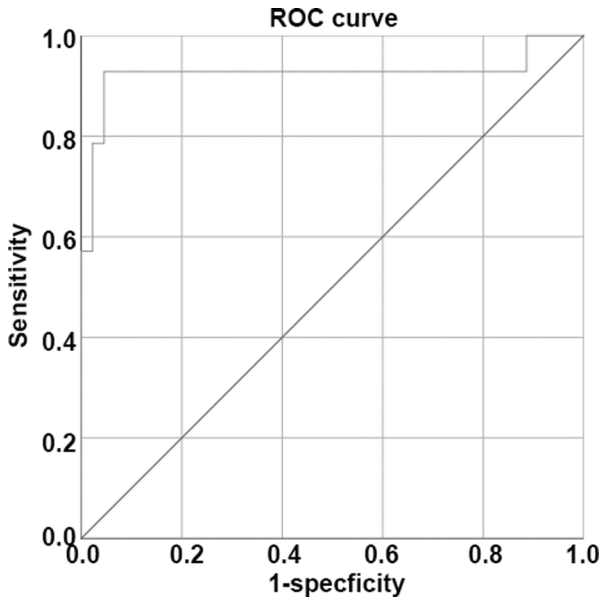


**Fig. 2.** ROC curve of hsCRP fluctuation for transfer to the ICU in young and middle-aged patients.

## 4. Discussion

The global outbreak of COVID-19 caused a substantial number of infections and deaths [5]. There are remarkable differences in the clinical features and risk factors affecting the outcome of COVID-19 between young and middle-aged severe patients to elderly severe patients [4]. These characteristics indicate different underlying mechanisms and main causes of critical COVID-19 in non-elderly and elderly severe patients, indicating the need for different treatments for patients of different ages. Although the mechanisms and treatments of COVID-19 have been demonstrated by numerous studies, there is a lack of research on the different reasons for disease progression to critical COVID-19 to distinguish between the clinical outcomes of non-elderly and elderly patients. According to the guidelines, glucocorticoid therapy was recommended for severe and critical COVID-19 patients for suppression of inflammation in addition to general supportive treatment and antiviral therapy [6]. However, there is no recommendation about different treatment strategies for patients of different ages.

We filled this gap by comparing clinical characteristics and risk factors in 273 severe COVID-19 patients diagnosed with COVID-19 in Tongji Hospital, Wuhan and we explored the relationship between predictive factors and ICU admission by multivariable logistic regression. Patients in Wuhan showed more typical features, and the disease had a high incidence in this susceptible population before the following virus mutations, which allowed for the assessment of the relationship between different clinical characteristics and clinical outcomes. The clinical implications of this study are that we proposed the differences in mechanisms and main causes of critical COVID-19 between severe young and middle-aged patients and severe elderly patients; moreover, we identified predictive factors and recommendations for treatment strategies in the non-elderly and elderly patients. We revealed that worsening of inflammatory state in young and middle-aged severe patients, which was indicated by an increased inflammatory response with elevated hsCRP fluctuation during hospitalization, was the main reason for ICU admission. However, acute inflammation in elderly critical patients was associated with remission during hospitalization and worse cardiovascular function contributed more to their admission to the ICU, implying an age-based differential immune response in critical patients. In addition, we provided predictive factors for clinical assessment of severe patients to predict critical COVID-19. The hsCRP fluctuation and proBNP were underlying predictive factors

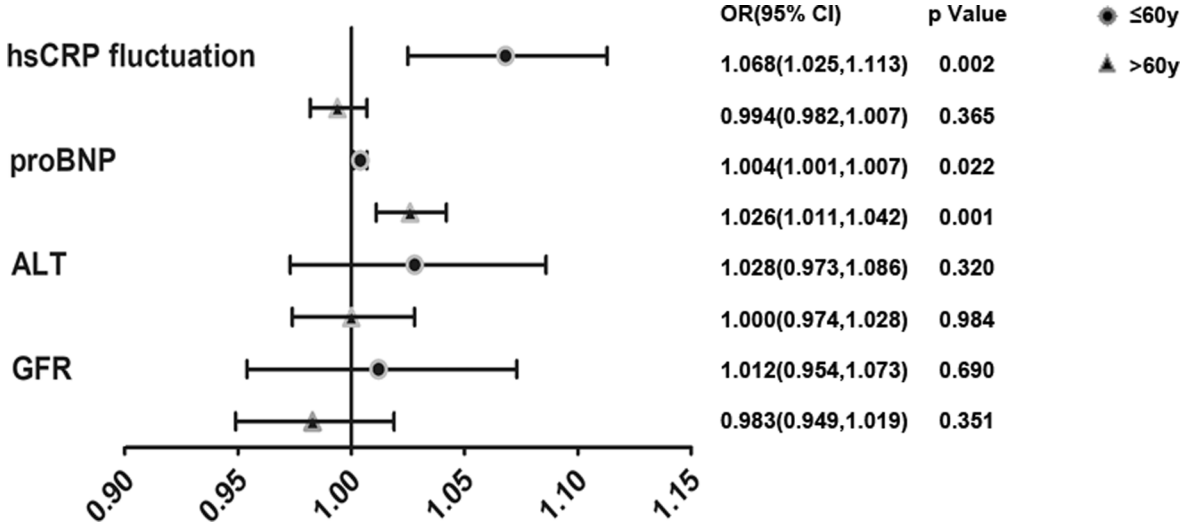


**Fig. 1.** OR values of different variables in young and middle-aged patients and the elderly patients.

for ICU admission in young and middle-aged and elderly severe patients, respectively. The ROC curve suggested that hsCRP fluctuation could be considered as an indicator of disease prognosis in young and middle-aged severe patients, and the cutoff value was 13.2 mg/L, indicating that young and middle-aged severe patients with hsCRP fluctuations over 13.2 mg/L compared with the level on the day of admission might have a poorer prognosis than patients with lower hsCRP fluctuations.

Thus this study proposed the association between the worsening of the inflammatory state and ICU admission in young and middle-aged severe patients, which was different from the findings in elderly severe patients. Recently, the preliminary studies reported that hyperactive immune responses mainly manifesting as increased inflammatory markers could be associated with COVID-19 disease severity and outcomes [8–10]. There was a proposed inflammatory model to explain the mechanism by which worsening of the inflammatory state was the main reason for critical COVID-19 in young and middle-aged patients that distinguished COVID-19 development into three stages [11]. The first stage is the asymptomatic stage with virus incubation; this stage then transitions to the second stage, the direct toxicity and inflammatory activation of the lung, leading to aggravation of respiratory symptoms. In the third stage, patients experience multisystem damage and loss of regulatory control of proinflammatory cytokine production, causing a cytokine storm and hyperinflammatory state, which develop a strong and lethal inflammatory response [11–14].

The heavier inflammatory response, which could be evaluated with hsCRP fluctuation, was able to predict clinical outcomes in young and middle-aged patients with other diseases in addition to COVID-19. It was suggested that changes in inflammatory state were associated with disease progression and hsCRP fluctuation was regarded as an indicator [15–19]. Although hsCRP is a sensitive indicator of disease activity and an independent risk factor for a variety of diseases [20,21], studies have demonstrated that hsCRP fluctuation is a better indicator of inflammation severity to guide treatment in sepsis, systemic inflammatory response syndrome (SIRS) and community-acquired pneumonia [15,22–24], indicating that low hsCRP fluctuation was related to better prognosis [23,24]. Studies on patients have suggested that compared to the initial hsCRP level itself, hsCRP fluctuation was a better indicator of the prognosis, which could control the bias due to patients' confounding factors [23–25]. Regarding COVID-19, changes in inflammation stimulation were also revealed to be closely associated with the disease progression and prognosis of COVID-19, which was indicated by hsCRP fluctuations. In previous studies, higher hsCRP fluctuation was related to an increase in the inflammatory response and was associated with disease prognosis in young and middle-aged patients [3,9,16,21,26], indicating a greater inflammatory response in critical patients than severe patients, which supported our finding. Furthermore, worsening of the inflammatory state was not only the main cause of poor COVID-19 prognosis, but this finding could also be extended to other coronaviruses, including severe acute respiratory syndrome (SARS) [27].

However, the remission of the inflammatory state during hospitalization in critical elderly patients reflected a lighter inflammatory response and different mechanisms of critical COVID-19 infection in elderly patients. Among elderly severe patients, hsCRP fluctuation was not predictive of ICU admission, revealing that the change in inflammatory state was not a determinant in the mechanism of disease progression in elderly severe patients Therefore, worsening of the inflammatory state was not the main reason for the development of critical COVID-19, and a decline in hsCRP was not associated with better outcome in elderly severe patients. The hsCRP fluctuation showed poor predictive ability of ICU admission, which was significantly different from the findings in the young and middle-aged critical patients. There are likely other mechanisms of critical COVID-19 development in elderly severe patients. We also found that proBNP was an independent risk factor for ICU admission in elderly patients, while hsCRP was not, indicating worse cardiovascular function associated with poor prognosis in elderly patients. Elderly patients had a higher prevalence of hypertension, which may also affect cardiovascular function [5].

In addition to the causes of critical COVID-19 infection, our study suggested different treatment recommendations for non-elderly and elderly severe patients, which are of great importance in clinical practice. The mechanisms of critical COVID-19 development indicated different responses to anti-inflammatory therapy in non-elderly and elderly severe patients. To date, anti-inflammatory drugs are applied for all patients in addition to anti-viral therapy and general therapy, including interleukin-6 inhibitors, interleukin-1 inhibitors and glucocorticoids [28]. When severe or critical COVID-19 patients' conditions deteriorate dramatically, low-dose glucocorticoids are recommended by the current guidelines [6]. Studies have also shown that the administration of corticosteroids might accelerate recovery from COVID-19 and decrease all-cause mortality in critically ill patients [29]. According to our results, early prevention of the worsening of the inflammatory state with glucocorticoid therapy should be considered the main treatment strategy to reduce the risk of ICU admission in young and middle-aged severe patients, since early remission of the inflammatory state predicted a good prognosis in young and middle-aged severe patients. Moreover, anti-inflammatory therapy with glucocorticoids may not be beneficial for the prevention of critical COVID-19 in elderly severe patients. Since decreased proBNP increased the risk of critical COVID-19 infection and a decline in hsCRP was not associated with better outcomes in elderly severe patients, anti-inflammatory therapy with glucocorticoids may increase the risk of cardiovascular injury by elevating the volume load in elderly severe patients. The potential best treatment options should emphasize the evaluation and improvement of cardiovascular function for elderly severe patients instead of anti-inflammatory therapy to avoid additional increased risks of ICU admission. More studies are needed to explore the role of aggravation of the inflammatory state in predicting the clinical outcome of elderly severe COVID-19 patients.

There were still some limitations in our study. First, we included a relatively small sample size in this study, because we included only critical and severe COVID-19 patients in one hospital and some of them did not undergo hsCRP examination, which may cause bias in the results. Additionally, only the maximum value of hsCRP was available to collect during the hospitalization with no temporal trends and dynamic curves.

## 5. Conclusion

In conclusion, this study revealed different characteristics and prognostic factors of ICU admission and offered insights into main causes of critical COVID-19 by comparing the young and middle-aged severe patients to the elderly severe patients. Moreover, we provided predictive factors and recommendations for treatment strategies for non-elderly and elderly severe patients. Worsening of the inflammatory state was the main cause of ICU admission in severe young and middle-aged COVID-19 patients. Anti-inflammatory therapy with corticosteroids should be considered in the early stage among non-elderly severe patients, but cardiovascular protection plays a more important role in elderly severe patients.

## CRediT authorship contribution statement

**Zhelong Liu:** Data curation, Investigation. **Danning Wu:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Xia Han:** Data curation. **Wangyan Jiang:** Data curation. **Lin Qiu:** Resources. **Rui Tang:** Project administration, Supervision. **Xuefeng Yu:** Resources.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

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