

# HsCRP Variation is the Main Risk Factor for Clinical Outcome in COVID-19 Hospitalized Young and Middle-Aged Patients

**Zhelong Liu**

Huazhong University of Science and Technology Tongji Medical College

**Danning Wu**

Peking Union Medical College Hospital <https://orcid.org/0000-0003-0968-7227>

**Xia Han**

Huazhong University of Science and Technology Tongji Medical College

**Wangyan Jiang**

Huazhong University of Science and Technology Tongji Medical College

**Lin Qiu**

Huazhong University of Science and Technology Tongji Medical College

**Rui Tang** (✉ [tangrui80@126.com](mailto:tangrui80@126.com))

**Xuefeng Yu**

Huazhong University of Science and Technology Tongji Medical College

---

## Research

**Keywords:** COVID-19, hsCRP variation, admission to ICU, young and middle-aged patients

**Posted Date:** July 7th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-40110/v1>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

**Background:** The clinical characteristics and risk factors of clinical outcomes of COVID-19 in elderly and non-elderly patients show great difference. We are the first to explore the relationship between hsCRP variation and intensive care unit (ICU) admission in young and middle-aged COVID-19 patients compared with elderly patients.

**Methods:** We included 273 hospitalized patients with confirmed COVID-19 from Tongji Hospital, Wuhan, China from Feb 10, 2020 to Mar 8, 2020. Clinical characteristics and risk factors of outcomes were compared between young and middle-aged patients with elderly patients.

**Results:** Among young and middle-aged patients, hsCRP variation in those admitted to ICU was significantly higher than that in discharged patients. Among patients admitted to ICU, hsCRP variation showed significantly difference between young and middle-aged patients and elderly patients (median, 67.9 vs -10.2,  $P < 0.01$ ). The hsCRP variation was an independent risk factor for ICU admission in young and middle-aged patients (OR = 1.068) and ROC curve revealed hsCRP variation significant for the prediction of ICU admission (AUC = 0.925) with 92.9% sensitivity and 95.5% specificity.

**Conclusion:** HsCRP variation is the major independent risk factors for ICU admission in young and middle-aged COVID-19 inpatients, but not in the elderly patients.

## Background

COVID-19 was confirmed to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus (1). According to the most recent situation report of the World Health Organization (WHO), the disease has covered nearly 7,300,000 diagnosed cases and over 410,000 deaths until Jun 11, 2020 (2). The clinical spectrum of this disease goes from asymptomatic infection to severe respiratory tract disease, and viral pneumonia is the main reason of patients' hospitalization and even 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).

The age of 60 is regarded as the cut-off time between the elderly population and the young and middle-aged population in China. Although the elderly and the young and middle-aged population are both likely to develop COVID-19, the elderly patients are more susceptible to severe illness with higher mortality (4). Comparing the young and middle-aged patients to the elderly patients, there is difference in the clinical characteristics as well as risk factors affecting the outcome of COVID-19. However, the current studies mainly focus on the whole age (3, 5), there remains lack of attention on the prognostic risk factors and treatment of young and middle-aged patients and elderly patients respectively.

C-reactive protein is an inflammatory biomarker which is produced from the liver and reflects patient's inflammatory state (6). High sensitivity C reactive protein (hsCRP) levels has been acknowledged to be an independent risk factor for predicting clinical outcome of various diseases (7). Nevertheless, there are

also studies that suggest the hsCRP variation as indicator of change in inflammatory stimulation intensity, which may be more substantial than hsCRP value itself (8, 9).

HsCRP level elevates significantly in COVID-19 inpatients and shows difference in severe and critically ill patients (10), suggesting that the variation of C-reactive protein may affect the development of the disease. It is reported that hsCRP level shows difference in elderly patients and non-elderly patient (4). However, there have been no studies on hsCRP variation in COVID-19 patients. Thus we are the first to explore the relationship between hsCRP variation and prognosis in the young and middle-aged patients, compared with elderly patients.

As admission to intensive care unit (ICU) is an important factor affecting in-hospital mortality and patient prognosis, the purpose of this study is to investigate the relationship between hsCRP variation and ICU admission in young and middle-aged COVID-19 patients compared with the elderly patients.

## Methods

### Study Design and Participants

A retrospective study was performed on COVID-19 patients hospitalized from Feb 10, 2020 to Mar 8, 2020, at Tongji Hospital in Wuhan, China. All patients were diagnosed as severe cases according to WHO guidance. According to the age, patients were divided into 2 groups: the elderly (more than 60 years old) and the young and middle-aged (no more than 60 years old). Patients who had no clinical outcome observed or less than 18 years old were excluded in this study.

### Data Collection

Data were extracted from the hospital's electronic medical record system, including patients' demographics, clinical characteristics, past history, laboratory examination on admission. Laboratory examination consisted of a complete blood count, blood chemical analysis, assessment of liver, renal and cardiovascular function, high sensitivity C reactive protein (hsCRP), procalcitonin (PCT). As disease progressed, maximum value of laboratory examination in hospital was also collected. HsCRP variation was obtained by calculating the difference between the maximum hsCRP value in hospital and hsCRP value on admission. Positive value indicated elevation of hsCRP, while negative value showed decline. Clinical outcomes of patients were observed and evaluated by admitted to intensive care unit (ICU) or discharged.

### Statistical Analysis

Categorical variables were represented as frequencies and percentages, and compared using the chi-square and Fisher's exact test. Continuous variables were represented as medians and interquartile ranges or mean and SD, compared using Mann–Whitney U test and t-test as appropriate. The association

between hsCRP variation and admission to ICU was evaluated by multivariable logistic regression. Three models were constructed to adjust potential confounding factors, including GFR, ALT and proBNP. The ROC curve was used to calculate the cut-off value of hsCRP variation. All statistical analyses and graphs were generated by using SPSS 25.0 and GraphPad Prism version 5, and p value < 0.05 was considered statistically significant.

## Results

### Demographic, clinical and laboratory characteristics of hospitalized patients

Table 1 shows the demographic, clinical and laboratory characteristics of hospitalized patients. A total of 273 hospitalized patients diagnosed as COVID-19 were included in this study, with 188 of them were over 60 years old, with an average age of 69.5 years old, and 85 patients were no more than 60 years old, with an average age of 51.0 years old. About half of patients were male both in the elderly patients (50.4%) and the young and middle-aged (55.3%). The prevalence of hypertension in the elderly patients is 58.5%, which is significantly higher than that in the young and middle-aged (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 the young and middle-aged patients (133 vs 123 mmHg,  $P < 0.01$ ), which was consistent with the hypertension history. In addition, the median oxygen saturation showed no difference in two groups (95%).

Table 1  
Demographic, clinical and laboratory characteristics of hospitalized patients

<b>Variables</b>	<b>Age ≤ 60y (n = 85)</b>	<b>Age &gt; 60y (n = 188)</b>	<b>P value</b>
Gender, No(%)			0.81
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(%)			0.00
No	53 (63.1%)	141 (41.5%)	
Yes	31 (36.9%)	46 (58.5%)	
Diabetes history			0.89
No	64 (85.1%)	101 (78.3%)	
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
Oxygen saturation, %	95 (95, 95) (n = 83)	95 (94.5, 95) (n = 182)	0.41
Hemoglobin, g/L	129 (116, 141) (n = 85)	125 (114, 134) (n = 186)	0.04
Leukocytes, ×10 <sup>9</sup> /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, ×10 <sup>9</sup> /L	265 (176, 330) (n = 83)	234 (168, 309) (n = 184)	0.17

<sup>a</sup>The in hospital value of hsCRP is the maximum value collected during hospitalization.

Variables		Age ≤ 60y (n = 85)	Age > 60y (n = 188)	P value
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
Procalcitonin (PCT), ng/mL		0.07 (0.06, 0.18) (n = 36)	0.08 (0.06, 0.17) (n = 97)	0.86
hsCRP, mg/L	Admission	9.4 (1.5, 50.6) (n = 85)	25.9 (2.5, 83.8) (n = 184)	0.02
	In hospital <sup>a</sup>	3.4 (1.0, 84.7) (n = 58)	14.9 (2.6, 52.6) (n = 129)	0.20
proBNP, ng/L		70 (30, 178) (n = 66)	184 (96, 559) (n = 164)	0.00
cTnl, ng/L		2.6 (1.9, 9.2) (n = 75)	6.3 (3.1, 16.0) (n = 168)	0.00
<sup>a</sup> The in hospital value of hsCRP is the maximum value collected during hospitalization.				

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

Laboratory examination on admission revealed that compared with the elderly group, the young and middle-aged hospitalized patients showed higher hemoglobin (HGB) (median, 129 vs 125,  $P = 0.04$ ), and there was no difference in leukocytes counts (median, 5.64 vs 5.70,  $P = 0.31$ ) and platelet counts (median, 265 vs 234,  $P = 0.17$ ). The young and middle-aged patients showed lower neutrophil percentage (median, 61.3 vs 71.6,  $P < 0.01$ ), higher lymphocyte percentage (median, 27.3 vs 19.0,  $P < 0.01$ ), higher ALT (median, 23 vs 20,  $P = 0.03$ ), higher Albumin (mean, 37.6 vs 34.4,  $P < 0.01$ ), lower total bilirubin (median, 7.2 vs 8.0,  $P = 0.02$ ) and lower direct bilirubin (median, 3.3 vs 3.7,  $P = 0.01$ ). Blood urea nitrogen (median,

4.3 vs 5.0,  $P < 0.01$ ), 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 the elderly on admission (median, 9.4 vs 25.9,  $P = 0.02$ ), but the hsCRP level in both the young and middle-aged patients and the elderly patients reduced significantly during hospitalization ( $P < 0.01$ ). The maximum hsCRP value in hospital in the young and middle-aged patients was still lower than that in the elderly, but showed no significance (median, 3.4 vs 14.9,  $P = 0.02$ ). As for 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 that in the elderly, indicating a greater impairment of cardiovascular function (Table 1).

## Characteristics Of Young And Middle-aged Patients

In young and middle-aged patients, 16 patients were admitted to ICU and 69 patients were discharged. Compared with discharged patients, laboratory examination of patients admitted to ICU showed higher leukocytes count on admission (median, 7.4 vs 5.2,  $P = 0.01$ ) and in hospital (median, 11.8 vs 5.5,  $P < 0.01$ ), higher neutrophil percentage (median, 82.4 vs 58.1,  $P < 0.01$ ), lower lymphocytes percentage (median, 6.9 vs 30.1,  $P < 0.01$ ), and lower platelet count (median, 175.5 vs 278,  $P < 0.01$ ). The total number of leukocytes in patients admitted to ICU increased significantly during hospitalization ( $P < 0.01$ ). The patients admitted to ICU had higher ALT (median, 38 vs 22,  $P = 0.01$ ), higher AST (median, 53.5 vs 21.0,  $P < 0.01$ ), higher ALP (median, 83.5 vs 67,  $P = 0.01$ ) and higher 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,  $P = 0.04$ ), 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 patients admitted to ICU than in discharged patients (Table 2).

Table 2  
Characteristics of young and middle-aged patients

Variables		Discharged (n = 69)	Admitted to ICU (n = 16)	P value
Hemoglobin, g/L		129 (122, 139) (n = 69)	133 (115, 134) (n = 16)	0.51
Leukocytes, × 10 <sup>9</sup> /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, × 10 <sup>9</sup> /L		278 (211, 334) (n = 67)	175.5 (127, 305) (n = 16)	0.03
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
proBNP, ng/L		51 (28, 113) (n = 55)	408 (70, 769) (n = 11)	0.01
cTnl, ng/L		2.2 (1.9, 6.1) (n = 61)	13.0 (4.1, 215.4) (n = 14)	0.00
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 variation, mg/L		-2.95 (-16.25, -0.1) (n = 44)	67.9 (36.9, 77.1) (n = 14)	0.00

As for the inflammatory indicators of young and middle-aged patients who were transferred to ICU, hsCRP (median, 89.7 vs 5.0,  $P < 0.01$ ) and PCT (median, 0.32 vs 0.06,  $P < 0.01$ ) were higher than those of discharged patients on admission, and the hsCRP variation of young and middle-aged patients admitted to ICU was 67.9 mg/L, indicating hsCRP increased during hospitalization, while hsCRP variation of discharged patients was - 2.95 mg/L indicating decreased hsCRP. The hsCRP variation in patients admitted to ICU was significantly higher than that in discharged patients ( $P < 0.01$ ).

## Characteristics Of Patients Admitted To Icu

Among the patients admitted to ICU, characteristics are showed in Table 3. The mean age of young and middle-aged patients was 50.8 years old and that of the elderly patients was 75.7 years old. The comparison between young and middle-aged patients and the elderly found 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 the young and middle-aged patients were significantly lower than that of the elderly. The young and middle-aged patients showed higher ALT (median, 38 vs 20,  $P = 0.01$ ), higher GGT (median, 54 vs 25,  $P < 0.01$ ) and higher GFR (median, 89.7 vs 72.7,  $P = 0.01$ ). The proBNP level of young and middle-aged patients was lower than that of the elderly (median, 408 vs 999,  $P < 0.01$ ). 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 of 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 patients who were admitted to ICU. However, the maximum hsCRP value in hospital of young and middle-aged patients was significantly higher than the elderly patients (median, 153 vs 65.2,  $P < 0.01$ ), as well as the hsCRP variation during hospitalization (median, 67.9 vs -10.2,  $P < 0.01$ ).

Table 3  
Characteristics of patients admitted to ICU

Variables	Age ≤ 60y (n = 16)	Age > 60y (n = 40)	P value	
Age, y	50.8 ± 11 (n = 16)	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	
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	
proBNP, ng/L	408 (70, 769) (n = 11)	988 (681, 4285) (n = 27)	0.01	
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 variation, mg/L	67.9 (36.9, 77.1) (n = 14)	-10.2 (-29.6, 12.7) (n = 35)	0.00	

### Risk factors for ICU admission in the young and middle-aged and the elderly patients

In young and middle-aged patients, Table 4 shows that the increase of hsCRP variation was significantly correlated with the increased risk of ICU admission. After excluding the interference of GFR, ALT and proBNP by multivariate logistic analysis, hsCRP variation was still an independent risk factor for ICU admission, and OR value was 1.068. Table 4 also shows that the increase of proBNP was correlated with the risk of ICU admission in the elderly patients (OR = 1.026), while hsCRP variation was not related to the risk of ICU admission in the elderly. The OR values of different variables for ICU admission in the young and middle-aged people and the elderly people are shown in Fig. 1 respectively.

Table 4  
Association between hsCRP variation and risk of ICU admission in 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 variation		Model 1- proBNP	
Model 2- hsCRP variation, proBNP		Model 2- hsCRP variation, proBNP	
Model 3- hsCRP variation, GFR, ALT, proBNP		Model 3- hsCRP variation, GFR, ALT, proBNP	

### Prediction of hsCRP variation on ICU admission in young and middle-aged patients

Figure 2 shows the ROC curve of hsCRP variation for ICU admission in young and middle-aged 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 was significant for the prediction of ICU admission in young and middle-aged patients. The optimal cut-off value was 13.2 mg/L, with sensitivity of 92.9% and specificity of 95.5%. The area under the curve in the elderly was 0.528 ( $P = 0.632$ ), which had no statistical significance. Therefore, the hsCRP variation in the elderly had no predictive significance. After comparing the AUC of the two curves, AUC in young and middle-aged patients was greater than that in the elderly patients ( $Z = 4.49$ ,  $P < 0.001$ ).

## Discussion

The global outbreak of COVID-19 caused horrendous number of infection and death (5). The clinical characteristics of COVID-19 showed remarkable difference in young and middle-aged patients and elderly patients (4). However, there is a lack of research on the risk factors of disease progression to distinguish between the young and middle-aged patients and the elderly patients. This study is the first study proposing the relationship between hsCRP variation and ICU admission in the young and middle-aged patients, compared with elderly patients. We filled the gap by comparing the characteristics of young and middle-aged patients with elderly patients in 273 hospitalized patients diagnosed with COVID-19 in Tongji hospital, Wuhan and evaluating the relationship between hsCRP variation and ICU admission by multivariable logistic regression.

Some studies suggested that hsCRP variation indicated the change in the intensity of inflammatory stimulation, which may be associated with disease progression and prognosis (8, 9, 11). CRP is an inflammatory biomarker produced by the liver, which is released into the blood during the acute phase of inflammation, while hsCRP is a sensitive indicator of disease activity and independent risk factor for a variety of diseases (7, 12). However, as hsCRP is affected by a variety of factors, studies suggested that

the hsCRP variation was also of important value, indicating that the change in the intensity of inflammatory stimulation may be more important than the hsCRP value itself (8, 9, 11).

Thus we focused on the association between hsCRP variation and ICU admission in the young and middle-aged patients, which was different from that in elderly patients. Baseline characteristics between the young and middle-aged patients and the elderly patients showed significant differences, indicating different factors affecting the ICU admission during hospitalization between two groups. On admission, the level of hsCRP in young and middle-aged patients was significantly lower than that in elderly patients, associated with lighter lung damage in COVID-19 (12), while they showed no significant difference in the maximum value of hsCRP during hospitalization, suggesting that hsCRP variation might be associated with disease progression and prognosis (13, 14). Among young and middle-aged patients, we found hsCRP variation was the main independent risk factor for ICU admission in young and middle-aged patients. HsCRP increased significantly during hospitalization, indicating intense inflammatory response in young and middle-aged patients admitted to the ICU, while hsCRP decreased in the discharged patients during hospitalization, indicating the improvement of inflammation. There was a proposed inflammatory model which distinguished COVID-19 development into three stages to explain hsCRP variation as an independent risk factor of the ICU admission in young and middle-aged patients (15). The first stage is the asymptomatic stage with virus incubation and then turns to the second stage, the direct toxicity and inflammatory activation of the lung, leading to aggravation of respiratory symptoms. In the third stage, patients experienced multi-system damage and hyperinflammatory state, which developed strong and lethal inflammatory response (15).

However, in the elderly patients, hsCRP variation was not the main risk factor of the ICU admission. At the time of admission, hsCRP level of elderly patients was significantly higher and suggested heavier basic infection due to the basic diseases and weaker defense barrier (4, 12). Poor cardiovascular function in elderly patients contributed to high hsCRP level on admission (16, 17). The hsCRP variation in the elderly patients admitted to ICU suggested a decrease of hsCRP during hospitalization, which showed significant difference to the young and middle-aged patients admitted to ICU. There may be two reasons for explaining the negative value of hsCRP variation in the elderly patients admitted to ICU. On the one hand, the elderly patients admitted to ICU experienced more severe dissociation of bilirubin and enzyme, suggesting more impairment of hepatic cells and lessor liver function reservation than young and middle-aged patients, which resulted in reduced hsCRP production (18, 19). In ICU patients, the elderly patients showed significantly lower ALT (median, 320 vs 38,  $P < 0.01$ ) and higher TBIL (median, 11.2 vs 9.5,  $P < 0.01$ ) than the young and middle-aged patients, suggesting more severe dissociation of bilirubin and enzyme in the elderly patients. Also among the elderly patients, TBIL was higher in patients admitted to ICU (median, 11.2 vs 7.8,  $P < 0.01$ ) and there was a significant difference in TBIL/ALT values compared with discharged patients. On the other hand, there might be an increased blood volume and diluted plasma hsCRP level due to heart failure of elderly patients admitted to ICU (20). The elderly patients admitted to ICU showed higher proBNP than discharged elderly patients (median, 988 vs 156.5,  $P < 0.01$ ) and young and middle-aged patients admitted to ICU (median, 988 vs 408,  $P = 0.01$ ), suggesting more severe heart failure in elderly patients admitted to ICU. 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 higher prevalence of hypertension, which may also affected in the cardiovascular function storage. In addition to controlling inflammation, improving cardiovascular function should be emphasized in treatment of elderly patients. More studies were needed to explore the role of aggravation of inflammation state in predicting the clinical outcome of elderly hospitalized patient.

Studies also showed hsCRP variation as a predictor of change in inflammation response and dynamic indicator of clinical outcome (21, 22). In sepsis patients, hsCRP increased early in multiple organ injury stage (23) and hsCRP decrease in survivors was significantly greater than that of non-survivor (9), which demonstrated the low hsCRP variation would lead to better prognosis. There were also studies that used the reduction of hsCRP as an indicator of sepsis and SIRS severity to guide treatment (11, 23–25), indicating that the reduction of hsCRP was related to the reduction of patients' mortality (24, 25). Studies on community acquired pneumonia patients suggested that compared to initial hsCRP itself, hsCRP variation was a better indicator of the prognosis, which could control the bias due to patients' confounding factors (25, 26).

Other studies on COVID-19 were searched in PubMed and we implemented the following search strategy with these key words (in the title/abstract): "COVID-19" OR "coronavirus" AND "hsCRP" OR "CRP" OR "characteristics" OR "laboratory". After excluding irrelevant articles, 17 studies with observed hsCRP value were found, among those 4 studies contained hsCRP variation and disease outcomes, including 3 in COVID-19 and 1 in SARS. In those studies, higher hsCRP variation was found to suggest an increase in inflammatory response and was associated with disease prognosis in young and middle-aged patients (3, 15). Young and middle-aged discharged patients showed decreased hsCRP with mean hsCRP variation as -18.6 mg/L (13, 21, 22), indicating a lighter inflammatory response in discharged patients consistent with our study. Also in SARS patients with mean age of 43, the hsCRP variation in patients admitted to ICU was significantly higher than that in discharged patients (122 vs 12 mg/L) (27). But in elderly COVID-19 patients with mean age of 69, hsCRP in those with poor prognosis as dead did not increase, but decreased with hsCRP variation as -27.65 mg/L instead (13).

Although in the studies above, none had clearly proposed the association between hsCRP variation and disease prognosis, the results still suggested that higher hsCRP variation was associated with the poor prognosis of young and middle-aged patients with coronavirus, but not in elderly patients, which proved the correctness of our finding. Furthermore, hsCRP variation was not only applied in indication of COVID-19 prognosis, but also could be extended to other coronavirus. In our study, the ROC curve suggested that hsCRP variation could be considered as an indicator of disease prognosis in young and middle-aged patients, and the cut-off value was 13.2 mg/L, indicating that young and middle-aged patients with the hsCRP variation over 13.2 mg/L compared with the day of admission might have a poor prognosis than patients with lower hsCRP variation.

There were still some limitations in our study. First, we included a relatively small sample size in this study, because we only covered COVID-19 hospitalized patients in one hospital and some of them didn't take the examination of hsCRP, which may cause bias in the results. Also, only the maximum value of hsCRP was available to collect during the hospitalization with no time span and dynamic curves.

## Conclusion

In conclusion, this study found that hsCRP variation was the major independent risk factors for ICU admission in young and middle-aged COVID-19 inpatients, but not in the elderly patients. Early detection of hsCRP variation is a good indicator of clinical outcome, and early prevention of deterioration of inflammatory state may reduce the risk of ICU admission in young and middle-aged patients.

## Abbreviations

AUC

Area under the curve; BUN:Blood urea nitrogen; CI:Confidence interval; DBP:Diastolic blood pressure; cTnl:Cardiac troponin I; DBIL:Direct bilirubin; GFR:Glomerular filtration rate; hsCRP:High sensitivity C reactive protein; ICU:intensive care unit; OR:Odds ratio; PCT:Procalcitonin; PLT:Platelet; SBP:Systolic blood pressure; SD:Standard deviation; TBIL:Total bilirubin; WBC:White blood cell count; WHO:World Health Organization

## Declarations

### Ethics approval and consent to participate

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 the Tongji Hospital, Huazhong University of Science and Technology (No.TJ-IRB20200404). Written informed consent was waived by the ethics commission for this retrospective study.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used for the analysis in the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

## Funding

This work was supported by National Major Scientific and Technological Special Project for Significant New Drugs Development (Grants No: 2017ZX09304022) and China Ying-cai Young Scientific Talent Research Project (Grant No: 2017-N-07).

## Authors' contributions

ZLL, WDN, RT and XFY designed the study. XH, WYJ, LQ, managed

data and its quality. ZLL and WDN performed the statistical analysis. All

authors participated in the data interpretation. WDN drafted the manuscript.

RT and XFY contributed substantially to its revision. All authors read the

manuscript carefully and approved the final version.

## Acknowledgements

We would like to thank the patient for their support and for providing their consent regarding the publication of this manuscript, and also thank the nursing staff for collection of the blood samples.

## Author details

<sup>1</sup>Department of Endocrinology, Tongji Hospital, Huazhong University of Science and Technology. <sup>2</sup>Eight-year Program of Clinical Medicine, Peking Union Medical College hospital, Chinese Academe of Medical Sciences & Peking Union Medical College, Beijing, 100730, China. <sup>3</sup>Department of Allergy, Peking Union Medical College hospital, Chinese Academe of Medical Sciences & Peking Union Medical College, Beijing, 100730, China. <sup>4</sup>Department of Pharmacy, Tongji Hospital, Huazhong University of Science and Technology

## References

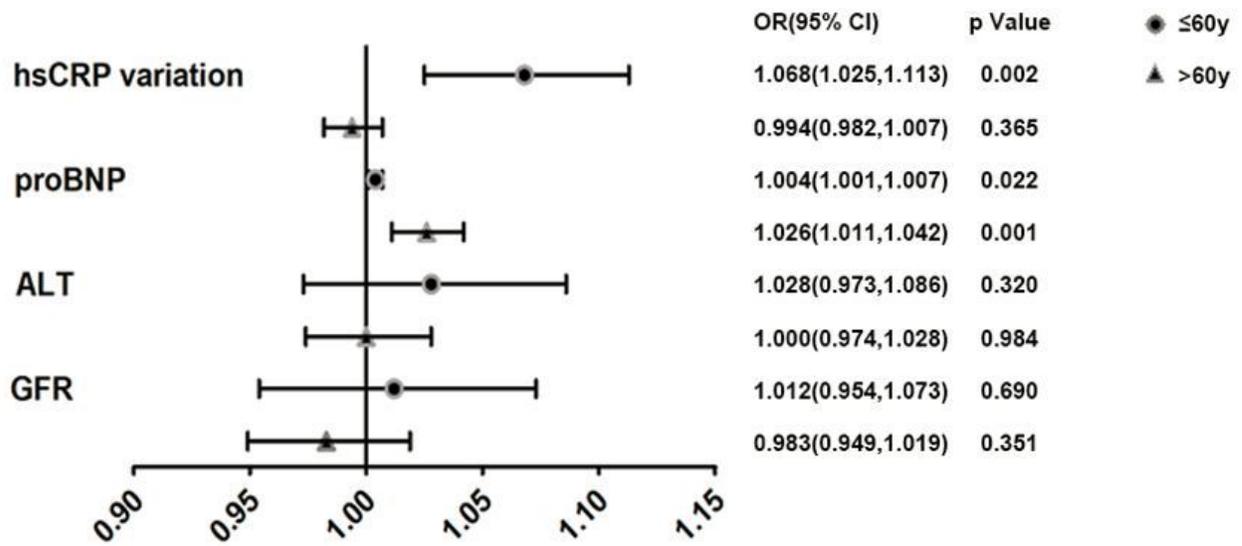
1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395(10224):565–74.
2. <https://>.
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507–13.
4. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. *The Journal of infection*. 2020.

5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–62.
6. Moutachakir M, Lamrani Hanchi A, Baraou A, Boukhira A, Chellak S. Immunoanalytical characteristics of C-reactive protein and high sensitivity C-reactive protein. *Ann Biol Clin*. 2017;75(2):225–9.
7. Li Y, Zhong X, Cheng G, Zhao C, Zhang L, Hong Y, et al. Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: A meta-analysis. *Atherosclerosis*. 2017;259:75–82.
8. Ranzani OT, Prada LF, Zampieri FG, Battaini LC, Pinaffi JV, Setogute YC, et al. Failure to reduce C-reactive protein levels more than 25% in the last 24 hours before intensive care unit discharge predicts higher in-hospital mortality: a cohort study. *J Crit Care*. 2012;27(5):525.e9-15.
9. Yentis SM, Soni N, Sheldon J. C-reactive protein as an indicator of resolution of sepsis in the intensive care unit. *Intensive care medicine*. 1995;21(7):602–5.
10. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA internal medicine*. 2020.
11. Hassan EA, Abdel Rehim AS, Ahmed AO, Abdullahtif H, Attia A. Clinical Value of Presepsin in Comparison to hsCRP as a Monitoring and Early Prognostic Marker for Sepsis in Critically Ill Patients. *Medicina (Kaunas, Lithuania)*. 2019;55(2).
12. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Science China Life sciences*. 2020;63(3):364–74.
13. Deng Y, Liu W, Liu K, Fang YY, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. *Chinese medical journal*. 2020.
14. Guan WJ, NZY, Zhong NS, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *Med Rxiv*. 2020. <https://doi.org/10.1101/2020.02.06.20020974>. [Epub ahead of print].
15. Atri D, Siddiqi HK, Lang J, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the Cardiologist: A Current Review of the Virology, Clinical Epidemiology, Cardiac and Other Clinical Manifestations and Potential Therapeutic Strategies. *JACC Basic to translational science*. 2020.
16. Peikert A, Kaier K, Merz J, Manhart L, Schafer I, Hilgendorf I, et al. Residual inflammatory risk in coronary heart disease: incidence of elevated high-sensitive CRP in a real-world cohort. *Clinical research in cardiology: official journal of the German Cardiac Society*. 2020;109(3):315–23.
17. Muhlestein JB, May HT, Galenko O, Knowlton KU, Otvos JD, Connelly MA, et al. GlycA and hsCRP are independent and additive predictors of future cardiovascular events among patients undergoing angiography: The intermountain heart collaborative study. *American heart journal*. 2018;202:27–32.
18. Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: A retrospective study. *Liver international: official*

journal of the International Association for the Study of the Liver. 2020.

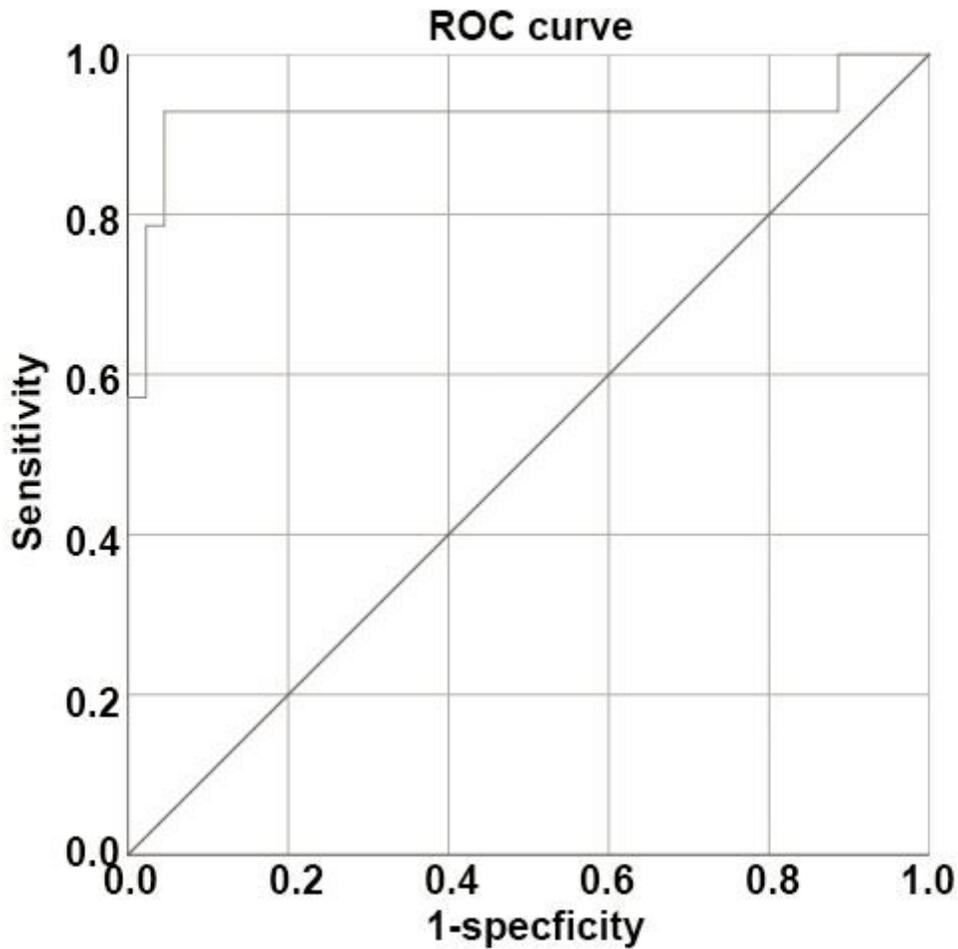
19. Horvatits T, Drolz A, Trauner M, Fuhrmann V. Liver Injury and Failure in Critical Illness. *Hepatology*. 2019;70(6):2204–15.
20. Hrymak C, Strumpher J, Jacobsohn E. Acute Right Ventricle Failure in the Intensive Care Unit: Assessment and Management. *Can J Cardiol*. 2017;33(1):61–71.
21. Liu F, Xu A, Zhang Y, Xuan W, Yan T, Pan K, et al. Patients of COVID-19 may benefit from sustained Lopinavir-combined regimen and the increase of Eosinophil may predict the outcome of COVID-19 progression. *International journal of infectious diseases: IJID : official publication of the International Society for Infectious Diseases*. 2020;95:183–91.
22. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *Journal of medical virology*. 2020.
23. Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. *Crit Care (London England)*. 2004;8(4):R234-42.
24. Claeys R, Vinken S, Spapen H, ver Elst K, Decochez K, Huyghens L, et al. Plasma procalcitonin and C-reactive protein in acute septic shock: clinical and biological correlates. *Critical care medicine*. 2002;30(4):757–62.
25. Lobo SM, Lobo FR, Bota DP, Lopes-Ferreira F, Soliman HM, Melot C, et al. C-reactive protein levels correlate with mortality and organ failure in critically ill patients. *Chest*. 2003;123(6):2043–9.
26. Pova P, Coelho L, Almeida E, Fernandes A, Mealha R, Moreira P, et al. Pilot study evaluating C-reactive protein levels in the assessment of response to treatment of severe bloodstream infection. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2005;40(12):1855–7.
27. Jang TN, Yeh DY, Shen SH, Huang CH, Jiang JS, Kao SJ. Severe acute respiratory syndrome in Taiwan: analysis of epidemiological characteristics in 29 cases. *J Infect*. 2004;48(1):23–31.
28. **LEGEND.**

## Figures



**Figure 1**

OR values of different variables in young and middle-aged patients and the elderly patients. The OR values of hsCRP variation, proBNP, ALT, GFR in the young and middle-aged people and the elderly people were shown with 95% CI and p value < 0.05 was considered statistically significant. The round symbol indicated OR values in the young and middle-aged patients, and the triangle symbol indicated OR values in the elderly patients.



**Figure 2**

ROC curve of hsCRP variation on transferring to ICU in young and middle-aged patients ROC analysis of hsCRP variation for ICU admission in young and middle-aged patients showed the area under the curve of hsCRP was 0.925 ( $P < 0.001$ ), indicating that hsCRP was significant for the prediction of ICU admission in young and middle-aged patients. The optimal cut-off value was 13.2 mg/L, with sensitivity of 92.9% and specificity of 95.5%.