Clinical features of COVID-19 patients with comorbid coronary heart disease

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1. A retrospective analysis of the clinical characteristics of patients of early COVID-19 with coronary heart disease.
2. explored possible mechanisms related to the effects of coronary heart disease on the pathogenesis of COVID-19.
3. Revealed coronary heart disease, high white blood cell counts, and low lymphocyte counts are pivotal predictive values for the pathophysiological progression of COVID-19.
Abstract

Background: In addition to the lungs, the coronavirus disease 2019 (COVID-19) also affects multiple organs throughout the body. The relationship between COVID-19 infection and cardiovascular disease, and the mechanisms by which this disease causes damage to the cardiovascular system are unclear. Coronary heart disease (CHD) is one of the common comorbidities of COVID-19, but there is insufficient evidence for its clinical features and impact on clinical outcomes. The aim of this study was to analyze the clinical characteristics of COVID-19 patients with comorbid CHD and the possible risk factors for the occurrence of critical illness.

Methods: A single-center, retrospective study was conducted to analyze COVID-19 patients admitted to the Sino-French New City Campus of Tongji Hospital in Wuhan, Hubei Province and treated by the Peking University National Medical Assistance Team between January 29 and March 10, 2020. Patients testing positive for SARS-CoV-2 viral nucleic acid in nasopharyngeal swab specimens and who had comorbid CHD, were included in the study. Clinical data and laboratory test results of eligible patients were collected, and the factors associated with the occurrence of critical illness among these patients were evaluated.

Results: A total of 205 patients were enrolled in this study, including 20 CHD patients and 185 non-CHD patients. The mean age was 66.7 years. Compared to non-CHD patients, more CHD patients had comorbid hypertension and diabetes ($P < 0.05$). In terms of laboratory tests, the CHD group did not differ significantly from the non-CHD group in blood routine, blood chemistry, and various inflammatory cytokines. More CHD patients experienced myocardial injury (25% vs 8.1% $P < 0.031$) and CHD patients were more likely to progress to critical illness (40% vs 16.8% $P = 0.012$).

Univariate logistic regression analysis indicated that a history of CHD, occurrence of myocardial injury, high white blood cell (WBC) count, low lymphocyte count, and elevated levels of Cr, ferritin, IL-2R, IL-8 at admission were factors associated with the occurrence of critical illness. Multivariate regression analysis found that a history of CHD ($OR=3.529$, 95% CI =1.032-12.075, $P =0.044$), high WBC count ($OR=1.289$, 95% CI =1.136-1.463, $P < 0.001$) and low lymphocyte count ($OR=0.215$, 95% CI =0.075-0.616, $P =0.004$) were independent factors for the occurrence of critical illness among COVID-19 patients.

Conclusion: COVID-19 patients with comorbid CHD commonly exhibited myocardial injury and were prone to developing critical illness. Among COVID-19 patients, a history of CHD, high WBC count and low lymphocyte count were independent risk factors for the occurrence of critical illness. Greater attention and vigilance are needed in this regard during clinical practice.

Keywords: COVID-19, coronary heart disease, risk factors, myocardial injury
Introduction

COVID-19 is a type of enveloped beta-coronavirus \cite{1}, and infections mainly affect the respiratory system, giving rise to typical symptoms, such as fever, cough, fatigue and dyspnea. In severe cases, hypoxemia, acute respiratory distress syndrome (ARDS) and multiple organ dysfunction may occur \cite{2}. Cardiovascular disease is a common comorbidity of COVID-19. Patients with cardiovascular disease have a higher prevalence of COVID-19, a higher rate of critical illness, and a higher mortality rate. However, the underlying mechanisms for this phenomenon are unclear \cite{3,4}.

In this study, the clinical characteristics and risk factors for critical illness among COVID-19 patients with coronary heart disease were analyzed to provide a basis for the early identification and diagnosis of high-risk patients.

Methods

A retrospective analysis was performed on COVID-19 patients admitted to the Sino-French New City Campus of Tongji Hospital in Wuhan, Hubei Province and treated by the Peking University National Medical Assistance Team between January 29 and March 10, 2020.

Data Collection

After patients were admitted to the hospital, their complete medical history was recorded, and measurements of their vital signs and blood oxygen saturation without oxygen inhalation were taken. The patients were then divided according to their condition into mild, normal, severe, and critical cases. The criteria for the clinical classification of patients was based on the “Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7)” released by the National Health Commission of the People’s Republic of China. The details are as follows: (1) Mild: patients with mild clinical symptoms and no imaging manifestations of pneumonia. (2) Normal: patients presenting with fever, respiratory tract and other symptoms, and imaging shows manifestations of pneumonia. (3) Severe: patients meeting any one of the following conditions: shortness of breath, respiratory rate (RR) > 30 breaths/min; resting peripheral oxygen saturation < 93%; arterial blood partial pressure of oxygen (PaO$_2$)/fraction of inspired oxygen (FiO$_2$) < 300 mmHg (1 mmHg = 0.133 kPa). (4) Critical: patients presenting with any one of the following conditions: respiratory failure requiring mechanical ventilation; shock; concomitant occurrence of other organ failures requiring treatment in the intensive care unit (ICU).

Upon admission, patients underwent complete measurements of blood routine, blood biochemistry, coagulation function, ferritin, markers of myocardial injury [high sensitivity cardiac troponin I (hs-cTnI) and creatine kinase-myocardial band (CK-MB)], inflammatory cytokines [ferritin, interleukin (IL)-1β, IL-2 receptor (IL-2R), IL-6, IL-8, IL-10, and tumor necrosis factor α (TNF-α)], and the presence of myocardial injury. Myocardial injury was based on the fourth universal definition of myocardial infarction issued by the European Society of Cardiology in September 2018 \cite{5}: hs-cTnI increase above the 99th percentile upper reference limit, i.e. hs-cTnI > 4.2 pg/mL. All patients were routinely tested for SARS-CoV-2 viral nucleic acid using nasopharyngeal or oral swabs.

Inclusion and exclusion criteria

Inclusion criteria were as follows: 1. aged 18 years and over; 2. patients diagnosed with COVID-19 based on the criteria described in the “Diagnosis and Treatment Protocol for
COVID-19 (Trial Version 7)”; 3. collection of a complete medical history.

Exclusion criteria were as follows: 1. patients who failed to complete tests of myocardial injury markers or inflammatory cytokines; 2. pregnant women; 3. patients with severe concomitant autoimmune diseases, hematological diseases or malignant tumors.

Statistical analysis

Statistical analysis was performed using SPSS 23.0. Categorical data were expressed as a percentage or ratio. Between-group comparisons were performed using Pearson’s chi-squared test or Fisher’s exact test. Continuous data with a normal distribution were expressed as the mean ± standard deviation. Continuous data with a non-normal distribution were expressed as the median (interquartile range, IQR). Between-groups comparisons were performed using an independent sample t-test or Mann-Whitney U tests. Univariate and multivariate logistic regressions were performed for risk factor analysis, and the results were expressed using the odds ratio (OR) and 95% confidence intervals (CI). P < 0.05 was considered statistically significant.
Results

A total of 205 patients were included in this study; 20 had coronary heart disease (CHD) and 185 were non-CHD patients. The mean age was 66.7 years. The basis for diagnosing a history of CHD was as follows: 1. past coronary angiography or coronary CT showing coronary stenosis of more than 50%; 2. past clinical symptoms of typical angina; 3. a clear history of acute myocardial infarction or old myocardial infarction.

The mean medical history of the 20 CHD patients was 7.7 years. One patient had myocardial bridging of the coronary artery, and seven patients had previously undergone percutaneous coronary intervention (PCI, one patient had undergone PCI twice). The specific concomitant symptoms are shown in Table 1.

| Symptom          | CHD patients (n = 20) | Non-CHD patients (n = 185) | X²   | P       |
|------------------|-----------------------|----------------------------|------|---------|
| Fever (%)        | 16 (80)               | 155 (83.8)                 | 0.187| 0.666   |
| Cough (%)        | 17 (85)               | 153 (82.7)                 | 0.067| 0.795   |
| Sputum (%)       | 14 (70)               | 105 (56.8)                 | 1.3  | 0.254   |
| Dyspnea (%)      | 11 (55)               | 118 (63.8)                 | 0.597| 0.44    |
| Headache (%)     | 5 (25)                | 55 (29.7)                  | 0.195| 0.659   |
| Sore throat (%)  | 6 (30)                | 40 (21.6)                  | 0.728| 0.398   |
| Fatigue (%)      | 10 (50)               | 94 (50.8)                  | 0.005| 0.945   |
| Nausea and vomiting (%) | 6 (30) | 60 (32.4) | 0.049 | 0.825 |
| Diarrhea (%)     | 5 (25)                | 83 (44.9)                  | 2.907| 0.088   |

Table 1: Concomitant symptoms of patients with COVID-19

Thirteen patients regularly used secondary preventive medication for CHD before admission, of whom 10 patients were treated with aspirin or clopidogrel antiplatelet therapy alone and 3 patients were treated with aspirin combined with clopidogrel antiplatelet therapy; 3 patients were treated with lipid-lowering drugs alone, 3 patients were treated with traditional Chinese medicine (TCM)/TCM preparations (Sanqi powder, Wenxin granules, or Baoxin pills), and 1 patient did not take medications regularly.

If patients were not contraindicated for antiplatelet drugs after admission, they continued to receive secondary preventive medication for CHD regularly, and close monitoring of their electrocardiogram (ECG), vital signs and whether they exhibited symptoms related to myocardial ischemia, such as chest tightness and chest pain, was performed. Seven patients experienced chest tightness and precordial discomfort during their hospital stay. Three patients complained that their symptoms had worsened significantly compared to before admission.

Among the 20 CHD patients, 4 patients died in hospital, while 16 patients recovered and were discharged. Among the deaths, one patient exhibited typical ischemic chest pain, anterior wall ST segment elevation in their ECG and a significant increase in myocardial injury markers during
their hospital stay, all of which point to the occurrence of acute myocardial infarction; the final
cause of death was cardiogenic shock. The other three patients died from multiple organ failure
associated with hypoxemia.

Patients were divided into the CHD and non-CHD groups for analysis, which revealed that more
CHD patients had comorbid hypertension and diabetes \( (P < 0.05) \). In terms of laboratory tests, the
CHD group did not differ significantly from the non-CHD group with respect to blood routine,
blood chemistry and various inflammatory cytokines. More CHD patients experienced myocardial
injury \( (P < 0.001) \) and CHD patients were more likely to progress to critical illness \( (P = 0.012) \)
(Table 2).
|                                | CHD group (n = 20) | Non-CHD group (n = 185) | t/Z/p²  | P    |
|--------------------------------|--------------------|-------------------------|---------|------|
| **General information**        |                    |                         |         |      |
| Age                            | 68.0 (58.3, 73.3)  | 64.0 (50.0, 69.5)       | -1.923  | 0.059|
| Male (%)                       | 13 (65.0)          | 94 (50.8)               | 1.456   | 0.228|
| **Medical history**            |                    |                         |         |      |
| Hypertension                   | 14 (70.0)          | 64 (34.6)               | 9.598   | 0.002|
| Diabetes                       | 7 (35.0)           | 29 (15.7)               | 4.656   | 0.031|
| **Blood routine**              |                    |                         |         |      |
| White blood cell (WBC) count (×10⁹/L) | 5.4 (4.2, 7.8) | 5.3 (4.3, 7.6)         | -0.016  | 0.987|
| Neutrophil count (×10⁹/L)      | 3.8 (2.6, 6.3)     | 3.9 (2.6, 5.6)         | -0.011  | 0.992|
| Lymphocyte count (×10⁹/L)      | 0.9 (0.7, 1.2)     | 1.0 (0.7, 1.4)         | -0.902  | 0.367|
| Platelet count (×10⁹/L)        | 247.0 (163.0, 303.0)| 210.0 (153.0, 283.5)   | -0.849  | 0.396|
| **Blood biochemistry**         |                    |                         |         |      |
| Alanine aminotransferase (ALT) | 22.5 (14.0, 32.5)  | 23.0 (15.0, 40.0)       | -0.645  | 0.519|
| Aspartate aminotransferase (AST)| 25.0 (19.0, 38.8)  | 28.0 (20.0, 43)         | -1.053  | 0.293|
| Albumin (ALB)                  | 31.6 (30.6, 38.8)  | 34.4 (31.2, 37.3)       | -0.293  | 0.77 |
| Total bilirubin (TBIL)         | 9.3 (6.4, 13.2)    | 8.9 (6.8, 13.4)         | -0.287  | 0.774|
| Blood creatinine (Cr)          | 93.0 (66.0, 148.8) | 71.5 (57.0, 86.0)       | -2.785  | 0.456|
| Blood urea nitrogen (BUN)      | 5.6 (3.6, 12.5)    | 4.3 (3.4, 6.1)          | -1.901  | 0.061|
| **Myocardial injury markers**  |                    |                         |         |      |
| CK-MB (ng/mL)                  | 1.4 (0.6, 4.0)     | 0.8 (0.5, 1.8)          | -1.594  | 0.111|
| hs-cTNI (pg/mL)                | 10.3 (3.5, 33.4)   | 4.6 (2.3, 11.1)         | -2.262  | 0.056|
| Presence of myocardial injury  | 5 (25)             | 15 (8.1)                | 5.849   | 0.031|
| **Inflammatory cytokines**     |                    |                         |         |      |
| Ferritin (µg/L)                | 626.0 (410.0, 896.0)| 729.0 (381.0, 1243.0)   | -0.537  | 0.591|
| IL-2R (U/mL)                   | 579.0 (221.0, 1063.0)| 716.0 (480.0, 1142.0)  | -1.266  | 0.22 |
| IL-6 (pg/mL)                   | 13.9 (5.7, 48.6)   | 19.4 (5.6, 45.3)        | -0.609  | 0.543|
| IL-8 (pg/mL)                   | 12.4 (5.0, 24.5)   | 14.9 (8.1, 27.4)        | -0.819  | 0.413|
| IL-10 (pg/mL)                  | 5.0 (5.0, 6.3)     | 5.0 (5.0, 7.48)         | -1.385  | 0.166|
| TNF-α (pg/mL)                  | 8.4 (5.6, 11.4)    | 9.0 (6.2, 12.2)         | -0.694  | 0.488|
| D-Dimer                        | 1.3 (0.5, 1.9)     | 1.2 (0.5, 2.0)          | -0.619  | 0.536|
| **Critical cases**             | 8 (40)             | 31 (16.8)               | 6.33    | 0.012|

Table 2: Statistical information and basic data of COVID-19 patients with comorbid CHD
Using univariate logistic regression analysis, we found that a history of CHD, occurrence of myocardial injury, high WBC count, low lymphocyte count, and elevated levels of Cr, ferritin, IL-2R, IL-8 at admission were factors related to the occurrence of critical illness in COVID-19 patients. Factors with $P < 0.1$ in the univariate analysis were included in the multivariate analysis model. Use backward LR method to filter variables, which indicated that a history of CHD, high WBC count and low lymphocyte count were independent risk factors of critical illness in COVID-19 patients (Table 3).

| Factor                        | Univariate regression | Multivariate regression |
|-------------------------------|-----------------------|-------------------------|
|                               | OR (95% CI)           | $P$                     | OR (95% CI)           | $P$                     |
| CHD history                   | 3.312 (1.250, 8.774)  | 0.016                   | 3.529 (1.032, 12.075) | 0.044                   |
| Neutrophil count (×10⁹/L)    | 1.256 (1.138, 1.385)  | <0.001                  | 1.289 (1.136, 1.463)  | <0.001                  |
| Lymphocyte count (×10⁹/L)    | 0.193 (0.078, 0.473)  | <0.001                  | 0.215 (0.075, 0.616)  | 0.004                   |
| Albumin (ALB)                | 0.909 (0.838, 0.986)  | 0.021                   |                         |                         |
| Blood creatinine (Cr)        | 1.003(1.000,1.006)    | 0.023                   |                         |                         |
| hs-cTNI (pg/mL)              | 1.001(1.000,1.001)    | 0.013                   |                         |                         |
| Ferritin (μg/L)              | 1.001(1.000,1.001)    | 0.007                   |                         |                         |
| IL-2R (U/mL)                 | 1.001(1.000,1.001)    | 0.021                   |                         |                         |
| IL-8 (pg/mL)                 | 1.014(1.001,1.027)    | 0.036                   |                         |                         |

Table 3: Logistic regression analysis of risk factors for critical illness in patients with COVID-19
Discussion

Cardiovascular disease is a common comorbidity among patients with COVID-19. COVID-19 patients with comorbid cardiovascular disease have a high incidence and high mortality rate. Among patients infected with COVID-19, the prevalence of diabetes and CHD was 11% and 8%, respectively, while the coexistence of these two conditions increased the risk of death by 12-fold [6-7]. In certain early reports on the clinical characteristics of COVID-19 cases in Wuhan, about 8%-15% of patients had comorbid CHD [3,4]. SARS-CoV-2 infection is achieved through the binding of the spike protein on the surface of the virus to human angiotensin converting enzyme 2 (ACE2) receptors [8]. ACE2 is mainly expressed in alveolar type II cells [9]; hence, pulmonary manifestations are the most typical and prominent of COVID-19 patients. ACE2 is also highly expressed in the heart, where its role is to counteract the overactivation of ACE2 in the renin-angiotensin system caused by factors, such as hypertension, congestive heart failure and atherosclerosis [10]. Patients with cardiovascular disease have relatively high levels of ACE2, and some scholars believe that this may be one of the possible mechanisms underlying the high prevalence of COVID-19 among them [11].

Chen R et al. [12] analyzed the clinical features of 1,590 patients with COVID-19, and found that having a history of CHD is a factor associated with a fatal outcome. This could be mainly attributed to the fact that COVID-19 infection can cause severe inflammation storms. On the one hand, this can promote thrombosis and myocardial infarction. On the other hand, the virus or inflammation can directly cause myocardial injury [13,14]. These effects may be especially pronounced among CHD patients with underlying coronary artery lesions. Our findings indicated that COVID-19 patients with comorbid CHD were more susceptible to myocardial injury and more likely to progress to critical illness. The main feature of myocardial injury is the elevation of myocardial injury markers. Zhou F et al. [3] found that 7.2% of COVID-19 inpatients have myocardial injury (elevated hs-cTnI, or new ECG or echocardiography abnormalities). Furthermore, non-survivors showed an increasing trend in hs-cTnI compared to survivors. Another multi-center, retrospective study with 1,099 COVID-19 patients [15] found that compared to patients who do not experience endpoint events, a higher proportion of patients who experience composite endpoint events (including ICU admission, mechanical ventilation, and death) show elevated myocardial injury markers ($P = 0.021$). A small number of cardiac injuries related to COVID-19 manifest as stress cardiomyopathy or fulminant myocarditis [16-18]. Currently, the exact mechanisms underlying the myocardial injury in COVID-19 patients are unclear. It has been speculated that myocardial injury may be related to direct damage inflicted by the virus on cardiomyocytes, severe hypoxemia and high-grade inflammation. Our study suggests that for COVID-19 patients with comorbid CHD, myocardial injury is a clinically important issue that should not be overlooked.

Zhou X [19] et al indicated that in the early phase of infection, platelet inhibition may reduce intravascular fibrin and thrombus formation, thereby preventing the ensuing consequences. But we also need safety concerns regarding dual antiplatelet therapy on life-threatening bleeding complications among COVID-19 infected patients, especially the risk for diffuse alveolar hemorrhage. In our study, patients with coronary heart disease continued to receive regular antiplatelet therapy during the treatment period, and no fatal bleeding event was detected.

SARS-CoV and Middle East respiratory syndrome (MERS)-CoV infections induce an inflammatory response, activate dendritic cells, monocytes and other peripheral blood
mononuclear cells (PBMCs), and upregulate proinflammatory cytokines such as TNF and IL-6. The levels of these inflammatory cytokines are higher in critical cases than in mild cases \(^{[20]}\). Existing research has also shown that cytokines storms can be observed in COVID-19 patients, with significantly elevated levels of various cytokines in the blood \(^{[21]}\). We found that elevated levels of the cytokines IL-2R and IL-8 were factors associated with the occurrence of critical illness. These findings supported the view that high-grade inflammation occurred in patients with COVID-19. Furthermore, a higher WBC count implied that the patient might have other infections that worsen their condition. The study by Zheng Z et al. \(^{[22]}\) shows that for patients with COVID-19, low WBC count signifies better clinical outcomes. Our study also found that high WBC count was an independent risk factor for COVID-19 patients to develop critical illness.
Conclusion

In summary, our research findings indicated that concomitant myocardial injury was common among COVID-19 patients with comorbid CHD, and such cases were prone to develop into critical illness. Among COVID-19 patients, a history of CHD, occurrence of myocardial injury, high WBC count, low lymphocyte count, and elevated levels of Cr, BUN, ferritin, IL-2R, IL-8 and D-dimer at admission were factors associated with the occurrence of critical illness. Additionally, a history of CHD, high WBC count and low lymphocyte count were independent risk factors of critical illness.

The limitations of this study were as follows:
This was a single-center retrospective study with a small sample size. It will affect the efficiency of the logistic regression model. Some of the clinical indicators, such as NT-ProBNP, oxygen saturation without inhalation at admission and deaths within 30 days were incomplete, and hence were not included in the study. Furthermore, aside from the 20 patients with CHD, the remaining patients were not followed up. Attention should be given to the long-term prognosis of these patients.

Ethical Approval and Consent to participate
This work is approved by Peking University Third Hospital Medical Science Research Ethics Committee. Project Number: IRB00006761-M2020060. All the data of the patients were used with the written consent of themselves or their family members.

Consent for publication
Written informed consent for publication was obtained from all participants.

Availability of supporting data
The data sets supporting the results of this article are included within the article.

Competing interests
The authors declare that they have no competing financial interests.

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Authors' contributions
Hang Yang and Yunpeng Ling designed the concept.
Hang Yang wrote the manuscript, designed tables.
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