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Cardiac injury on admission linked to worse outcomes in hospitalized COVID-19 patients

Povezanost oštećenja srca na prijemu u bolnicu sa lošim ishodom kod obolelih od COVID-19

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Abstract

Background/Aim. The novel severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) has triggered a pandemic that causes a disease with complex clinical manifestations (coronavirus disease 2019, COVID-19). Soon it became clear that patients who had some comorbidities had a bigger chance of getting the severe form of COVID-19. The aim of the study was to investigate if there was a link between cardiac injury and COVID-19 severity and mortality in patients. **Methods**. All consecutive patients with laboratory-confirmed COVID-19 were included and followed up until discharge or death from January 30, 2020, to April 5, 2020. **Results**. A total of 261 COVID-19 patients were included, and 29 (11.1%) had cardiac injury on admission. Patients with cardiac injury were older than those without cardiac injury (72.8 *vs* 55.8 years old) and more likely to be male (82.8% *vs* 42.2%). Patients with cardiac injury were also more likely to be smokers (31.0% *vs* 12.5%), more likely to have chronic cardiovascular disease (24.1% *vs* 7.8%), chronic pulmonary disease (17.2% *vs* 3.0%), and chronic kidney disease (10.3% *vs* 2.2%) compared to patients without cardiac injury. Laboratory findings suggested that patients with cardiac injury were more likely to have leukocyte counts > 10×10^9/L, pronounced lymphopenia, direct bilirubin, myohemoglobin, blood urea nitrogen, C-reactive protein, and pro-B-type natriuretic peptide but lower levels of serum total protein and estimated glomerular filtration rates compared to patients without cardiac injury. Patients with cardiac injury experienced more complications (72.4% *vs* 47.8%), including acute respiratory distress syndrome (20.7% *vs* 2.7%), acute kidney injury (10.3 *vs* 0.4%), severe COVID-19 (58.6% *vs* 11.6%) and death (55.2% *vs* 3.9%) compared to patients without cardiac injury. Multivariate analyses showed that cardiac injury was associated with an increased risk of severe COVID-19 [hazard ratio (HR) = 8.71, 95% confidence interval (CI) = 2.37−32.04] and death (HR = 20.84, 95% CI = 1.32−328.22). **Conclusion**. Cardiac injury on admission was associated with a higher risk of disease progression and death in patients with COVID-19.

Key words:
patient admission; cardiovascular diseases; COVID-19; disease progression; mortality; prognosis; risk factors; cardiomyopathies.

Apstrakt

Uvod/Cilj. Novi korona virus *severe acute respiratory syndrome coronavirus 2* (SARS-Cov-2) izazvao je pandemiju bolesti sa složenim kliničkim manifestacijama (*coronavirus disease 2019,* COVID-19). Ubrzo je postalo jasno da su bolesnici sa određenim komorbiditetima imali veću šansu da obole od teškog oblika COVID-19. Cilj rada bio je da se utvrdi povezanost između oštećenja srca (OS) i težine bolesti i mortaliteta kod obolelih od COVID-19. **Metode**. Svi bolesnici sa laboratorijski potvrđenim COVID-19 bili su uključeni i praćeni do otpusta ili smrti u periodu od 30. januara 2020. do 5. aprila 2020. **Rezultati**. Ukupno je bilo obuhvaćeno 261 bolesnika sa COVID-19, od kojih je 29 (11,1%) imalo OS pri prijemu. Bolesnici sa OS bili su starijeg životnog doba od bolesnika bez OS (72,8% *vs* 55,8%) i većina (82,8% *vs* 42,2%) su bili muškarci. Bolesnici sa OS su češće bili pušači (31,0% *vs* 12,5%), imali hroničnu kardiovaskularnu bolest (24,1% *vs* 7,8%), hroničnu bolest pluća (17,2% *vs* 3,0%) kao i hroničnu bolest bubrega (10,3% *vs* 2,2%) u poređenju sa bolesnicima bez OS. Prema laboratorijskim analizama, bolesnici sa OS su značajno češće imali vrednosti leukocita više od 10×10^9/L, izraženiju limfopeniju, više vrednosti direktnog bilirubina, miohemoglobina, uree u krvi kao i C-reaktivnog proteina i pro-B-tipa natriuretičkog peptida, ali niže nivoe ukupnih proteina u serumu i procenjene stope glomerularne filtracije, u poređenju sa bolesnicima bez OS. Bolesnici sa OS imali su više komplikacija (72,4% *vs* 47,8%), uključujući sindrom akutnog respiratornog distresa (20,7% *vs* 2,7%), akutno oštećenje bubrega (10,3% *vs* 0,4%), teški oblik COVID-

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19 (58,6% *vs* 11,6%) kao i veću smrtnost (55,2% *vs* 3,9%) u poređenju sa bolesnicima bez OS. Multivarijantne analize su pokazale da je OS povezano sa povišenim rizikom od obolevanja od teškog oblika COVID-19 (HR = 8,71, 95% CI = 2,37–32,04) i smrti [*hazard ratio* (HR) = 20,84, 95% *confidence interval* (CI) = 1,32−328,22]. **Zaključak**. Oštećenje srca na prijemu u bolnicu kod bolesnika sa COVID-19 bilo je povezano sa višim rizikom od progresije bolesti i smrtnog ishoda.

Ključne reči:
bolesnik, prijem; kardiovaskularne bolesti; COVID-19; bolest, progresija; mortalitet; prognoza; faktori rizika; kardiomiopatije.

Introduction

Since its first outbreak in Wuhan, Hubei, China, in December 2019, coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread across the whole world. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic [1].

The clinical outcome of COVID-19 patients who already have cardiovascular disease (CVD) appears to be worse [2–5]. COVID-19 can cause progressive cardiac injury and worsen the condition in patients who already had cardiac injury through multiple mechanisms, which are closely related to the severity of the disease and the prognosis of death. A small sample size study found that 12% of COVID-19 patients had acute cardiac injury manifesting as an ejection fraction decrease and troponin I (TNI) elevation [6]. Another study involving 416 hospitalized patients suggested that 19.7% of patients had COVID-19-associated cardiac injury and presented with significantly elevated levels of creatine kinase-MB (CK-MB), myohemoglobin (Mb), hypersensitive troponin I (hs-TNI), and N-terminal (NT) pro-B-type natriuretic peptide (NT-proBNP). Notably, COVID-19 patients with cardiac injury had a much higher mortality rate than those without cardiac injury, according to Shi et al. [7]. Another study from Wuhan also confirmed that cardiac injury is significantly associated with fatal outcomes from COVID-19. Cardiac injury was an independent risk factor for mortality from COVID-19 [8].

However, there have been few studies on the characteristics of cardiac injury and its related risks in COVID-19 patients. This study aimed to explore the characteristics of cardiac injury and the prognoses of COVID-19 patients with cardiac injury. Early assessment of myocardial injury in patients with COVID-19 and the development of a targeted cardio protective program can improve the poor prognosis of patients.

Methods

Patients' characteristics

A total of 1,087 patients with COVID-19 were recruited from Hubei and Sichuan Provinces from January 30, 2020, to April 5, 2020. This study was approved by the Ethics Committee of West China Hospital, Sichuan University, and Hubei Red Cross Hospital, Wuhan [2020 (272)]. All of the patients were at least 18 years old. Clinical information was collected, including demographic data, comorbidities, symptoms, laboratory findings, treatment measures, and outcomes. Cardiac biomarkers measured on admission were collected, including hs-TNI, CK-MB, and Mb. Pediatric and asymptomatic patients and those without cardiac biomarkers (hs-TNI) were excluded. Finally, 261patients with complete cardiac markers and complete clinical outcomes were included in this study. All of the patients were followed up until discharge or death.

Cardiac injury was identified when blood levels of hs-TNI were greater than the 99th-percentile upper reference limit, regardless of any new electrocardiographic and echocardiographic abnormalities. All patients were divided according to the presence or absence of cardiac injury into two groups: a group of patients with cardiac injury and a group of patients without cardiac injury. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition [9]. Liver dysfunction was diagnosed based on aminotransferase and bilirubin levels greater than the upper reference limits of the local hospital. Acute kidney injury (AKI) was defined according to the definition from Kidney Disease: Improving Global Outcomes [10].

COVID-19 and severity definition

The patients with severe COVID-19 enrolled in this study were diagnosed according to the guidelines for the diagnosis and treatment of COVID-19 and confirmed by RNA detection of SARS-CoV-2 by nasopharyngeal swab. The severity of COVID-19 was defined according to the diagnostic and treatment guidelines for SARS-CoV-2 issued by the Chinese National Health Committee (version 7) [11]. Severe COVID-19 was designated when the patient had one of the following criteria: (1) respiratory distress with respiratory frequency $\geq$ 30/min; (2) surplus pulse oximeter oxygen saturation $\leq$ 93% at rest; (3) oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, PaO2/FiO2) $\leq$ 300 mmHg; (4) respiratory failure and mechanical ventilation required; (5) shock; or (6) other organ failure requiring intensive care unit monitoring and treatment.

Statistical analyses

Descriptive statistics were obtained for all of the study variables. Categorical variables were summarized as percentages and compared using the χ^2 test or Fisher's exact test (if the expected number was less than five). Continuous variables were expressed as the mean value, standard deviation (SD), or median with interquartile ranges and compared using Student's *t*-test or the Mann-Whitney *U* test, if appropri-

ate. Logistic regression analysis was performed to determine the predictors of cardiac injury and the predictive value of cardiac injury in the disease progression and mortality. Variables with $p < 0.1$ in the univariate analysis were included in the multivariate logistic analysis. Statistical analysis was conducted using SPSS software, version 25.0 (IBM, Chicago, IL, USA). The value of $p < 0.05$ was considered statistically significant.

Results

Patients' characteristics

Out of the 261 patients included, 29 (11.1%) had cardiac injury on admission. Compared with patients without cardiac injury, patients with cardiac injury were older (72.8 ± 13.7 *vs* 55.8 ± 13.9, $p < 0.001$) and more likely to be male (82.8% *vs* 42.2%, $p < 0.001$) and smokers (31% *vs* 12.5%, $p = 0.021$). Comorbidities, including CVD (24.1% *vs* 7.8%, $p = 0.012$), chronic pulmonary disease (17.2% *vs* 3%, $p = 0.005$) and chronic kidney disease (CKD) (10.3% *vs* 2.2%, $p = 0.047$), were more prevalent among the patients with cardiac injury (Table 1).

The laboratory findings are shown in Table 2. Patients with cardiac injury were more likely to have leukocyte counts > 10×10^9/L (21.4% *vs* 6.5%), lymphopenia (58.6% *vs* 24.0%), and lower antithrombin III (90.2% *vs* 81.3%) compared to patients without cardiac injury. They also had a higher international normalized ratio (INR) (1.10 *vs* 1.02), total bilirubin (17.19 *vs* 11.20, μmol/L), direct bilirubin (7.14 *vs* 3.87, μmol/L), aspartate aminotransferase (55.12 *vs* 32.29, IU/L), creatine kinase (469.83 *vs* 85.83, IU/L), Mb (283.9 *vs* 49.9, IU/L), hs-TNI (2.83 *vs* 0.01, ng/mL), blood urea nitrogen (14.18 *vs* 5.31, mmol/L), uric acid

Table 1

Demographic and clinical characteristics of included patients

Characteristics	Cardiac injury (n = 29)	Without cardiac injury (n = 232)	*p*-value
Age (years), mean (SD)	72.76 (13.72)	55.76 (13.94)	< 0.001
Period from first symptoms to hospital admission (days), mean (SD)	4.62 (6.86)	3.78 (4.27)	0.522
Sex, n (%)			
male	24 (82.8)	98 (42.2)	< 0.001
female	5 (17.2)	134 (57.8)	
Drinking, n (%)			
yes	26 (89.7)	204 (87.9)	1
no	3 (10.3)	28 (12.1)	
Smoking, n (%)			
yes	20 (69.0)	203 (87.5)	0.021
no	9 (31.0)	29 (12.5)	
Chronic CVD, n (%)			
yes	7 (24.1)	18 (7.8)	0.012
no	22 (75.9)	214 (92.2)	
CPD, n (%)			
yes	5 (17.2)	7 (3.0)	0.005
no	24 (82.8)	225 (97)	
CKD, n (%)			
yes	3 (10.3)	5 (2.2)	0.047
no	26 (89.7)	227 (97.8)	
CLD, n (%)			
yes	2 (6.9)	10 (4.3)	0.627
no	27 (93.1)	222 (95.7)	
Cancer, n (%)			
yes	3 (10.3)	7 (3)	0.089
no	26 (89.7)	225 (97)	
Diabetes, n (%)			
yes	4 (13.8)	40 (17.2)	0.796
no	25 (86.2)	192 (82.8)	
Hypertension, n (%)			
yes	14 (48.3)	71 (30.6)	0.061
no	15 (51.7)	161 (69.4)	
Temperature on admission (°C), mean (SD)	36.7 (0.6)	36.8 (0.7)	0.567
Heart rate (beats/min), mean (SD)	89 (15)	89 (14)	0.779
Systolic blood pressure (mmHg), mean (SD)	132 (16)	129 (16)	0.347
Diastolic blood pressure (mmHg), mean (SD)	80 (11)	77 (10)	0.374
Respiratory rate (breaths/min), mean (SD)	22 (6)	21 (3)	0.124

CVD – cardiovascular disease; CPD – chronic pulmonary disease; CKD – chronic kidney diseases; CLD – chronic liver disease; SD – standard deviation.

Table 2

Laboratory findings between patients with and without cardiac injury

Parameters	Cardiac injury (n = 29)	Without cardiac injury (n = 232)	*p*-value
WBC (> 10 × 10^9/L), n (%)	6 (21.4)	14 (6.5)	0.016
Lymphopenia (< 1.5 × 10^9/L), n (%)	17 (58.6)	52 (24)	< 0.001
Neutrophils (%), mean (SD)	76.86 (17.98)	64.65 (14.71)	0.001
Eosinophils (%), mean (SD)	0.62 (1.2)	1.2 (1.58)	0.064
Basophils (%), mean (SD)	0.28 (0.22)	0.41 (0.32)	0.006
Monocytes (%), mean (SD)	6.05 (3.63)	8.2 (3.9)	0.007
Hematocrit (%), mean (SD)	0.36 (0.08)	1.17 (5.99)	0.467
D-dimer (ng/mL), mean (SD)	13.47 (34.66)	1.64 (2.99)	0.082
Fibrinogen (FIB) (g/L), mean (SD)	9.5 (22.69)	5.08 (8.74)	0.325
Antithrombin III (ATIII) (%), mean (SD)	81.33 (16.71)	90.22 (12.06)	< 0.001
APTT (S), mean (SD)	29.04 (3.57)	27.94 (3.77)	0.152
PT (S), mean (SD)	14.52 (9.42)	12.25 (4.7)	0.227
INR, mean (SD)	1.1 (0.17)	1.03 (0.12)	0.006
TBIL (μmol/L), mean (SD)	17.19 (10.76)	11.2 (6.06)	0.008
DBIL (μmol/L), mean (SD)	7.14 (4.51)	3.87 (2.24)	0.001
IBIL (μmol/L), mean (SD)	8.04 (3.29)	7 (2.97)	0.204
ALT(U/L), mean (SD)	48.64 (54.61)	35.48 (43.57)	0.255
AST (U/L), mean (SD)	55.12 (38.57)	32.29 (53.07)	0.038
Serum total protein (g/L), mean (SD)	59.39 (5.22)	62.64 (6.52)	0.013
ALB (g/L), mean (SD)	34.49 (4.2)	38.76 (4.6)	< 0.001
GLB (g/L), mean (SD)	25.3 (3.42)	24.14 (4.29)	0.178
TG (mmol/L), mean (SD)	1.58 (0.93)	1.43 (0.83)	0.39
CHOL (mmol/L), mean (SD)	3.81 (0.78)	4.29 (2.84)	0.396
HDL-C (mmol/L), mean (SD)	0.9 (0.35)	1.07 (0.4)	0.038
LDL-C (mmol/L), mean (SD)	2.35 (0.83)	2.56 (0.79)	0.215
CK (U/L), mean (SD)	469.83 (730.67)	85.63 (87.63)	0.019
CK-MB (U/L), mean (SD)	4.73 (6.4)	2.53 (15.44)	0.466
Glucose (mmol/L), mean (SD)	7.1 (3.28)	6.89 (5.28)	0.842
BUN (mmol/L), mean (SD)	14.18 (15.05)	5.31 (6.15)	0.005
Serum creatinine (μmol/L), mean (SD)	158.77 (295.95)	63.17 (28.95)	0.105
eGFR (mL/min/1.73 m^2), mean (SD)	65.49 (31.56)	103.45 (22.61)	< 0.001
Uric acid (μmol/L), mean (SD)	372.63 (233.75)	273.99 (101.08)	0.039
Hypersensitive troponin-I (ng/mL), mean (SD)	2.83 (8.55)	0.01 (0)	0.006
Mb (U/L), mean (SD)	283.9 (300.15)	49.9 (65.08)	< 0.001
CD3 (%), mean (SD)	60.86 (11.85)	67 (10.29)	0.016
CD4 (%), mean (SD)	39.17 (8.01)	41.54 (9.52)	0.31
CD8 (%), mean (SD)	18.71 (9.19)	28.07 (41.51)	0.329
CD3 cell count (cell/μL), mean (SD)	488.79 (255.86)	823.91 (421.2)	< 0.001
CD4 cell count (cell/μL), mean (SD)	312.21 (171.22)	513.56 (287.33)	< 0.001
CD8 cell count (cell/μL), mean (SD)	155.32 (119.38)	279.1 (160.95)	0.001
CD4/CD8, mean (SD)	2.57 (1.33)	2.14 (1.15)	0.124
IgG (g/L), mean (SD)	12.46 (2.7)	12.03 (3.17)	0.578
IgM (mg/L), mean (SD)	0.91 (0.35)	60.75 (278.62)	0.365
IgE (IU/mL), mean (SD)	126.67 (139.63)	165.4 (652.32)	0.802
C3 (mg/L), mean (SD)	1.02 (0.26)	1.06 (0.2)	0.474
C4 (mg/L), mean (SD)	0.25 (0.12)	0.27 (0.1)	0.61
CRP (mg/L), mean (SD)	91.32 (71.06)	34.97 (45.53)	0.002
Procalcitonin (ng/mL), mean (SD)	0.77 (1.17)	0.09 (0.16)	0.008
pro-BNP (pg/mL), mean (SD)	2,469.54 (3,894.11)	265.97 (1,508.47)	0.021

WBC – white blood cell; APTT – activated partial thromboplastin time; PT – prothrombin time; INR – international normalized ratio; TBIL – total bilirubin; DBIL – direct bilirubin; IBIL – indirect bilirubin; ALT – alanine aminotransferase; AST – aspartate transaminase; ALB – albumin; GLB – globulin; TG – triglyceride; CHOL – cholesterol; HDL-C – high-density lipoprotein; LDL-C – low-density lipoprotein; CK – creatine kinase; CK-MB – creatine kinase-MB; BUN – blood urea nitrogen; eGFR – estimated glomerular filtration rate; Mb – myohemoglobin; IgG – immunoglobulin G; IgM – immunoglobulin M; IgE – immunoglobulin E; C3 – complement 3; C4 – complement 4; CRP – C-reactive protein; pro-BNP – pro-B-type natriuretic peptide; SD – standard deviation.

(372.63 *vs* 273.99, μmol/L), C-reactive protein (CRP) (91.32 *vs* 34.97, mg/L), procalcitonin (PCT) (0.77 *vs* 0.09 ng/mL), and pro-BNP (2,469.54 *vs* 265.97, pg/L), but a lower high-density lipoprotein (0.9 *vs* 1.07, mmol/L), serum total protein (59.39 *vs* 62.64, g/L), albumin (34.49 *vs* 38.76, g/L), estimated glomerular filtration rate (eGFR) (65.49 *vs* 103.45, mL/min), $CD3^+$ cells (488.79 *vs* 823.91, cell/μL), $CD4^+$ cells (312.23 *vs* 513.56, cell/μL), $CD8^+$ cells (155.32 *vs* 279.1, cell/μL), with significant difference ($p < 0.05$) compared to patients without cardiac injury. There was no difference in complement and immunoglobulin level.

All patients with cardiac injury underwent electrocardiographic (ECG) examinations after admission, and 22 (91.7%) ECGs were abnormal, with findings compatible with myocardial ischemia, such as T-wave depression and inversion, ST-segment depression, and Q waves.

Treatment and complications

The mean time from symptom onset to admission was similar between the two groups (4.62 days *vs* 3.78 days, $p = 0.522$). Compared with patients without CI, those with CI required more ventilation, including noninvasive (17.2% *vs* 3%) and invasive mechanical (6.9% *vs* 0.4%) approaches, and eventually more intensive care unit admission (13.8% *vs* 1.7%). Most of the patients received antivirals, antibiotic therapy, and traditional Chinese medicine, and no difference was found between the two groups. Notably, patients with cardiac injury received more corticosteroid therapy (44.8% *vs* 24.1%) and nutritional support (34.5% *vs* 10.3%). Overall, patients with cardiac injury experienced more complications (72.4% *vs* 47.8%), including higher ARDS (20.7% *vs* 2.7%), AKI (10.3 *vs* 0.4%), severe COVID-19 (58.6% *vs* 11.6%) and death (55.2% *vs* 3.9%) (Table 3).

Table 3

Treatment and complications in patients with and without cardiac injury

Treatment/complications	Cardiac injury (n = 29)	Without cardiac injury (n = 232)	*p*-value
ICU admission, n (%)			
yes	4 (13.8)	4 (1.7)	0.006
no	25 (86.2)	228 (98.3)	
Noninvasive ventilation, n (%)			
yes	5 (17.2)	7 (3)	0.005
no	24 (82.8)	225 (97)	
Invasive ventilation, n (%)			
yes	2 (6.9)	1 (0.4)	0.033
no	27 (93.1)	231 (99.6)	
Antiviral drugs, n (%)			
yes	29 (100)	212 (91.4)	0.142
no	0 (0)	20 (8.6)	
Antibiotics, n (%)			
yes	22 (75.9)	154 (66.4)	0.304
no	7 (24.1)	78 (33.6)	
Corticoids, n (%)			
yes	13 (44.8)	56 (24.1)	0.017
no	16 (55.2)	176 (75.9)	
Nutritional support, n(%)			
yes	10 (34.5)	24 (10.3)	0.001
no	19 (65.5)	208 (89.7)	
TCM, n(%)			
yes	18 (62.1)	178 (76.7)	0.085
no	11 (37.9)	54 (23.3)	
Total complications, n (%)			
yes	21 (72.4)	111 (47.8)	0.013
no	8 (27.6)	121 (52.2)	
ARDS, n (%)			
yes	6 (20.7)	6 (2.7)	0.001
no	23 (79.3)	220 (97.3)	
Hydrothorax, n (%)			
yes	0 (0)	6 (2.6)	1
no	29 (100)	221 (97.4)	
AKI, n (%)			
yes	3 (10.3)	1 (0.4)	0.005
no	26 (89.7)	226 (99.6)	
Death, n (%)			
yes	13 (44.8)	223 (96.1)	< 0.001
no	16 (55.2)	9 (3.9)	
Severe pneumonia, n (%)			
yes	12 (41.4)	205 (88.4)	< 0.001
no	17 (58.6)	27 (11.6)	

ICU – intensive care unit; TCM – traditional Chinese medicine; ARDS – acute respiratory distress syndrome; AKI – acute kidney injury.

Risk factors for cardiac injury

Univariate analysis indicated that male patients, older age (> 65 years old), smoking status, comorbidities, WBC > 10^9/L, lymphopenia, and PCT were risk factors for cardiac injury. In addition, multivariate analysis showed that male patients [hazard ratio (HR) = 6.13, 95% confidence interval (CI) 1.46–25.69)], older age (> 65 years old) (HR = 4.98, 95% CI 1.25–19.87), CVD (HR = 8.5, 95% CI 1.6–45.18), and PCT (HR = 30.57, 95% CI 3.67–254.98) were independently associated with an increased risk of cardiac injury on admission (Figure 1).

Predictive value of cardiac injury in severe COVID-19 and mortality

More severe COVID-19 was seen among patients with cardiac injury. In univariate analysis, older age (> 65 years old), WBC > 10 × 10^9/L, lymphopenia, eGFR < 60 mL/min, PCT, and cardiac injury were associated with an increased incidence of severe COVID-19. The multivariable-adjusted analysis found that only WBC > 10 × 10^9/L (HR = 4.26, 95% CI 1.09–16.7) and cardiac injury (HR = 8.71, 95% CI 2.37–32.04) were independent risk factors for severe COVID-19 (Figure 2).

Similarly, more deaths were detected in patients with cardiac injury. In univariate analysis, males, older age (> 65 years old), CVD, CKD, hypertension, WBC > 10 × 10^9/L, lymphopenia, eGFR < 60 mL/min, PCT, cardiac injury, and severe COVID-19 were associated with an increased risk of death. In multivariate analysis, only PCT (HR = 3,382.66, 95% CI 3.75–3,051,538.4) and cardiac injury (HR = 20.84, 95% CI 1.32–328.22) were independent risk factors for death (Figure 3).

Discussion

As a rapidly spreading disease with increasing mortality, COVID-19 seriously threatens human life and health, and global economic development. Combating COVID-19 virus

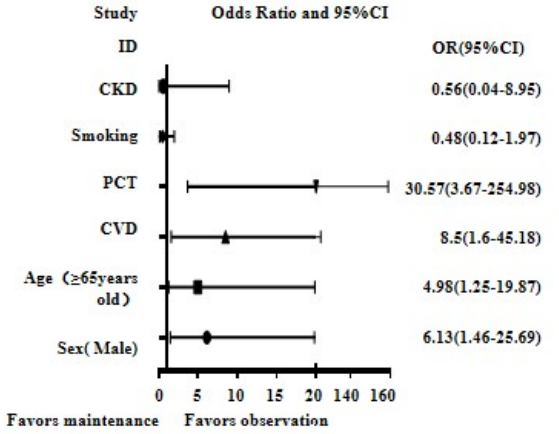


Fig. 1 – Logistic regression analysis of risk factors associated with cardiac injury. CKD – chronic kidney disease; PCT– procalcitonin; CVD – cardiovascular disease; OR – odds ratio; CI – confidence interval.

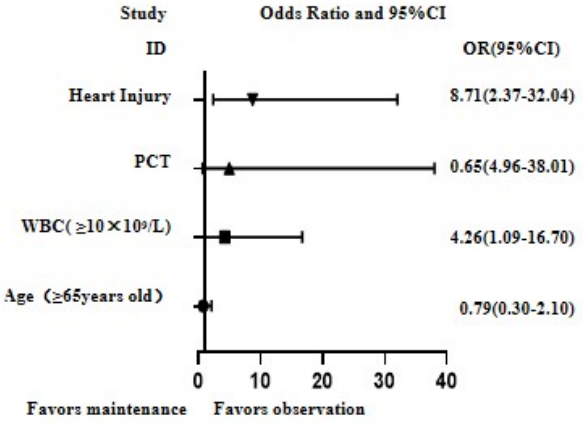


Fig. 2 – Logistic regression analysis of risk factors associated with severe COVID-19. PCT– procalcitonin; WBC – white blood cells; OR – odds ratio; CI – confidence interval.

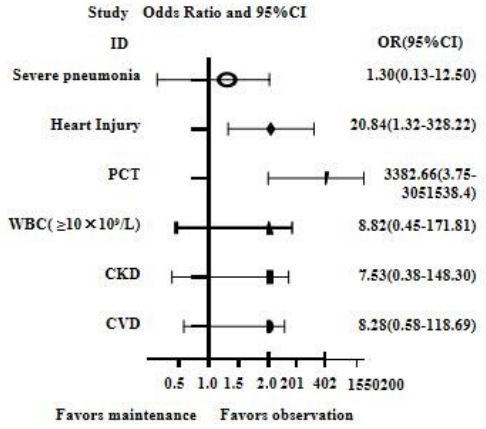


Fig. 3 – Logistic regression analysis of risk factors associated with in-hospital mortality. PCT– procalcitonin; WBC – white blood cells; CKD – chronic kidney disease; CVD – cardiovascular disease; OR – odds ratio; CI – confidence interval.

infection is a global battle in the medical and health industries. The virus mainly invades the lungs; however, it also affects cardiac function through multiple mechanisms [12]. The exact mechanism of cardiac involvement in COVID-19 remains under investigation. A recent study found that angiotensin-converting enzyme 2 (ACE-2) is also highly expressed in the heart [13]. Given that the spike protein can bind to ACE-2, it is plausible that the SARS-CoV-2 virus can infect the human heart, and this speculation was confirmed by a positive real-time polymerase chain reaction (PCR) assay for SARS-CoV-2 in heart tissue [14]. It is known that cyclooxygenase 2 (COX2) is an evolutionary enzyme involved in a variety of physiological and pathological processes and also plays an important role in viral infections [15–17]. Studies have shown that it induces lung developmental damage through the endoplasmic reticulum stress pathway and leads to pulmonary interstitial fibrosis while participating in inflammatory cell infiltration and fibroblast proliferation leading to cardiac injury [18–20]. Chronic basic CVD and risk factors for CVD include the risk of increased COVID-19 and worse clinical outcomes [21]. This study mainly explored the risk factors and clinical characteristics of patients with COVID-19 combined with cardiac injury, examined its risk factors, and identified that early cardiac injury and early intervention for COVID-19 in the progress of the disease improved the prognoses of patients.

This study found that cardiac injury occurred in elderly, male, and smoking patients. These factors are also classic risk factors for CVD [22]. There are vascular lesions and coronary atherosclerotic plaque formation in elderly patients. Long-term smoking can also lead to increased arteriosclerosis, vascular endothelial changes, and atherosclerotic plaque formation in elderly patients and smokers, in addition to direct cardiomyocyte apoptosis induced by inflammatory cell storms [23]. Uncontrolled release of inflammatory cytokines after infection can lead to impaired myocardial endothelial function, a progressive decrease in coronary blood flow, decreased oxygen supply, unstable coronary plaque, and microthrombosis, leading to further cardiac injury [24], consistent with the findings of Wang et al. [25]. This study found that men are more prone to myocardial injury because women secrete estrogen before menopause, which plays an antiatherosclerotic role, while men are more likely to smoke, and smoking accelerates coronary atherosclerotic plaque formation [26, 27]. Therefore, compared with women, coronary artery disease is more serious, and cardiac injury is more likely to occur in men in case of viral invasion and inflammation. For elderly men and COVID-19 patients with bad smoking habits, we should be alert to cardiac injury through early prevention of coronary atherosclerotic plaque formation, and cessation of smoking and other bad habits should be recommended.

In this study, 11.1% of the patients infected with the new coronavirus had cardiac injury. Some studies have shown that 5-38% of COVID-19 patients have cardiac injury [28]. This study found that the WBC counts, CRP, PCT, and other inflammatory indicators in patients with myocardial injury were significantly higher than those in patients without cardiac injury [29, 30]. The same as the results of Shi et al. [7], our study found that the CD3 positive, CD4 positive, and CD8 positive cell counts of patients with CI were significantly lower than those of patients without CI. This may be related to the patient's impaired immune function, indicating that the patient's immune function impairment may also be related to cardiac injury [31]. Moreover, Sandoval et al. [32] found a positive correlation between plasma TNI levels and high-sensitivity CRP levels, supporting the idea that a severe inflammatory response might play an important role in the development of cardiomyocyte injury. Consistent with the PCT-independent risk factor for cardiac injury, a PCT increase of 1 ng/mL will increase the risk of cardiac injury more than 30 times. As a result, COVID-19 patients with high inflammatory responses are more prone to cardiac injury. In addition, 91.7% of patients with cardiac injury had ECG changes, with findings compatible with myocardial ischemia. The main manifestations were T-wave depression and inversion, ST-segment depression, and Q waves. Electrocardiograms can be used as an efficient method for evaluating cardiac injury in COVID-19 patients. Combined with the level of the inflammatory response, early inhibition of inflammatory response, according to the changes in electrocardiography, could guide the treatment decisions for patients with COVID-19 CI.

In this study, the Intensive Care Unit occupancy rate of patients with cardiac injury increased significantly, the support rate of patients with ventilators was higher, and more patients with severe COVID-19 were diagnosed, which was also an independent risk factor for death. Once again, as it is emphasized by Rocco et al. [33], COVID-19 patients with cardiac injury have a worse clinical prognosis, similar to the findings of some other authors [4, 34, 35].

There are several limitations of our study. First, as a retrospective study and with most of our focus on the respiratory system, not all COVID-19 patients had measured cardiac biomarkers, and only 261 patients were included. In addition, other specific information regarding cardiac injury, such as ECG data and echocardiography, was not available. Second, regarding the cytokine storm, we only included parameters CRP and PCT, while inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha, were not presented in the study because the data were incomplete. Third, all cardiac injuries were assumed to be due to SARS-CoV-2 infection. However, it is difficult to differentiate the real cause of cardiac injury, such as medications and other underlying conditions or infections. Therefore, a prospective study with more complete data collection is needed. Finally, we did not evaluate any intervention for cardiac injury, and whether an improved heart condition can result in better clinical outcomes in COVID-19 remains unknown. Thus, future studies which will focus on the effectiveness of treatments specific to cardiac injury are necessary.

Other limitations of our study are: retrospective design, sample size, and in some cases incomplete data on symptoms, laboratory tests, and imaging examinations, given the variation in the structure of electronic databases across different participating hospitals and an urgent data extraction schedule. Besides, we did not collect treatment-related data, which may be critical to the patient's outcome.

Conclusion

Cardiac injury is a common condition in COVID-19 patients on admission, especially in elderly, male, and smoking patients. It is often accompanied by ECG myocardial ischemia and high inflammatory response, which are related to the progression of the disease and fatal outcomes and can not be ignored.

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Conflict of interest

The authors have no conflict of interest to declare.

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