# The Prognostic Value of Myocardial Injury in COVID-19 Patients and Associated Characteristics

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Research article

# Abstract

**Background:** Since December 2019, Coronavirus disease 2019 (COVID-19) has emerged as an international pandemic. COVID-19 patients with myocardial injury might need special attention. However, understanding on this aspect remains unclear. This study aimed to illustrate clinical characteristics and the prognostic value of myocardial injury to COVID-19 patients.

**Methods:** This retrospective, single-center study finally included 304 hospitalized COVID-19 cases confirmed by real-time RT-PCR from January 11 to March 25, 2020. Myocardial injury was determined by serum high-sensitivity troponin I (Hs-TnI). The primary endpoint was COVID-19 associated mortality.

**Results:** Of 304 COVID-19 patients (median age, 65 years; 52.6% males), 88 patients (27.3%) died (61 patients with myocardial injury, 27 patients without myocardial injury on admission). COVID-19 patients with myocardial injury had more comorbidities (hypertension, chronic obstructive pulmonary disease, cardiovascular disease, and cerebrovascular disease); lower lymphocyte counts, higher C-reactive protein (CRP, median, 84.9 vs 28.5 mg/L, p<0.001), procalcitonin levels (median, 0.29 vs 0.06 ng/ml, p<0.001), inflammatory and immune response markers; more frequent need for noninvasive ventilation, invasive mechanical ventilation; and was associated with higher mortality incidence (hazard ratio, HR=7.02, 95% confidence interval, CI, 4.45-11.08, p<0.001) than those without myocardial injury. Myocardial injury (HR=4.55, 95% CI, 2.49-8.31, p<0.001), senior age, CRP levels, and novel coronavirus pneumonia (NCP) types on admission were independent predictors to mortality in COVID-19 patients.

**Conclusions:** COVID patients with myocardial injury on admission is associated with more severe clinical presentation and biomarkers. Myocardial injury and higher HsTNI are both strongest independent predictors to COVID related mortality after adjusting confounding factors. In addition, senior age, CRP levels and NCP types are also associated with mortality.

**Trial registration:** Not applicable.

# Background

Coronavirus disease 2019 (COVID-19) is a newly recognized infection which was first reported in Wuhan, China [1]. Since the beginning of the outbreak, COVID-19 has emerged as a pandemic globally [2], and the number of cases is rising at an exponential rate [3]. As of November 15, 2020, there have been a total of more than 53,766,728 laboratory-confirmed cases of COVID-19 globally, and it poses a great threat to public health in the world as evidenced by 1,308,975 deaths [4]. COVID-19 is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The clinical spectrum appears to be very wide, including asymptomatic infection, mild upper respiratory disease, and severe viral pneumonia with respiratory failure, and even death [5]. The condition of some patients with COVID-19 may deteriorate rapidly, particularly in older patients with underlying comorbidities including cardiovascular disease [6]. Furthermore, SARS-CoV-2 can affect the cardiovascular system in multiple ways, increasing morbidity in patients with potential cardiovascular disease and causing myocardial injury and dysfunction [3]. High-sensitivity troponin I (Hs-TnI) provides the potential to earlier identify myocardial injury and assists treatment [7]. Some studies provide insights into the incidence of cardiac complications associated with SARS-CoV-2 [8, 9], while imaging manifestations, cytokine levels and the prognostic value of cardiovascular risk factors in COVID-19 patients are poorly understood. We aimed to comprehensively define clinical characteristics, laboratory results, outcomes, and management strategies of COVID-19 patients, then to find whether there is an association of myocardial injury and other biomarkers with mortality. This study may also provide clues to potential mechanisms associated with myocardial injury.

# Methods

## Study Design And Patients

In this study, we retrospectively enrolled 320 COVID-19 patients admitted to the Renmin Hospital of Wuhan University from January 11, 2020 to March 25, 2020 with approval from the Research Ethics Committee of the Renmin Hospital of Wuhan University, Wuhan, China (approval number: WDRY2020-K038). 16 cases without significant biomarkers, including Hs-TnI and creatinine kinase−myocardial band (CK-MB) levels, were excluded. Thus, a total of 304 patients were finally included in the study.

The confirmed diagnosis of COVID-19 was defined as a positive result by using real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) detection for routine nasal and pharyngeal swab specimens or anti-SARS-CoV-2 antibody assay.

## Data Collection

The demographic characteristics, clinical data, and results of cardiac biomarkers were obtained from the hospital's electronic medical records according to previously designed standardized data collection forms. The date of symptom onset, initial diagnosis of COVID-19, and death were recorded. The clinical features of symptoms and signs and comorbidities were collected on admission. Laboratory analyses included complete blood count, hepatic function, kidney function, coagulation function, C-reactive protein (CRP), lactate dehydrogenase (LDH), myocardial enzymes, procalcitonin (PCT), electrolytes test, and status of other viral infection. Cardiac biomarkers including N-terminal pro-B-type natriuretic peptide (NT-proBNP), Hs-TnI, CK-MB, and myoglobin were measured on admission and during hospitalization. Routine bacterial and fungal examinations were also performed. Radiologic assessments included digital radiography (DR) and/or computed tomography (CT). Two researchers collected and checked the final database.

## Definitions

Fever was defined as an axillary temperature of 37.5°C or higher [10]. The date of onset was defined as the day when any symptom was noticed. Myocardial injury was defined as serum levels of Hs-TnI were above the 99th percentile upper reference limit at admission (0.04ng/mL, measured in the laboratory of Renmin Hospital of Wuhan University) [11]. The novel coronavirus pneumonia (NCP) types (mild, common, severe, critically severe) was defined according to the diagnostic and treatment programme for SARS-CoV-2 issued by Chinese National Health Committee (version 7) [12]. The primary end point was COVID-19 associated death. Hospital discharge was allowed after the relieved clinical symptoms, normal body temperature for at least three days, significant improvement in radiological findings, and at least two consecutive negative results shown by RT-PCR for COVID-19 [12].

## Statistical analysis

Categorical variables are shown as frequency rates or percentages. Continuous variables as mean ± standard deviation (SD) or median (interquartile range [IQR]) as appropriate. Student's $t$ test, Mann Whitney test, $\chi^2$ test or Fisher exact test was used where appropriate to assess the difference between different cohorts. The Pearson correlation coefficient and Spearman rank correlation coefficient were used for correlation analysis. Survival curves were plotted using the Kaplan-Meier method between patients with and without myocardial injury. Univariate and multivariate Cox regression models were used to determine the independent risk factors for death in hospital. The NCP types was listed as rank variable. Statistical analysis was performed with SPSS, version 21.0 (IBM, USA). A two-sided $P < 0.05$ was considered statistically significant.

## Results

A total of 304 hospitalized patients with COVID-19 were consecutively enrolled in our study, including 96 patients (31.6%) with myocardial injury and 208 patients (68.4%) without myocardial injury. The demographic and clinical characteristics of the patients are listed in Table 1. On admission, over half of the COVID-19 patients (198, 65.1%) had comorbidities, including hypertension (42.8%), diabetes (16.4%), and cardiovascular disease (16.1%), like coronary artery disease (10.5%), arrythmia (4.3%), and cardiomyopathy (0.7%). COVID-19 patients with myocardial injury were older, more males, and more likely to have pre-existing comorbidities, and were associated with more severe presentation (critically severe, 26.0% vs 7.2%, all p < 0.001).

| Characteristic | All patients (n = 304) | Myocardial injury | | P value |
| --- | --- | --- | --- | --- |
| | | With (n = 96) | Without (n = 208) | |
| Male (%) | 160 (52.6) | 61 (63.5) | 99 (47.6) | **0.010** |
| Age, median (IQR) | 65.0 (54.0 – 74.0) | 70.5 (60.1 – 79.0) | 62.0 (52.0 – 69.0) | **< 0.001** |
| NCP types, (%) | | | | |
| Mild / Common | 117 (38.5) | 22 (22.9) | 95 (45.7) | **< 0.001** |
| Severe | 147 (48.4) | 49 (51.0) | 98 (47.1) | |
| Critically severe | 40 (13.2) | 25 (26.0) | 15 (7.2) | |
| Comorbidities, (%) | 198 (65.1) | 76 (79.2) | 122 (58.7) | **< 0.001** |
| Diabetes | 50 (16.4) | 17(17.7) | 33 (15.9) | 0.687 |
| Hypertension | 130 (42.8) | 52 (54.2) | 78 (37.5) | **0.006** |
| COPD | 21 (6.9) | 12 (12.5) | 9 (4.3) | **0.009** |
| Cardiovascular disease | 49 (16.1) | 27 (28.1) | 22 (10.6) | **< 0.001** |
| Coronary artery disease | 32 (10.5) | 18 (18.8) | 14 (6.7) | **0.002** |
| Cerebrovascular disease | 21 (6.9) | 13 (13.5) | 8 (3.8) | **0.002** |
| Kidney disease | 12 (3.9) | 4(4.2) | 8 (3.8) | 1 |
| Hepatic disease | 8 (2.6) | 3 (3.1) | 5 (2.4) | 0.711 |
| Cancer, Auto-immune disease | 32 (10.5) | 11 (11.5) | 21 (10.1) | 0.719 |

P-values are calculated by Student's t-test, Mann–Whitney U test, or $\chi^2$ test as appropriate. IQR, interquartile range. NCP: novel coronary pneumonia; COPD: chronic obstructive pulmonary disease.

On admission, the median leukocyte counts, neutrophil counts, platelet counts, hemoglobin, immunoglobulin G (IgG), IgM, IgA and complement 3 (C3) levels were all within the normal range in both groups (Table 2). However, significant differences were noted in neutrophil and platelet counts between the two groups (p < 0.001). Comparing with patients without myocardial injury, patients with myocardial injury had even lower CD3, CD4, CD8 counts, higher IL-6, CRP, and PCT levels (all p < 0.001), and CD3, CD4, CD8 counts showed strong correlations (R > 0.77) with lymphocytes counts and moderate correlations (R: -0.39~-0.45) with CRP levels (Fig. 1). Log-transformed serum Hs-TnI levels in patients with COVID-19 correlated significantly with both log-transformed serum NT-proBNP levels (β = 0.37, p < 0.001) and serum urea nitrogen levels (β = 4.23, p < 0.001) (Fig. 2).

Table 2
Laboratory examinations and radiographic presentation in COVID-19 patients

| Characteristic | Normal range | All patients (n = 304) | Myocardial injury | | P value |
| --- | --- | --- | --- | --- | --- |
| | | | With (n = 96) | Without (n = 208) | |
| **Immunologic markers, median (IQR)** | | | | | |
| Leucocyte counts,$10^9$/L | 3.5−9.5 | 6.3 (4.3−8.1) | 7.1 (5.0-10.1) | 6.0 (4.4−7.8) | 0.058 |
| Neutrophil counts,$10^9$/L | 1.8−6.3 | 4.9 (3.0-7.4) | 6.7 (4.2−10.3) | 4.4 (2.8−6.4) | **< 0.001** |
| Lymphocyte counts,$10^9$/L | 1.1−3.2 | 0.9 (0.6−1.3) | 0.6 (0.4-1.0) | 1.0 (0.7−1.3) | **< 0.001** |
| Platelet counts, $10^9$/L | 130−175 | 200.0 (145.0-258.0) | 151.5(105.0-237.2) | 210.0 (165.5−264.0) | **< 0.001** |
| Hemoglobin, g/L | 125−350 | 123.0 (111.3−136.0) | 122.0 (110.0-137.0) | 123.0 (113.0-135.2) | 0.872 |
| CD 3 counts, /uL | 723−2737 | 502.0 (275.8−765.0) | 317.5 (177.3−591.0) | 539.5 (324.0-862.5) | **< 0.001** |
| CD 4 counts, /uL | 404−1612 | 287 (161.5-464.5) | 193.5 (98.8-322.8) | 340.5 (201.8-528.3) | **< 0.001** |
| CD 8 counts, /uL | 220−1129 | 152.0 (73.0-278.0) | 77 (40.8-161.5) | 191.0 (106.0-304.0) | **< 0.001** |
| CD4/CD8 ratio | 0.9-2.0 | 1.8 (1.3−1.7) | 2.0 (1.3−3.4) | 1.8 (1.3−2.7) | 0.127 |
| IgG, g/L | 7.0−16.0 | 12.3 (10.2−15.4) | 13.7 (11.2−16.6) | 11.7 (9.6−14.6) | **0.003** |
| IgM, g/L | 0.4−2.3 | 1.0 (0.7−1.3) | 1.0 (0.7−1.3) | 1.0 (0.7−1.2) | 0.143 |
| IgA, g/L | 0.7-4.0 | 2.4(1.8−3.3) | 2.8 (2.1−3.8) | 2.2 (1.7-3.0) | **0.002** |
| C3, g/L | 0.9−1.8 | 1.0 (0.9−1.1) | 1.0 (0.8−1.1) | 1.0 (0.9−1.2) | **< 0.001** |
| CK-MB, ng/mL | 0−5 | 1.2 (0.7−2.6) | 4.2 (1.9−8.3) | 0.9 (0.7−1.5) | **< 0.001** |
| **Cardiac, hepatic and kidney injury markers, median (IQR)** | | | | | |
| Myoglobin, ug/L | 0-110 | 49.1 (27.4-130.9) | 177.4 (82.5-765.7) | 35.0 (25.0-59.7) | **< 0.001** |
| Hs-TNI, ng/mL | 0-0.04 | < 0.006 (< 0.006−0.068) | 0.22 (0.09−1.83) | < 0.006 (< 0.006−0.011) | **< 0.001** |
| NT-proBNP[#], pg/mL | 0-300 | 285.8 (86.7-835.8) | 799.7 (267.7−1719.0) | 220.1 (54.0-456.5) | **< 0.001** |
| NT-proBNP*, pg/mL | 0-300 | 647.8 (237.2-1996.3) | 2543.0 (953.0-9022.0) | 389.0 (141.0-1046.0) | **< 0.001** |
| LDH, U/L | 100−300 | 266 (202.8-413.3) | 433.5 (306.5-677.5) | 221.0 (188.0-284.0) | **< 0.001** |
| ALT, U/L | 9−50 | 24.0 (17.0−46.0) | 27.0 (18.0−48.0) | 24.0 (16.8−43.3) | 0.662 |

P-values are calculated by Student's t-test, Mann−Whitney U test, or $\chi^2$ test as appropriate. [#], NT-proBNP levels on admission; *, NT-proBNP levels during hospitalization. Abbreviation: IQR, interquartile range; CD, Cluster of Differentiation; Ig, Immunoglobulin; C3, Complement 3; IL-6, interleukin 6; PT, Prothrormbin time; APTT, Active Partial Thromboplastin Time; CK-MB, Creatinine kinase−myocardial band; Hs-TNI, High-sensitivity troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCT, Procalcitonin; LDH, Lactate Dehydrogenase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, alkaline phosphatase; ALB, Albumin; ECG, electrocardiogram.

| Characteristic | Normal range | All patients (n = 304) | Myocardial injury With (n = 96) | Without (n = 208) | P value |
|---|---|---|---|---|---|
| AST, U/L | 15−40 | 27.0 (19.0-43.5) | 42.0 (24.0−65.0) | 23.5 (17.3−32.0) | < 0.001 |
| ALP, U/L | 90−130 | 71.0 (56.4−94.0) | 75.0 (58.8−105.0) | 69.0 (56.0-90.3) | 0.219 |
| ALB, g/L | 40−55 | 37.0 (33.5−40.0) | 33.8 (30.1−37.1) | 38.7 (35.8−41.0) | < 0.001 |
| Urea, mmol/l | 3.6−9.5 | 5.4 (3.8-9.0) | 9.5 (5.4−19.4) | 4.6 (3.5−6.5) | < 0.001 |
| Creatinine, mmol/L | 57−111 | 58.0 (48.0−79.0) | 71.0 (53.0-126) | 56.0 (46.0-70.8) | < 0.001 |
| Potassium, mmol/L | 3.5−5.5 | 4.2 (3.8−4.5) | 4.1 (3.6−4.6) | 4.3 (3.9−4.5) | 0.255 |
| Sodium, mmol/L | 135−155 | 142.0 (139.0-146.0) | 141.0 (138.0-146.0) | 142.0 (139.0-146.0) | 0.542 |
| Inflammation markers, median (IQR) | | | | | |
| PCT, ng/mL | < 0.1 | 0.10 (0.05−0.32) | 0.29 (0.10−1.09) | 0.06 (0.04−0.14) | < 0.001 |
| C-reactive protein, mg/L | 0−10 | 51.3 (10.9−104.0) | 84.9 (53.7-173.8) | 28.5 (5.7−82.2) | < 0.001 |
| IL-6, pg/mL | < 10 | 10.5 (6.1−26.5) | 23.5 (10.7−98.1) | 9.0 (5.8−20.6) | < 0.001 |
| Coagulation markers, median (IQR) | | | | | |
| PT, sec | 9−13 | 12.4 (11.5−13.5) | 13.4 (12.2−14.4) | 12.1 (11.3−13.1) | < 0.001 |
| APTT, sec | 25-31.3 | 28.6 (26.2−31.5) | 29.2 (27.7−33.2) | 28.2 (25.9−31.0) | < 0.001 |
| D-dimer, mg/L | 0-0.55 | 2.5 (0.7−13.8) | 7.0 (1.9−21.7) | 1.6 (0.6−8.2) | < 0.001 |

P-values are calculated by Student's t-test, Mann−Whitney U test, or $\chi^2$ test as appropriate. #, NT-proBNP levels on admission; *, NT-proBNP levels during hospitalization. Abbreviation: IQR, interquartile range; CD, Cluster of Differentiation; Ig, Immunoglobulin; C3, Complement 3; IL-6, interleukin 6; PT, Prothrormbin time; APTT, Active Partial Thromboplastin Time; CK-MB, Creatinine kinase−myocardial band; Hs-TNI, High-sensitivity troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCT, Procalcitonin; LDH, Lactate Dehydrogenase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, alkaline phosphatase; ALB, Albumin; ECG, electrocardiogram.

Regarding the cardiac, hepatic, renal and coagulation function (Table 2), patients with COVID-19 had increased Hs-TnI, PCT and D-dimer levels on admission and NT-proBNP during hospitalization compared to the normal reference values. Patients with myocardial injury showed elevated myoglobin, LDH, PCT, and D-dimer levels (all p < 0.001) compared to patients without myocardial injury. Figure 2 shows the dynamic change of NT-proBNP of COVID-19 patients from admission to hospitalization.

The Imaging manifestations of the 304 patients with COVID-19 were listed in table S1. 135 (44.4%) underwent examination of electrocardiogram (ECG) after admission, and 83 of 135 ECGs (61.5%) indicated cardiac abnormalities, including T-wave depression and inversion, ST-segment depression, atrioventricular block, and the complex abnormality. 34 (11.2%) underwent examination with echocardiography and 27 (79.4%) of patients showed abnormalities, and the more common abnormalities are cardiac diastolic dysfunction, and complex echo abnormalities (tricuspid regurgitation). All patients underwent CT or DR examinations and 221 (72.6%) patients presented with pulmonary abnormalities including ground-glass opacities or consolidation (Fig S1). There was no statistically significant difference in the other imaging findings between patients with or without myocardial injury, only the patients with complex echo abnormalities had significant difference.

Oxygen treatment was provided to 206/304 (67.8%) patients. 62 (20.4%) patients received noninvasive ventilation, and 10.2% patients (31 patients) were placed in mechanical ventilation. The proportion treated with antiviral therapy was the highest (304, 100%), followed by high dose glucocorticoids therapy (142, 46.7%), intravenous immunoglobulin therapy (122, 40.1%), antibiotic therapy (118, 38.8%) and hemoperfusion (20, 6.6%). Only 8 patients (2.6%) among all participants were given plasmapheresis therapy. Overall, 100 patients (27.3%) had kidney injury during hospitalization, and 65 patients (21.4%) had hepatic injury.

Compared with those without myocardial injury, more COVID-19 patients with myocardial injury required oxygen inhalation; noninvasive ventilation, invasive mechanical ventilation, antibiotic treatment and hemoperfusion therapy (all p < 0.001) (Table 3). However, intravenous immunoglobulin treatment (24.0% vs 47.6%, P < 0.001) was lower in patients with myocardial injury. The comparison of typical managements, comorbidities, complications and time duration from symptom onset to death were made in 20 random patients with myocardial injury or not (Fig. 3), which tells us that myocardial injury may be associated with more severe presentation.

Table 3
Managements and clinical outcomes of COVID-19 patients

| Characteristic | All patients (n = 304) | Myocardial injury | | P value |
| --- | --- | --- | --- | --- |
| | | With (n = 96) | Without (n = 208) | |
| Managements, n (%) | | | | |
| Oxygen inhalation | 206 (67.8) | 85 (88.5) | 121 (58.2) | < 0.001 |
| Noninvasive ventilation | 62 (20.4) | 35 (36.5) | 27 (13.0) | < 0.001 |
| Invasive mechanical ventilation | 31 (10.2) | 20 (20.8) | 11 (5.3) | < 0.001 |
| Immunoglobulin | 122 (40.1) | 23 (24.0) | 99 (47.6) | < 0.001 |
| Antiviral | 304 (100) | 96 (100) | 208 (100) | - |
| Antibiotic | 118 (38.8) | 65 (67.7) | 53 (25.5) | < 0.001 |
| Glucocorticoids | 142 (46.7) | 44 (45.8) | 98 (47.1) | 0.835 |
| Hemoperfusion | 20 (6.6) | 12 (12.5) | 8 (3.8) | 0.005 |
| Plasmapheresis | 8 (2.6) | 5 (5.2) | 3 (1.4) | 0.114 |
| Clinical outcomes, n (%) | | | | |
| Death | 88 (27.3) | 61 (63.5) | 27 (13.0) | 0.005 |
| In hospital | 83 (28.9) | 11 (11.5) | 72 (34.6) | |
| Discharge | 133 (43.8) | 24 (25.0) | 109 (52.4) | |
| P-values are calculated by Student's t-test, Mann−Whitney U test, or $\chi^2$ test as appropriate. | | | | |

During the median durations for about 45.4 days from onset of symptoms to follow-up (range:3−84 days), a total of 88/304 patients (27.3%) died, among which 61 patients had myocardial injury, while 27 patients didn't have myocardial injury (Table 3). In the univariable analysis, the mortality rate was significantly higher in patients with myocardial injury (63.5% vs 13.0%, P < 0.001, Table 3). The Kaplan-Meier survival curves indicate significant survival differences between the patients with or without myocardial injury (p < 0.001, Fig. 4). The multivariate cox proportional hazard regression model showed significantly higher risk of death in patients with myocardial injury than in those without myocardial injury from symptom onset (hazard ratio, HR, 4.55, 95% CI, 2.49−8.31, p < 0.001) to primary end point, after adjusting for age, sex, preexisting comorbidities, CRP levels, D-dimer levels, NCP types (Table 4). Under this cox regression model, senior age (HR, 2.01, 95% CI, 1.03−3.92, P = 0.04), CRP levels (HR, 1.01, 95% CI, 1.00-1.01, P = 0.001) and NCP types (P = 0.007) were other independent risk factors for mortality with COVID-19. In addition, cox regression model with HsTNI as continuous variable showed that higher HsTNI was also associated with mortality (HR, 3.33, 95% CI, 1.96−5.66, P < 0.001) (Table S2).

Table 4
Multivariate Cox Regression Analysis on the Risk Factors Associated with Mortality in Patients With COVID-19 from symptom onset

| Factors | Univariate analysis | | Cox regression model | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | *P* value | Hazard ratio (95% CI) | *P* value |
| Age, > 65 years | 3.79 (2.32−6.20) | < 0.001 | 2.01 (1.03−3.92) | 0.04 |
| Sex | 0.53 (0.34−0.82) | 0.005 | | |
| Hypertension | 2.05 (1.34−3.13) | 0.001 | | |
| COPD | 2.95 (1.64−5.32) | < 0.001 | | |
| Chronic heart disease | 2.16 (1.34−3.47) | 0.002 | | |
| Cerebrovascular disease | 3.10 (1.72−5.59) | < 0.001 | | |
| Myocardial injury | 7.02 (4.45−11.08) | < 0.001 | 4.55 (2.49−8.31) | < 0.001 |
| CRP | 1.01 (1.01−1.02) | < 0.001 | 1.01 (1.00-1.01) | 0.001 |
| NT-proBNP on admission | 1.00 (1.00−1.00) | 0.082 | | |
| PCT | 1.00 (1.00-1.02) | 0.768 | | |
| D-dimer | 1.01 (1.00-1.01) | 0.003 | | |
| NCP types | | < 0.001 | | 0.007 |
| severe-common | 3.89 (1.95−7.76) | < 0.001 | 2.18 (0.92−5.15) | 0.075 |
| critically severe-common | 18.42 (9.06−37.41) | < 0.001 | 4.33 (1.65−11.36) | < 0.001 |

P-values by Cox regression analyses. PCT, CRP, and NT-proBNP on admission, D-dimer were performed as continuous variables. NT-proBNP, N-terminal pro-B-type natriuretic peptide; COPD: chronic obstructive pulmonary disease; PCT, Procalcitonin; NCP: novel coronary pneumonia.

## Discussion

This study summarizes the clinical characteristics, laboratory, cardiac, and radiographic findings in a large cohort of 304 hospitalized COVID-19 patients, and provides novel information of the prognostic value of pre-existing co-morbidities and myocardial injury. Myocardial injury, senior age, NCP types and CRP levels were independently associated with higher risk of mortality during hospitalization. The myocardial injury was probably associated with inflammation response. The prognostic value of elevated Hs-TnI in patients with COVID-19 should be of great interest to a broad readership, as a simple blood biomarker test was such a strong predictor of mortality and that sophisticated, expensive and time-consuming cardiac testing with CT and magnetic resonance imaging (MRI) are not needed.

With the high infectivity, COVID-19 has managed to supersede severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012 in terms of death toll [13]. The median age was 65 years in our study, greater than previous studies (55.6 and 49 years) [9, 14], mainly due to the severe clinical types and more comorbidities in our patient cohort tending to be older. This is supported by the evidence that the median age of patients is higher in group with myocardial injury than those without (70.5 vs 62.0 years). COVID-19 patients with myocardial injury were prone to develop severe types (77.0%), and more likely to have pre-existing comorbidities (79.2% vs 58.7%), like hypertension, cardiovascular disease and cerebrovascular disease, also confirmed by other studies [9, 15]. Li et.al analyzed six studies involving 1527 COVID-19 patients with previous cardiovascular metabolic diseases, and indicated that this patient group may face a greater risk of developing into the severe condition and that the comorbidities can also greatly affect the prognosis of the COVID-19 [16].

In our study, COVID-19 patients with myocardial injury had obviously elevated myoglobin, and NT-proBNP levels, providing independent corroborating evidence of myocardial injury [17]. In addition, the correlations between Hs-TnI levels and NT-proBNP

levels with urea nitrogen levels indicate multiorgan injury along with myocardial injury and worth early monitoring. In prior studies, no significant deviations in coagulation function from the normal range were found but some patients still presented with coagulation dysfunction [18, 19]. Our study further validated this result, especially in patients with myocardial injury or in critically severe and severe type. Hence, we speculate that coagulation may be not a very important pathophysiological process in all patients with COVID-19. Only some critically ill patients demonstrated abnormal coagulation function and multiple organ dysfunction at the end stage. COVID-19 patients with myocardial injury need active treatments to delay or reverse the progression of disease, supported by the fact that the clinical presentation and the severity of COVID-19, as well as more comorbidities in patients with myocardial injury group. However, patients without myocardial injury received more intravenous immunoglobulin therapy than patients with myocardial injury, and this may be attributable to rapid progression of COVID-19 disease in the later cohort, which makes it too late to use intravenous immunoglobulin therapy.

Two prior studies indicated that there was a strong correlation between myocardial injury and prognosis of COVID-19 patients during hospitalization [8, 9]. Adding to previous reports, our study further confirmed that myocardial injury, senior age, CRP levels and NCP types are all independent prognostic indicators of mortality in COVID-19 patient. Among these risk factors, myocardial injury, determined by serum Hs-TnI, was the strongest both as dichotomous and continuous variable. The Hs-TnI marker can be an ally for earlier identifying myocardial injury, rather than cardiac infarction, thus guiding timely intervention [7]. To date, the exact mechanism of cardiac involvement in COVID-19 remains under investigation. Current studies suggested immune change in patients with MERS [20], SARS [21] and influenza [22], especially changes in peripheral blood T cells, which may contribute to understanding the characteristics, diagnosis, monitoring, prevention and treatment of the disease. Many investigations have already reported that the pathophysiology and outcomes of COVID-19 may be linked to dysregulation of immune response, presenting with lower lymphocyte counts, higher leukocytes counts and significantly reduced CD4 + and CD8 + T lymphocytes levels [23, 24]. In our study, the CD3, CD4, CD8 counts correlated well with lymphocytes counts and CRP levels, and an elevated inflammation reaction (CRP) and suppressive immune response (CD4+, CD8+) in COVID-19 patients at admission. In addition, traditional cardiovascular risk factors such as diabetes and hyperlipidemia impact immune function, and conversely, dysregulated immunologic status corresponds with elevated risk of incident cardiovascular disease [25]. Another possible mechanism is the direct invasion via angiotensin converting enzyme 2 (ACE2) receptors in cardiovascular system [3]. In our study, we not only found that COVID-19 patients with comorbidities were associated with higher mortality, but also the CRP levels are significantly associated with mortality in multi-variate cox analysis, which indicated there would be inflammation reaction and this was associated with worse outcomes. In addition, IL-6 cytokines were elevated in COVID-19 patients with myocardial injury, justifying the emergence of and association with severity of inflammation, and immune-related markers, like CD3, CD4, CD8 molecules counts and lymphocyte counts were all reduced, more significant in patients with myocardial injury. It was reasonable to presume the invasive coronavirus may dysregulate the immune system, and further lead to severe damage to myocardial tissues. The data from all these studies taken together, suggest that clinicians should consider myocardial injury on presentation, NCP types and inflammation and immune dysregulation what caring for COVID-19 patients. The exact mechanism of myocardial injury merits further investigation, but the findings presented here highlight the prognostic value in identifying myocardial injury with noninvasive biomarker testing on admission in COVID-19 patients and raise the possibility that providers should consider close management of immune response, inflammation and comorbidities in COVID-19 hospitalized patients.

We acknowledge some limitations in our study. First, this was a retrospective, single center study of patients admitted to hospital; multi-center investigations for a larger cohort would be better to assess the clinical characteristics and confirm the outcomes of myocardial injury after infection with COVID-19. Second, because of the logistical limitations at the onset of these emerging infections in Wuhan, some data, such as inflammation biomarker and imaging data were lacked on admission, which limits the further confirmation of potential mechanisms of myocardial injury. Third, the data in this study permit a preliminary assessment of the clinical course and outcomes of patients with COVID-19. The causes of death may involve multiple organ dysfunction in most cases, and it is difficult to differentiate the myocardial injury as the main and direct cause in an individual case. Long-term observation and prospective study design on the effectiveness of treatments specific for the myocardial injury are needed.

## Conclusions

In conclusion, myocardial injury is common in patients hospitalized with COVID-19. Patients with myocardial injury had more severe presentation and complex comorbidities. Furthermore, myocardial injury is independently associated with increased in-hospital mortality in patients with COVID-19.

## Abbreviations

COVID-19 = Coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; Hs-TnI = High-sensitivity troponin I; CK-MB = creatinine kinase–myocardial band; RT-PCR = real-time reverse-transcriptase polymerase-chain-reaction; CRP = C-reactive protein; LDH = lactate dehydrogenase; PCT = procalcitonin; NT-proBNP = N-terminal pro-B-type natriuretic peptide; DR = digital radiography; CT = computed tomography; NCP = novel coronavirus pneumonia; MERS = Middle East respiratory syndrome.

## Declarations

### Ethics approval and consent to participate:

This study obtained approval from the Research Ethics Committee of the Renmin Hospital of Wuhan University, Wuhan, China (approval number: WDRY2020-K038). Written consent was obtained from all participants.

### Consent for publication:

Not applicable.

### Availability of data and materials:

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

### Competing interests

The authors declare that they have no competing interests

### Authors' contributions

JH, BZ, Quan Z, WY, JX, TL, HZ, ZW, DL, Qing Z, J, CZ: Data curation, Formal analysis; BZ, Quan Z, JZ: Data curation, Resources, Investigation; JH, WY, JX: Writing, Methodology; RW, GL, ZT, AS, HQ, SZ, AA, ML, XZ: Methodology, Project administration, Conceptualization; ML and XZ: Conceptualization, Validation, Supervision, Funding acquisition. All authors have read and approved the manuscript.

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# Figures
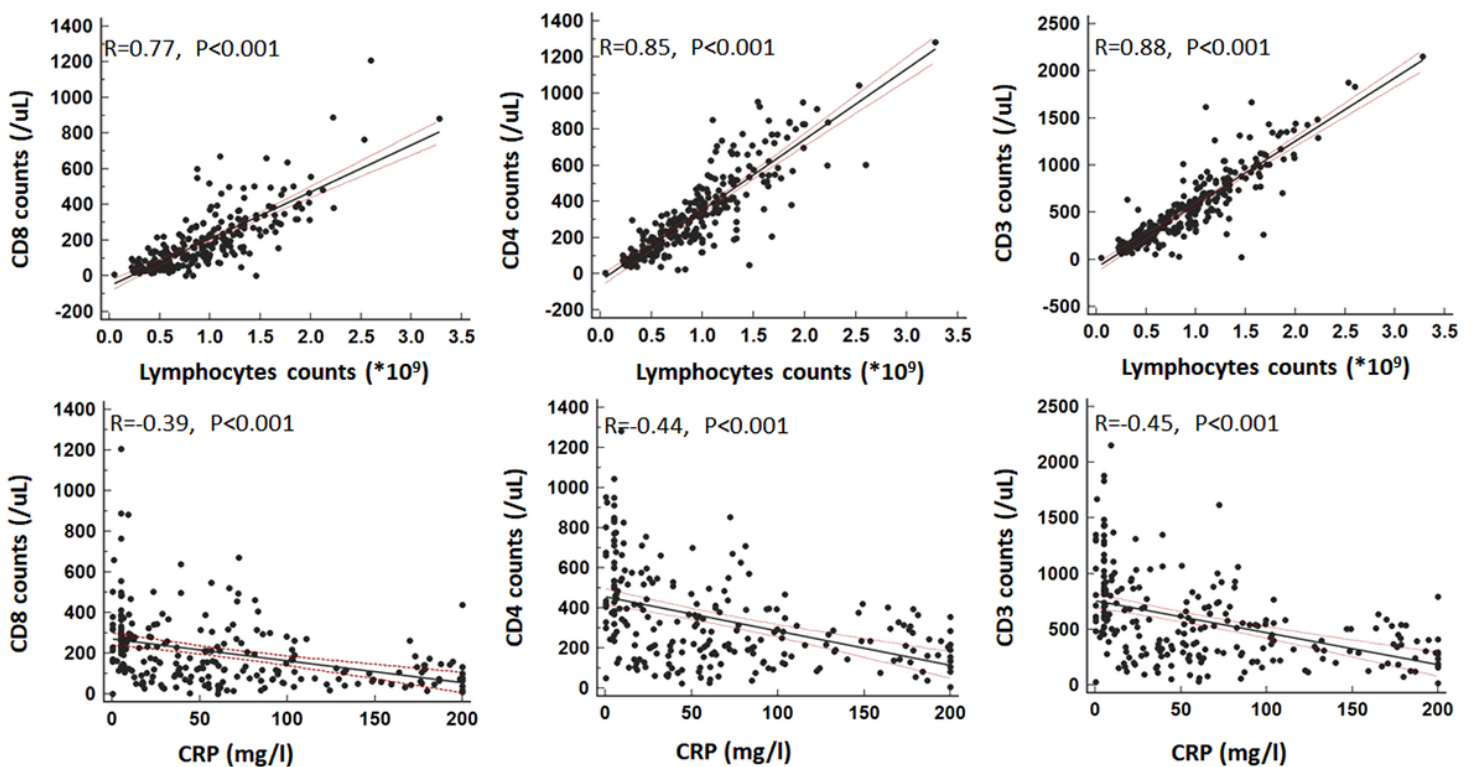


**Figure 1**

Associations between CD3, CD4, CD8 and lymphocytes biomarkers Strong correlations were found between CD3, CD4, CD8 and lymphocytes biomarkers. CD, Cluster of Differentiation of T cells.
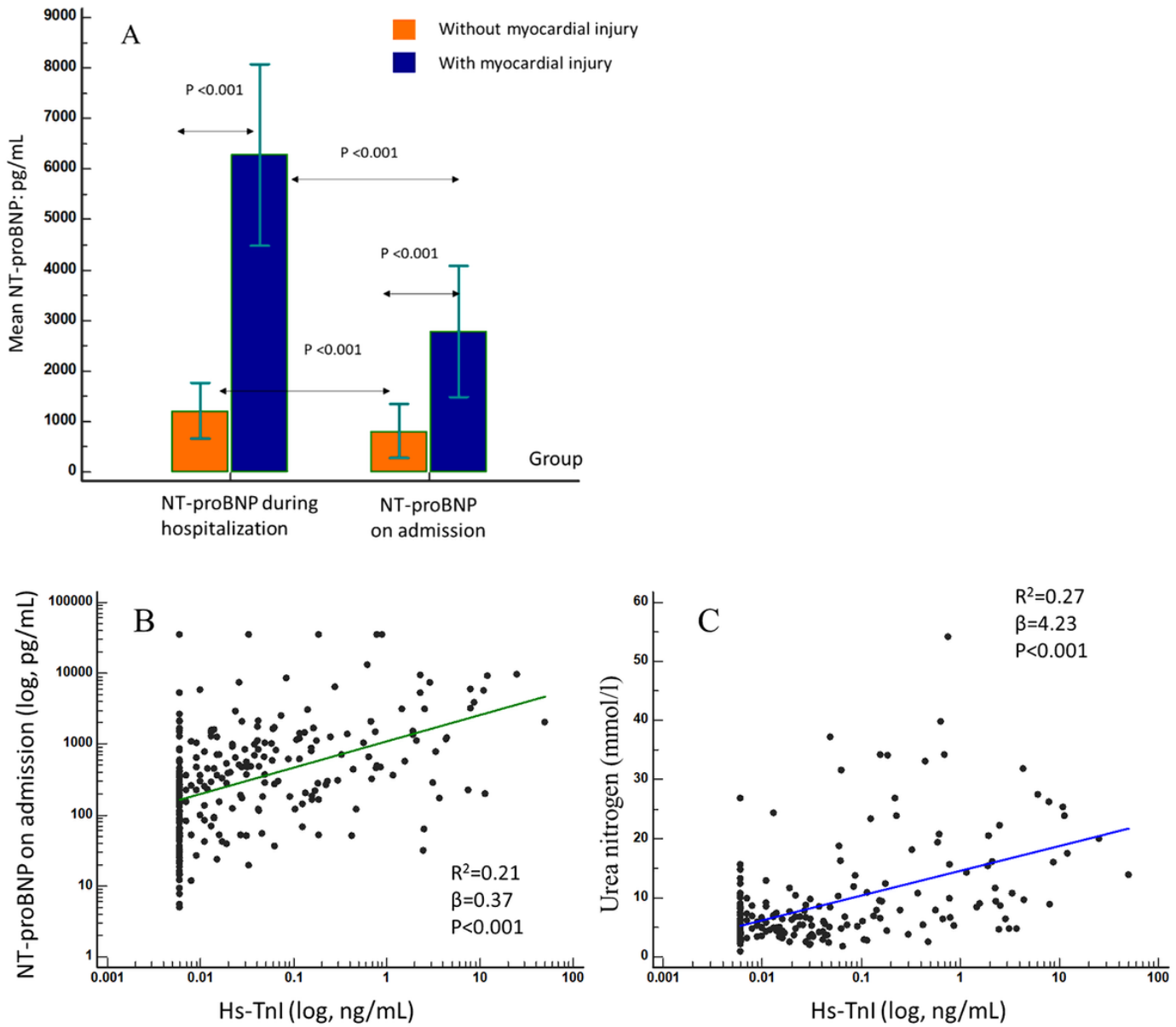
**Figure 2**

Progression of NT-proBNP of COVID-19 patients and correlation Between Serum high-sensitivity TnI and NT-proBNP With Urea nitrogen. The mean NT-proBNP progression of COVID patients on admission and during hospitalization. NT-proBNP, Nterminal pro-B-type natriuretic peptide, Hs-TnI: high-sensitivity troponin I. when High-sensitivity troponin I levels < 0.006 ng/mL, it was recorded as 0.006 ng/mL at convenience.

Figure 3 table (COVID-19 patients timeline):

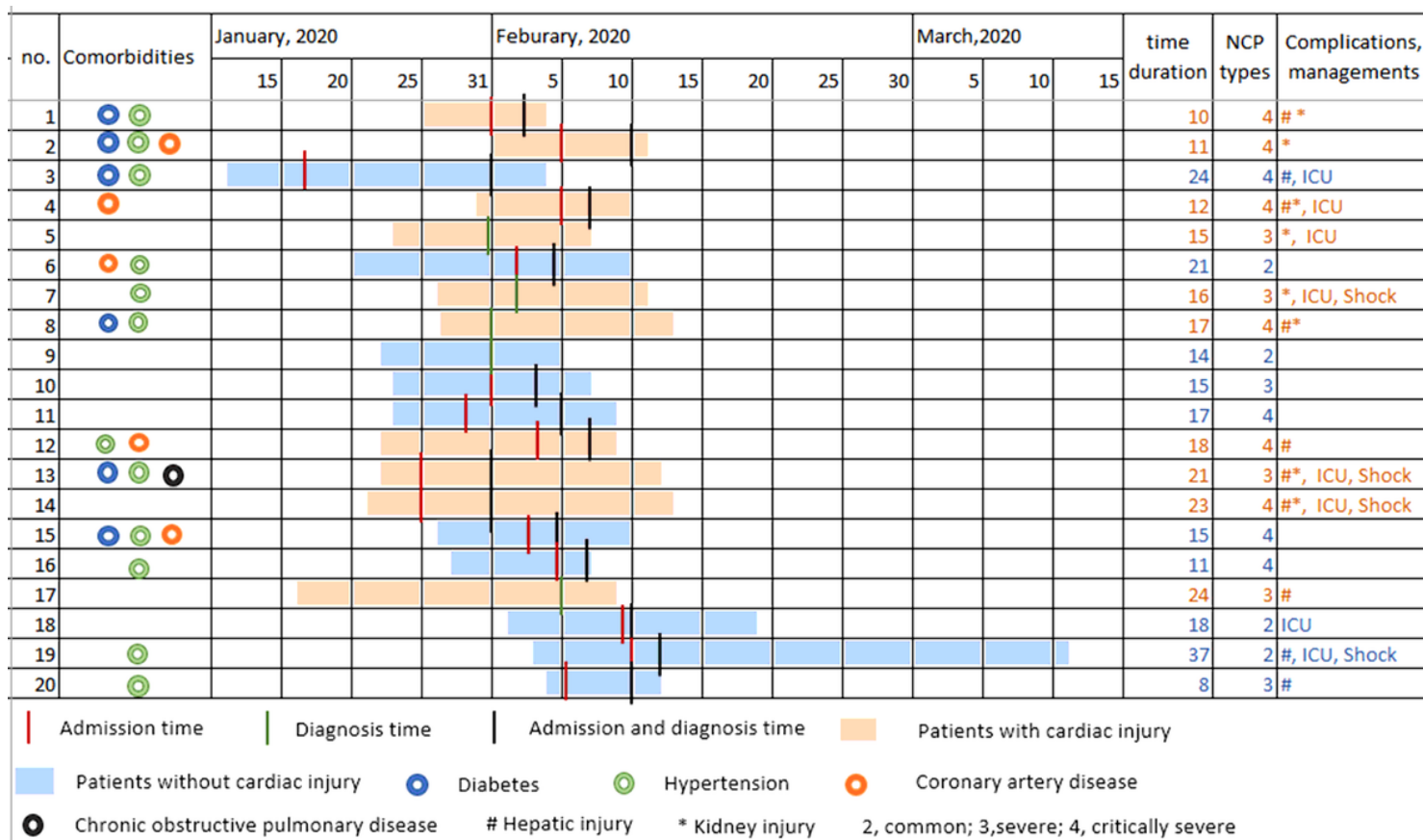| no. | Comorbidities | January, 2020 / February, 2020 / March, 2020 timeline | time duration | NCP types | Complications, managements |
|---|---|---|---|---|---|
| 1 | Diabetes, Hypertension | | 10 | 4 | # * |
| 2 | Diabetes, Hypertension, Coronary artery disease | | 11 | 4 | * |
| 3 | Diabetes, Hypertension | | 24 | 4 | #, ICU |
| 4 | Coronary artery disease | | 12 | 4 | #*, ICU |
| 5 | | | 15 | 3 | *, ICU |
| 6 | Coronary artery disease, Hypertension | | 21 | 2 | |
| 7 | Hypertension | | 16 | 3 | *, ICU, Shock |
| 8 | Diabetes, Hypertension | | 17 | 4 | #* |
| 9 | | | 14 | 2 | |
| 10 | | | 15 | 3 | |
| 11 | | | 17 | 4 | |
| 12 | Hypertension, Coronary artery disease | | 18 | 4 | # |
| 13 | Diabetes, Hypertension, Chronic obstructive pulmonary disease | | 21 | 3 | #*, ICU, Shock |
| 14 | | | 23 | 4 | #*, ICU, Shock |
| 15 | Diabetes, Hypertension, Coronary artery disease | | 15 | 4 | |
| 16 | Hypertension | | 11 | 4 | |
| 17 | | | 24 | 3 | # |
| 18 | | | 18 | 2 | ICU |
| 19 | Hypertension | | 37 | 2 | #, ICU, Shock |
| 20 | Hypertension | | 8 | 3 | # |

Legend:
Admission time | Diagnosis time | Admission and diagnosis time | Patients with cardiac injury
Patients without cardiac injury | Diabetes | Hypertension | Coronary artery disease
Chronic obstructive pulmonary disease | # Hepatic injury | * Kidney injury | 2, common; 3, severe; 4, critically severe

**Figure 3**

Days from symptom onset to death of COVID-19 patients with or without myocardial injury and their comorbidities, complications, managements. Comparison of days from symptom onset to death of typical 20 patients with COVID-19 with myocardial injury (10 patients) or without myocardial injury (10 patients) randomly selected from dead patients. Patients with myocardial injury were more likely to have comorbidities, severe presentation, and complications, shock and ICU managements. However, no significant difference was found for time duration from symptom onset to death in two groups. This figure tells us that myocardial injury may be associated with more severe presentation. ICU: intensive care unit.
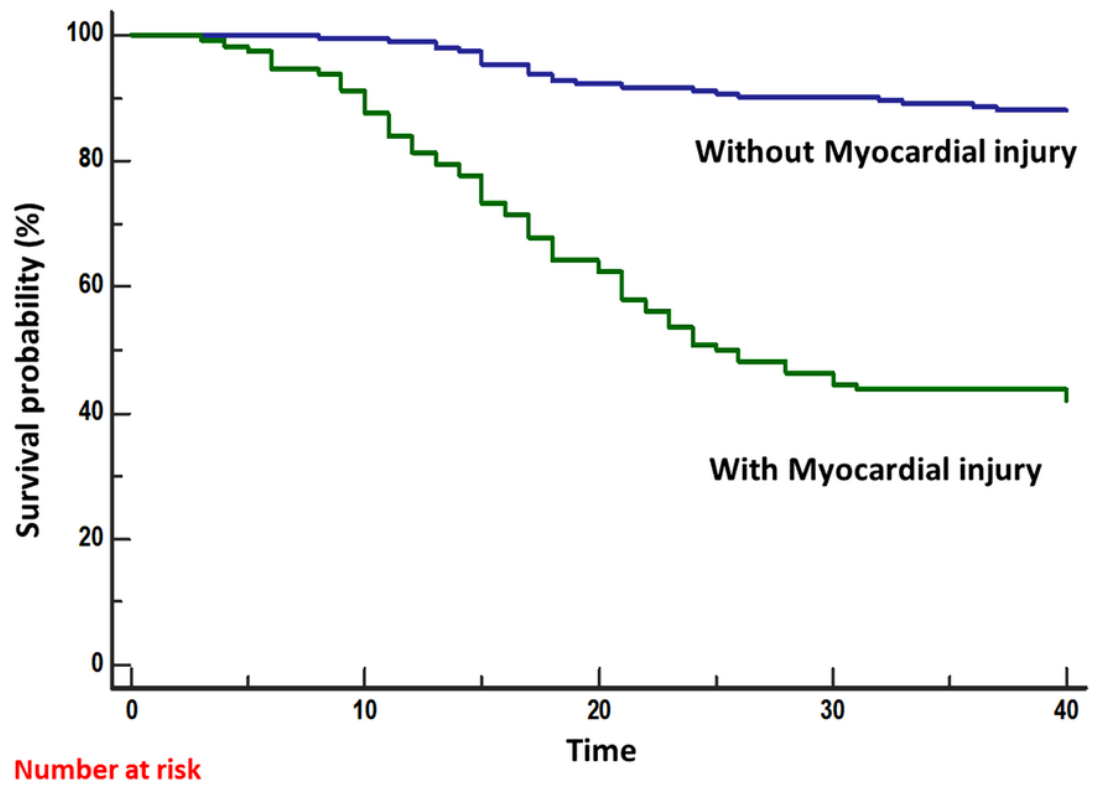
**Figure 4**

Mortality During Hospitalization Between Patients With vs Without Myocardial injury. Kaplan-Meier survival curves for mortality from symptom onset to follow-up date.

## Supplementary Files

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- SupplementaryFiles.docx