# The Cardiac Injury in Hospitalized Patients with Severe COVID-19 in Wuhan, China

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**Research Article**

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# Abstract

**Background:** The Coronavirus disease 2019 (COVID-19) has caused a global pandemic since December 2019, while the date on the relationship between cardiac injury and mortality in patients with COVID-19 is limited.

**Methods:** All consecutive lab-confirmed critically ill COVID-19 patients in intensive care unit of Wuhan Red Cross Hospital from December 30, 2019 to March 18, 2020, were enrolled. Data of patients were collected. The prevalence of cardiac injury and its association with in-hospital mortality was analyzed.

**Results:** Among the 50 ICU patients, 36 patients (72.0%) were complicated with cardiac injury and 14 patients (28.0%) without cardiac injury. Patients with cardiac injury had higher white blood cell counts, values of d-dimer, levels of lactate concentration, APACHE II score and lower $PaO_2/FiO_2$ at the time of admission than those without cardiac injury. The in-hospital case fatality ratio was higher in the cardiac injury than non-cardiac injury group (75.0% vs 21.4%;p=0.002).Multivariable-adjusted logistic proportional hazard regression analysis showed that a significantly higher risk of death in patients with cardiac injury than those without cardiac injury (OR, 5.876; 95% CI, 1.039–33.228).

**Conclusions:** Cardiac injury is a common compilation and associated with higher risk of in-hospital death in patients with severe COVID-19.


# Introduction

Since December 2019, there has been a series of unexplained cases of pneumonia reported in Wuhan, China. On January 12, 2020, the World Health Organization (WHO) tentatively named this new virus as the 2019 novel coronavirus (2019-nCoV). On February 11, 2020, the WHO formally named the disease triggered by 2019-nCoV as Corona Virus Disease 2019 (COVID-19)[1-5]. Most patients have mild symptoms and good prognosis. a few patients with 2019-nCoV have developed severe pneumonia, pulmonary edema, ARDS, or multiple organ failure and have died. The number of infections has exceeded that of the Severe Acute Respiratory Syndrome (SARS) outbreak in China in 2002[6,7]. The COVID-19 has caused a global pandemic since December 2019 [8,9].

Even though we know that the COVID-19 can cause acute respiratory distress syndrome (ARDS), pneumonia, Acute liver injury, shock, secondary infection and multiple organ failure [10,11], we still know little about cardiac injury after 2019-nCoV viral infection. There are few research reports that cardiac injury in patients with COVID-19. A recent study reported that Hypersensitive troponin I (hs-cTnI) was increased substantially in five patients, in whom the diagnosis of virus-related cardiac injury was made. In that study, the incidence of cardiac injury is almost 12%. Another study reported that complications occurred in 77cases (55.8%) of the 138 patients with COVID-19, including 10 cases (7.2%) with acute myocardial injury and 23 cases (16.7%) with arrhythmia. Cardiac injury occurs more frequently in ICU patients [12]. However, the risk factors of cardiac injury in COVID-19 patients were still not clear. In addition, there are few studies about the relationship between cardiac injury and risk of mortality among people with severe COVID-19.

We aim to explore the potential association between cardiac injury and mortality in patients with severe COVID-19.

# Methods

## Study Design and Participants

All consecutive patients with confirmed COVID-19 admitted to ICU of Wuhan Red Cross Hospital from December 30, 2019 to March 18, 2020, were enrolled. Informed consent was obtained from all patients and next of kin of the deceased patients. The study was approved by Wuhan Red Cross Hospital Ethics Committee (2020015). The study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. The authors were responsible for designing the trial and for compiling and analyzing the data. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol .Wuhan Red Cross hospital, located in Wuhan, Hubei Province, All patients with COVID-19 enrolled in this study were diagnosed according to World Health Organization interim guidance[13].2019-nCoV was confirmed by real-time RT-PCR on respiratory samples (nasal swab, throat swab, or endotracheal aspirates) collected from these patients upon admission[10].Additionally, all patients were given chest x-rays or chest CT. Cardiac testing was ordered by the treating physicians. Patients were followed up from admission to death during hospitalization or hospital discharge.

## Data Collection

We obtained demographic characteristics (age, gender), clinical characteristics (comorbidities, laboratory findings, severity of illness scores, treatments, complications, and outcomes date), and results of cardiac examinations (cardiac biomarkers) for participants during hospitalization from patients' medical records. Results of cardiac biomarkers included values of TNI. While TNI was counted on the 1st, f ICU admission. Cardiac injury was defined as blood levels of cardiac biomarkers (TNI) above the 99th percentile upper reference limit [10,14].

## Statistical analysis

Categorical data are expressed as proportions. Continuous data were presented as mean ± sd if they were normally distributed, or as median (interquartile range [IQR]). Continuous variables were compared by Student t test or Mann-Whitney U test, as appropriate, while differences in categorical variables were assessed using the Chi-square test or Fisher's exact test, as appropriate. Multivariate Logistic regression analysis was used to analyze the independent risk factors of death during hospitalization. The results of multivariable modeling are given in the form of adjusted odds ratio, 95% confidence interval and Wald test p value. Survival curves were plotted using the Kaplan-Meier method and compared between patients with or without cardiac injury using the log-rank test. Data were analyzed using SPSS 23.0 (IBM, Chicago, IL). Statistical charts were performed using Excel 2016, A two-tailed *p* value of less than 0.05 was considered statistically significant.

# Results

## Patient Characteristics

The flowchart of patients recruitment was presented in **Figure.1**. There are 72 patients in the medical record system who were screened initially from December 30, 2019 to March 18, 2020. Twenty two patients with missing key data of laboratory examination (TNI ) or medical records were excluded. The mean age of these 50 patients was 65.2 years, and 21 (42.0%) were female. The details of baseline characteristics were presented in the **Table.1**. Among the 50 patients hospitalized with confirmed COVID-19, 36 patients (72.0%) were complicated with cardiac injury and 14 patients (28.0%) without cardiac injury. Hypertension (19 patients [38%]), cardiovascular disease (9 patients [18%]) and diabetes (9 patients [18%]) were the most common comorbidities. The proportion of Cerebrovascular disease, chronic obstructive pulmonary disease and tumor was 6 patients (12%), 7 patients (14%), and 4 patients (8%), respectively. The median time from symptom onset to hospitalization is 10.0days.

## Laboratory, Complications, Treatment and Outcomes

Of 50 patients, the median levels of TNI, d-dimer, lactate concentration and Pao2/Fio2 on the first day of admission were 0.1 ug/L (IQR, 0.03-0.48), 10.0 ug/L (IQR, 1.9-36.1) ,2.1mmol/L (IQR, 1.4-3.3), 81mmHg (IQR, 65.5-134.0), respectively. The median value of APACHE II score, WBC count, PLT count on the first day of admission were 12.0(IQR,9.0-16.3),9.7(IQR,6.9-12.2)×$10^9$/L,146.0(IQR,91.5-205.0)×$10^9$/L, respectively. The details of baseline characteristics were presented in the **Table.2**. During hospitalization, 66% of the patients'$PaO_2/FiO_2$ was less than 100mmHg,44% (22 patients) of patients were treated with invasive mechanical ventilation,26% (23 patients) were treated with vasoactive drugs,14%(7patients) were treated with renal replacement therapy, and2%(1patients) were treated with extracorporeal membrane oxygenation. There were 5 patients (10%) with acute left heart failure, 2 patients (4%) with Malignant arrhythmia and 2 patients (4%) with acute coronary syndrome during the course of the disease. The median levels of length of ICU stay in days and hospital length of stay were 6.0 days (IQR, 3.8-13.0), were 15.5days (IQR, 6.0-30.3), respectively. The hospital mortality rate is 60% among 50 patients.

In terms of laboratory findings, patients with cardiac injury compared with patients without cardiac injury showed higher median white blood cell count (median [IQR], 10.4 [7.5-13.6] vs 8.0 [5.2-9.7] ×$10^9$/L; p =0.032), higher APACHE II score on day 1 (median [IQR], 14.0 [9.3-17.0] vs10.5[7.8-12.0]; p =0.019) and showed lower mean platelet count (median [IQR],136.0 [82.0-191.0] vs196.5 [129.0-298.3] ×$10^9$/L; p =0.015). Patients with cardiac injury presented with higher median values of d-dimer at the time of admission (median [IQR], 26.0 [2.3-69.9] vs 4.2 [1.6-8.7] ug/L; p =0.012), levels of TNI (median [IQR], 0.20[0.08-1.27] vs 0.02[0.01-003] ug/L; p□0.001), levels of lactate concentration(median [IQR], 2.2[1.6-3.6]vs 1.5[1.0-2.2] mmol/L; p =0.029), Furthermore, there is a higher proportion of patients with cardiac injury whose $PaO_2/FiO_2$ is less than 100mmHg(75.0% vs 42.9%; p= 0.031) and a greater proportion of patients with cardiac injury required invasive mechanical ventilation (52.8% vs 21.4%; p= 0.091) and vasopressor therapy (58.3% vs 14.3%;p =0.013)than those without cardiac injury. While the cardiac injury group had a

lower hospital length of stay (median [IQR], 10.5[4.0-25.8] vs 30[11.3-41.5] days; p =0.016) and a higher proportion of in-hospital death (75.0% vs 21.4%; p=0.002).

### Cardiac Injury and Mortality

Patients with cardiac injury had significantly higher in-hospital mortality than those without cardiac injury (log-rank p =0.002) (**Figure. 2**). After adjusting for age, preexisting cardiovascular diseases, APACHE II score and $PaO_2/FiO_2$ in the multivariable-adjusted logistic proportional hazard regression model, a significantly higher risk of death was shown in patients with cardiac injury than those without (OR, 5.876; 95% CI, 1.039–33.228) (**Table.3**). No significant association was found between preexisting cardiac conditions and mortality in all patients (OR,3.163;95% CI, 0.311-32.132).

# Discussion

In this retrospective study, we found that there was a high proportion of cardiac injury in COVID-19 patients (72%), characterized by elevated TNI levels, while patients with cardiac injury had higher white blood cell counts, values of d-dimer, levels of lactate concentration, APACHE II score and a higher proportion of $PaO_2/FiO_2$ less than 100mmHg at the time of admission than those without cardiac injury. At the same time, we found that the in-hospital mortality of patients with cardiac injury (75%) was significantly higher than that patients without cardiac injury (21.4%). cardiac injury was independently associated with an increased risk of mortality during hospitalization among patients with COVID-19.

Of the 50 patients with COVID-19, 36 patients (72%) had myocardial damage, which was characterized by an increase in the level of TNI. The mortality during hospitalization of patients with cardiac injury (75%) was significantly higher than that of patients without cardiac injury (21.4%). Another study reported the complications in 77 (55.8%) of 138patients with COVID-19, including 10 cases of acute myocardial injury (7.2%) and 23 cases of arrhythmias (16.7%), ICU patients were more likely to develop cardiac injury [12]. In our study, the incidence of cardiac injury is higher, and we speculate that it is related to the fact that all the patients in our study are ICU patients. The mortality during hospitalization of our patients is as high as 60%. ICU patients are more seriously ill and are more likely to be complicated with cardiac injury. Compared with patients without cardiac injury, patients with cardiac injury showed a more serious state of disease, such as abnormal laboratory indexes, such as white blood cell count, d-dimer levels and elevated levels of blood lactic acid and C-reactive protein levels and the proportion of patients with $PaO_2/FiO_2$ less than 100mmHg is higher, while more patients need invasive ventilation and vasoactive drugs to support treatment. Our study further confirms that cardiac injury is a common complication in severe patients with COVID-19.

At the present, the mechanism of cardiac injury caused by COVID-19 is not very clear. In a case report of cardiogenic shock caused by COVID-19, the pathological results of endocardial biopsy showed that the ultrastructural study of mild interstitial and endocardial inflammation and the accumulation of single or small groups of viral particles in the form of coronavirus, suggesting that there may be direct myocardial damage caused by viral infection [15]. Another study shows that cytokine storm may be one of the

mechanisms of cardiac injury, the plasma cytokine levels in COVID-19 patients are higher than those in non-cardiac injury group. Our study also found that leukocyte count and d-dimer levels in cardiac injury group were higher than those in non- cardiac injury group, and the activation or enhanced release of these inflammatory cytokines could lead to cardiomyocyte apoptosis or necrosis. The cytokine response is the mediator of atherosclerosis, which directly leads to plaque rupture, induces procoagulant factors, and hemodynamic changes prone to ischemia and thrombosis through local inflammation [16,17]. APACHE□ score system was proposed by KNAUS et al.[18] in 1985 as a method to evaluate the condition and prognosis of patients. Our study suggests that the cardiac injury group has a higher APACHE□ score and indicates that the patient is in a critical condition, is more likely to be complicated with multiple organ dysfunction, and is more likely to be complicated with hypoxemia. In this study, we found that there were more patients with cardiac injury whose $PaO_2/FiO_2$ was less than 100 mmHg.While continuous hypoxia will increase anaerobic glycolysis, cause acidosis, increase of intracellular oxygen free radicals and intracellular calcium overload, which is an important mechanism leading to cardiomyocyte injury [19]. Therefore, patients with increased white blood cell count, elevated d-dimer levels, $PaO_2/FiO_2$ less than 100mmHg and high APACHEII score at admission are more likely to be complicated with cardiac injury.

In this study, the mortality during hospitalization of patients with cardiac injury (75%) was significantly higher than that of patients without cardiac injury (21.4%). Cardiac injury is an independent risk of mortality in patients with COVID-19, and a recent study suggests that cardiac injury is a common complication in hospitalized patients with COVID-19, which is associated with higher in-hospital mortality [20]. While a recent study suggest that cardiac injury is associated with poor prognosis in patients with COVID-19. Cardiac injury is associated with impaired cardiac function and ventricular tachyarrhythmia[21]. Our study further confirmed that cardiac injury is an independent risk factor for mortality in patients with COVID-19.

There are some limitations in our study. Firstly, as a retrospective study, due to the limitations of isolation ward conditions and the urgency of controlling the COVID-19 epidemic, the study did not provide some other echocardiographic data and ECG data, which limited the determination of the underlying mechanism of heart injury. Secondly, this study is a single-center, retrospective study, the sample size is small, and its conclusion still needs to be confirmed by further larger sample size research.

# Conclusions

Cardiac injury is a common condition in patients with COVID-19. Cardiac injury is associated with higher risk of in hospital mortality in patients with COVID-19. Although the exact mechanism of cardiac injury needs to be further explored, the findings presented here emphasize the need to consider this complication in the treatment of patients with COVID-19. During hospitalization, the monitoring of myocardial injury markers and cardiac function in patients with COVID-19 should be strengthened.

# Abbreviations

COVID-19: Coronavirus disease 2019; ARDS: Acute respiratory distress syndrome; ECMO: Extracorporeal membrane oxygenation; APACHEII score: Acute physiology and chronic health evaluation score.

# Declarations


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### Authors' contributions

SL and HLH, manuscript writing; RAL, YQW,LD and PW, data collection and analysis; XBH, WWH, YP, HWX, GL,manuscript revision. The authors read and approved the final manuscript.


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### Availability of data and materials

The datasets used in the present study are available from the first author and corresponding authors on reasonable request.

### Ethics approval and consent to participate

The study was approved by Wuhan Red Cross hospital Ethics Committee.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### Additional information


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# Tables

**Table 1. Comparison of Demographic and Preexisting Medical Conditions in hospitalized patients** with COVID-19

| Characteristic | All Patients (n=50) | With Cardiac Injury (n=36) | Without Cardiac Injury (n=14) | | p |
|---|---|---|---|---|---|
| Age(yr), median (IQR) | 66.0(57.8-73.2) | 66.0(61.0-72.3) | 59.0(51.3-76.3) | 0.315 | |
| Female, n (%) | 21(42.0) | 14(38.9) | 7(50.0) | | 0.475 |
| Current smokers, n (%) | 9 (18.0) | 8(22.2) | 1(7.1) | | 0.403 |
| Preexisting condition, n (%) | | | | | |
| Cardiovascular disease [a] | 9(18.0) | 8(22.2) | 1(7.1) | | 0.403 |
| Diabetes | 9(18.0) | 7(19.4) | 2(14.3) | | 0.987 |
| Cerebrovascular disease [b] | 6(12.0) | 4(11.1) | 2(14.3) | | 1.000 |
| Hypertension disease | 19(38.0) | 15(41.7) | 4(28.6) | | 0.595 |
| COPD [c] | 7 (14.0) | 4(11.1) | 3(21.4) | | 0.624 |
| Tumor | 4 (8.0) | 3(8.3) | 1(7.1) | | 1.000 |
| Time from symptom onset to hospitalization（d）,mean ± sd | 10.0(7.0-14.2) | 10.0(7.0-14.8) | 10.0(6.8-14.3) | 0.649 | |

[a] Cardiovascular disease was defined as congestive heart failure, known conduction system abnormality, arrhythmia or ischemic heart disease.

[b] Cerebrovascular disease was defined as ischemic or hemorrhagic stroke.

[c] Chronic obstructive pulmonary disease

**Table2. Comparison of Laboratory findings, Treatment, and Outcomes in hospitalized patients with COVID-19**

| | All Patients (n=50) | With Cardiac Injury (n=36) | Without Cardiac Injury (n=14) | P |
|---|---|---|---|---|
| lings at admission, values are presented as median (IQR) | | | | |
| $10^9$/L) | 9.7(6.9-12.2) | 10.4(7,5-13.6) | 8.0(5.2-9.7) | 0.032 |
| (IQR) | 0.6(0.4-0.9) | 0.6(0.4-0.9) | 0.7(0.5-0.9) | 0.381 |
| $10^9$/L) | 146.0(91.5-205.0) | 136.0(82.0-191.0) | 196.5(129.0-298.3) | 0.015 |
| otein | 80.9(52.3-153.7) | 87.3(66.7-142.0) | 55(39.1-169.6) | 0.093 |
| L) (IQR) | 10.0(1.9-36.1) | 26.0(2.3-69.9) | 4.2(1.6-8.7) | 0.012 |
| g/L | 0.10(0.03-0.48) | 0.20(0.08-1.27) | 0.02(0.01-0.03) | 0.001 |
| mHg) | 81(65.5-134.0) | 78.0(65.3-106.5) | 138(66-193.5) | 0.118 |
| 00(mmHg), | 33(66.0) | 27(75.0) | 6(42.9) | 0.031 |
| mmol/L) | 2.1(1.4-3.3) | 2.2(1.6-3.6) | 1.5(1.0-2.2) | 0.029 |
| score on | 12.0(9.0-16.3) | 14.0(9.3-17.0) | 10.5(7.8-12.0) | 0.019 |
| %) | | | | |
| asive tilation | 22(44.0) | 19(52.8) | 3(21.4) | 0.091 |
| herapy | 23(46.0) | 21 (58.3) | 2(14.3) | 0.013 |
| uous renal erapy | 7(14.0) | 7(19.4) | 0(0.0) | 0.169 |
| orporeal genation | 1 (2.0) | 1(2.8) | 0 (0.0) | 1.000 |
| related events occurred during hospitalization, n (%) | | | | |
| heart | 5(10.0) | 3(8.3) | 2(14.3) | 0.916 |
| rhythmia [e] | 2((4.0) | 2(5.6) | 0(0.0) | 1.000 |
| ry | 2((4.0) | 2(5.6) | 0(0.0) | 1.000 |
| stay in | 6.0(3.8-13.0) | 6.0(3.0-12.8) | 6.5(4.0-14.5) | 0.617 |
| of stay | 15.5(6-30.3) | 10.5(4.0-25.8) | 30(11.3-41.5) | 0.016 |
| h, n (%) | 30(60.0) | 27(75.0) | 3(21.4) | 0.002 |

[a] WBC=White blood cell; [b] PLT= platelets; [c] TNI= Troponin

[d] Acute Physiology and Chronic Health Evaluation II score

[e] Malignant arrhythmia was defined as supraventricular tachycardia, ventricular fibrillation, ventricular tachycardia or frequent premature ventricular.

**Table 3. Multivariate Logistic regression analysis of cardiac injury associated with mortality in hospitalized patients with COVID-19**

| Variable | Aadjusted OR(95% CI) | p value |
|---|---|---|
| Age | 1.065 (0.980-1.158) | 0.138 |
| APACHE II score [a] | 1.129(0.927-1.376) | 0.228 |
| $PaO_2/FIO_2$ | 0.990(0.976-1.005) | 0.201 |
| Cardiac injury | 5.876(1.039-33.228) | 0.045 |
| Pre-existing cardiac conditions [b] | 3.163 (0.311-32.132) | 0.158 |

[a] APACHE II score was assessed within 24 hours of admission to hospital

[b] Cardiovascular disease was defined as congestive heart failure, known conduction system abnormality, arrhythmia or ischemic heart disease

# Figures

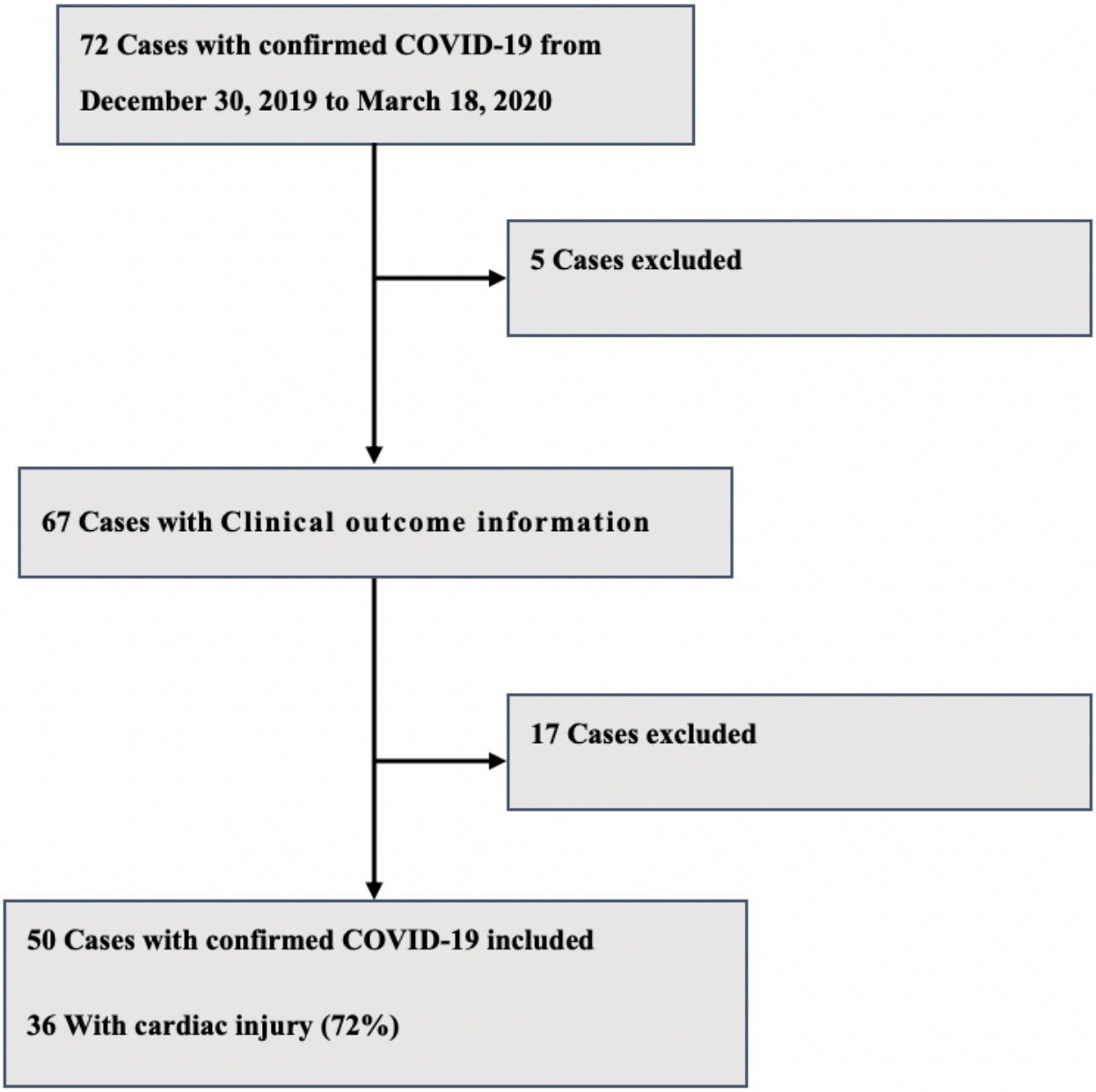
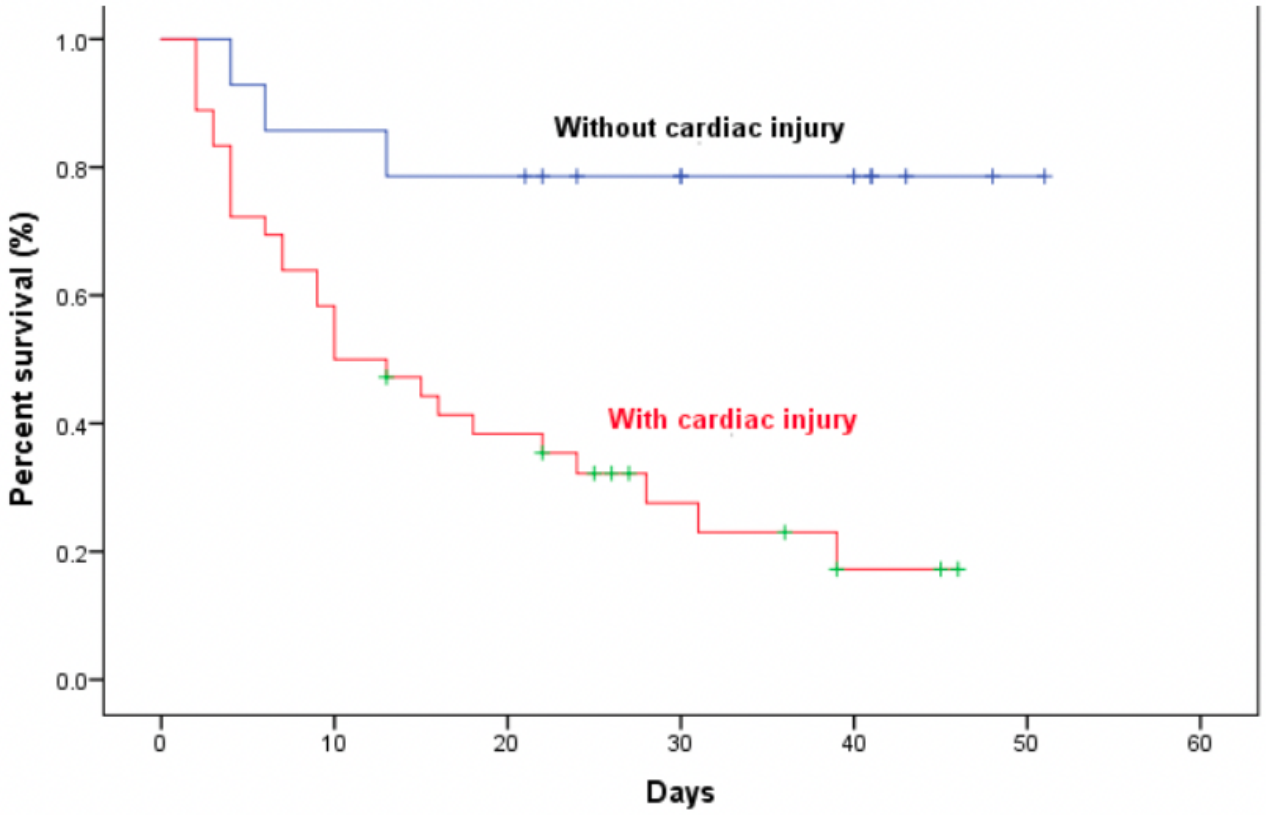



**Figure 1**

Flowchart of Patient Recruitment

**Figure 2. Kaplan-Meier survival curves for mortality during hospitalization**

| | | No. of events/ No. of patients | log-rank P |
|---|---|---|---|
| — | With cardiac injury | 3/14 | 0.002 |
| — | Without cardiac injury | 27/36 | |




| k | | | | | | | |
|---|---|---|---|---|---|---|---|
| diac injury | 36 | 18 | 13 | 6 | 2 | 0 | 0 |
| cardiac injury | 14 | 12 | 10 | 6 | 5 | 1 | 0 |

**The numbers under the graph represent the number of hospitalized patients with or without cardiac injury at risk of death on the indicated day.**

Figure 2