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Heart injury signs are associated with higher and earlier mortality in coronavirus disease 2019 (COVID-19)

Chaomin Wu[1,2*], Xianglin Hu[2*], Jianxin Song[3*], Chunling Du[1*], Jie Xu[4], Dong Yang[2], Dechang Chen[5], Ming Zhong[6], Jinjun Jiang[2], Weining Xiong[7], Ke Lang[2], Yuye Zhang[2], Guohua Shi[8], Lei Xu[9], Yuanlin Song[1,2,10,11†], Xin Zhou[12†], Ming Wei[13†], Junhua Zheng[13,14†].; The first batch of medical teams from Shanghai to support Hubei, China and study group.

1. Department of Pulmonary Medicine, QingPu Branch of Zhongshan Hospital Affiliated to Fudan University, Shanghai 201700, China.
2. Department of Pulmonary Medicine, Zhongshan Hospital, Fudan University, Shanghai 200032, China.
3. Department of Infectious Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 430030, Wuhan, China.
4. Department of Infectious Diseases, Fengxian Guhua Hospital, Shanghai, China.
5. Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China.
6. Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai 200032, China.
7. Department of Respiratory Medicine, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.
8. Department of Pulmonary Medicine, Qingpu Traditional Chinese Medicine Hospital, Shanghai, China.
9. Department of Emergency Medicine, Gongli Hospital, Pudong New Area, Shanghai, China.
10. Shanghai Respiratory Research Institute, Shanghai 200032, China.
11. National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University, Shanghai, China.

12. Department of Pulmonary Medicine, Shanghai General Hospital, School of Medicine in Shanghai Jiao Tong University, Shanghai, 200080, China.

13. Tuberculosis and Respiratory Department, Wuhan Jinyintan Hospital, Wuhan 430023, China.

14. Department of Urology, Shanghai General Hospital, School of Medicine in Shanghai Jiao Tong University, Shanghai, 200080, China.

* Chaomin Wu, Xianglin Hu, Jianxin Song and Chunling Du contributed equally to this work.

† **Corresponding author:**

Yuanlin Song, Department of Pulmonary Medicine, Zhongshan Hospital, Fudan University, Shanghai 200032, China. E-mail: ylsong70@163.com

Xin Zhou, Department of Pulmonary Medicine, Shanghai General Hospital, School of Medicine in Shanghai Jiao Tong University, Shanghai, 200080, China. E-mail: xzhou53@163.com

Ming Wei, Tuberculosis and Respiratory Department, Wuhan Jinyintan Hospital, Wuhan 430023, China. 1508257434@qq.com

Junhua Zheng, Department of Urology, Shanghai General Hospital, School of Medicine in Shanghai Jiao Tong University, Shanghai, 200080, China. E-mail: zhengjh0471@sina.com

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Key points

Question

Does coronavirus disease 2019 (COVID-19) cause heart injury and hereby impact mortality?

Findings

In this retrospective cohort study including 188 patients with COVID-19, patients with high levels of high-sensitivity cardiac troponin I (hs-TNI) on admission had significantly higher mortality (50.0%) than patients with moderate or low levels of hs-TNI (10.0% or 9.1%). hs-TNI level on admission was significantly negatively correlated with survival days (r= -0.42, 95% CI= -0.64~-0.12, P=0.005).

Meaning

COVID-19 patients with signs of heart injury on admission must be early identified and carefully managed by cardiologists, in order to maximally prevent or rescue heart injury-related mortality in COVID-19.

Abstract

Importance

Heart injury can be easily induced by viral infection such as adenovirus and enterovirus. However, whether coronavirus disease 2019 (COVID-19) causes heart injury and hereby impacts mortality has not yet been fully evaluated.

Objective

To explore whether heart injury occurs in COVID-19 on admission and hereby aggravates mortality later.

Design, Setting, and Participants

A single-center retrospective cohort study including 188 COVID-19 patients admitted from December 25, 2019 to January 27, 2020 in Wuhan Jinyintan Hospital, China; follow up was completed on February 11, 2020.

Exposures

High levels of heart injury indicators on admission (hs-TNI; CK; CK-MB; LDH; α-HBDH).

Main Outcomes and Measures

Mortality in hospital and days from admission to mortality (survival days).

Results

Of 188 patients with COVID-19, the mean age was 51.9 years (standard deviation: 14.26; range: 21~83 years) and 119 (63.3%) were male. Increased hs-TnI levels on admission tended to occur in older patients and patients with comorbidity (especially hypertension). High hs-TnI on admission ($\geq$ 6.126 pg/mL), even within the clinical

normal range (0~28 pg/mL), already can be associated with higher mortality. High hs-TnI was associated with increased inflammatory levels (neutrophils, IL-6, CRP, and PCT) and decreased immune levels (lymphocytes, monocytes, and CD4$^+$ and CD8$^+$ T cells). CK was not associated with mortality. Increased CK-MB levels tended to occur in male patients and patients with current smoking. High CK-MB on admission was associated with higher mortality. High CK-MB was associated with increased inflammatory levels and decreased lymphocytes. Increased LDH and α-HBDH levels tended to occur in older patients and patients with hypertension. Both high LDH and α-HBDH on admission were associated with higher mortality. Both high LDH and α-HBDH were associated with increased inflammatory levels and decreased immune levels. hs-TNI level on admission was negatively correlated with survival days (r= -0.42, 95% CI= -0.64~-0.12, P=0.005). LDH level on admission was negatively correlated with survival days (r= -0.35, 95% CI= -0.59~-0.05, P=0.022).

Conclusions and Relevance

Heart injury signs arise in COVID-19, especially in older patients, patients with hypertension and male patients with current smoking. COVID-19 virus might attack heart via inducing inflammatory storm. High levels of heart injury indicators on admission are associated with higher mortality and shorter survival days. COVID-19 patients with signs of heart injury on admission must be early identified and carefully managed by cardiologists, because COVID-19 is never just confined to respiratory injury.

Introduction

Viral infection is a common cause of heart injury such as myocarditis. It is well known that adenovirus, enterovirus and herpesvirus are the most common infectious etiologies for heart injury [1]. Since coronavirus-related carditis was first reported in 1980 [2], increasing studies noted that coronavirus is an uncommon but unneglectable pathogen for heart injury. For instance, we found the coronavirus of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003 in China had no obvious connections with heart injury. However, it was reported that the coronavirus of Middle East Respiratory Syndrome (MERS-CoV) in 2012 in Saudi Arabia could cause acute myocarditis and heart failure [3].

Coronavirus disease 2019 (COVID-19) is a novel infectious viral pneumonia breaking out in Wuhan, China since Dec, 2019 [4, 5]. By Feb 20, 2020 in China, 75,465 patients were diagnosed with COVID-19 and 2,236 patients deceased [6]. Based on our recent experts clinical experience on COVID-19, we found severe COVID-19 patients are difficult to rescue not only because respiratory failure but also susceptibility to heart failure. The coronavirus for COVID-19 is a new strain which was not previously identified. Whether the coronavirus for COVID-19 causes heart injury and thereby impacts mortality has not been fully evaluated. Therefore, in this retrospective cohort study, we fully assessed heart injury indicators on admission in COVID-19 patients. We aimed to explore whether heart injury already occurs in COVID-19 at early stage and hereby aggravates mortality later.

Methods

Study population

From Dec 25, 2019 to Jan 27, 2020, 188 COVID-19 patients admitted to Wuhan Jinyintan Hospital (Hubei, China) were selected. All enrolled patients were definitely diagnosed with COVID-19 pneumonia according to the previously reported criteria [7]. Patients with missing clinical information were excluded. Age of the enrolled patients ranged from 21 to 83 years old. Up to Feb 11, 2020, follow up in hospital was completed for all patients. One hundred and forty-five patients were cured and discharged while 43 patients deceased in hospital. This research was approved by the Review Board of Wuhan Jinyintan Hospital. Written informed consent was waived because this research was retrospective observation and deindividuation.

Data collection

Data were retrieved from electronic medical records. Demographic and clinical parameters included age, gender, history of Huanan seafood market exposure, history of family infection, smoking status, comorbidity, initial symptoms and signs, vital signs on admission, complications on admission and drug treatment regimen. Primary outcome was mortality in hospital. Days from admission to death (survival days) were also calculated for deceased patients. Whether transfer to intensive care unit (ICU) was recorded as a secondary outcome.

Heart injury indicators measured on admission were collected, including high-sensitivity cardiac troponin I (hs-TNI), creatine kinase (CK), creatine kinase-MB (CK-MB), lactic dehydrogenase (LDH) and α-hydroxybutyrate dehydrogenase

(α-HBDH). The clinical normal range of hs-TNI was 0~28 pg/mL. The clinical normal range of CK was 50~310 U/L. The clinical normal range of CK-MB was 0~24 U/L. The clinical normal range of LDH was 120~250 U/L. The clinical normal range of α-HBDH was 72~182 U/L. All Heart injury indicators were divided into three levels (low, moderate or high level) based on the cutoff values of 33th and 67th percentile.

Inflammatory levels indicators were collected, including white blood cells (WBC), neutrophils, interleukin-6 (IL-6), C-reaction protein (CRP), procalcitonin (PCT) and erythrocyte sedimentation rate (ESR). Immune levels indicators were collected, including lymphocytes, monocytes, T cells count, and $CD4^+$ and $CD8^+$ T cells count.

Statistical analysis

SPSS for Windows (Version 24.0, IBM) and Graphpad prism 7.0 software were used for statistical analysis. Continuous parameters were displayed by mean ± standard deviation (SD) or median with quartiles. Categorical parameters were displayed by percentage with number. One way ANOVA or Kruskal-Wallis test was performed for multiple comparisons of continuous data. Tukey's multiple comparisons test or Dunn's multiple comparisons test was used for adjusted P value. Chi-square test was performed for categorical data and Bonferroni method was used for adjusted P value. Spearman correlation was performed. Coefficient of r with 95% confidence interval (CI) was used to measure the correlation magnitude. P< 0.05 was considered statistically significant.

Results

The baseline clinical and laboratory characteristics were presented in **Table 1**. Patients' mean age was 51.9 ± 14.26 years old. Male accounted for 63.3% of the population. Huanan seafood market exposure accounted for 48.9% while infection by family members accounted for 8.0% of the population. There were 9.0% patients with current smoking. Hypertension (20.2%) and diabetes (10.6%) ranked as the most common comorbidities. Fever (92.6%) and cough (83.5%) were the most common initial symptoms and signs. Approximately 11.2% patients had hs-TNI exceeding clinical upper normal limit on admission. Approximately 68.6% patients had LDH exceeding clinical upper normal limit on admission. Approximately 76.1% patients had α-HBDH exceeding clinical upper normal limit on admission. Approximately 11.2% patients had CK exceeding clinical upper normal limit on admission. Approximately 10.1% patients had CK-MB exceeding clinical upper normal limit on admission. Antibiotics (98.4%) and non-specific antiviral drugs (84.0%) were used in most patients. There were 50 (26.6%) patients transferring to ICU. There were 43 (22.9%) patients deceasing in hospital. The median survival days for deceased patients were 7 (4-11) days.

As shown in **Table 2**, increased hs-TnI levels were more likely to occur in older patients and patients with hypertension or diabetes. High hs-TnI was independent of acute respiratory symptoms and respiratory failure ($P > 0.05$). High hs-TnI on admission ($\geq$ 6.126 pg/mL), even within the clinical normal range (0~28 pg/mL), already can be associated with higher mortality (50.0%). High hs-TnI was significantly

associated with increased inflammatory levels (neutrophils, IL-6, CRP, and PCT) and decreased immune levels (lymphocytes, monocytes, and CD4$^+$ and CD8$^+$ T cells). Survival days were obviously shorter for deceased patients with high hs-TNI (median: 7 days) when compared to patients with low and moderate hs-TNI (median: 11 and 8.5 days, respectively), although it was hard to reach statistical significance because the deceased cases in the three groups were extremely uneven distribution.

As shown in **Table 3**, increased CK-MB levels were more likely to occur in male patients and patients with current smoking. High CK-MB on admission ($\geq$ 18 U/L) was associated with higher mortality (34.9%). High CK-MB was significantly associated with increased inflammatory levels (WBC, neutrophils, CRP and PCT) and decreased lymphocytes levels. High CK-MB was independent of acute respiratory symptoms and respiratory failure (P> 0.05). CK was not associated with mortality (**Supplementary table 1**).

As shown in **Table 4**, increased LDH levels were more likely to occur in older patients and patients with hypertension. High LDH was significantly associated with acute respiratory symptoms and respiratory failure (P< 0.05). High LDH on admission ($\geq$ 354.5 U/L) was associated with higher mortality (53.2%). High LDH was significantly associated with increased inflammatory levels (WBC, neutrophils, IL-6, CRP, PCT and ESR) and decreased immune levels (lymphocytes, monocytes, T cells and CD4$^+$ T cells). Survival days were obviously shorter for deceased patients with high LDH (median: 7 days) when compared to patients with low and moderate LDH

(median: 11 days, both), although it was hard to reach statistical significance because the deceased cases in the three groups were extremely uneven distribution.

As shown in **Table 5**, increased α-HBDH levels were more likely to occur in older patients and patients with hypertension. High α-HBDH was significantly associated with acute respiratory symptoms and respiratory failure ($P < 0.05$). High α-HBDH on admission (≥ 305 U/L) was associated with higher mortality (53.4%). High α-HBDH was significantly associated with increased inflammatory levels (WBC, neutrophils, IL-6, CRP and PCT) and decreased immune levels (lymphocytes, monocytes, T cells and $CD4^+$ T cells).

As shown in **Figure 1**, the higher hs-TNI on admission was, the shorter survival days would be. hs-TNI level on admission was significantly negatively correlated with survival days ($r = -0.42$, 95% CI= -0.64~-0.12, P=0.005). The higher LDH on admission was, the shorter survival days would be. LDH level on admission was significantly negatively correlated with survival days ($r = -0.35$, 95% CI= -0.59~-0.05, P=0.022). CK-MB and α-HBDH were not significantly correlated with survival days (both P> 0.05).

Discussion

In this study, we first assessed the associations between heart injury indicators and mortality in COVID-19 patients. hs-TNI is a biomarker released into blood once myocardial necrosis. Aberrant hs-TNI usually specifically indicates acute myocardial infarction [8]. In our study, we found hs-TNI increase tended to occur in older

patients and patients with comorbidities (especially hypertension). Approximately 11.2% COVID-19 patients happened to acute myocardial infarction on admission (aberrant hs-TNI > 28 pg/mL), which was consistent to the previous reports [9, 10]. More importantly, we found high hs-TnI on admission ($\geq$ 6.126 pg/mL), even within the clinical upper normal limit ($\leq$ 28 pg/mL), already can be associated with higher mortality. hs-TNI level was significantly negatively correlated with survival days. Therefore, we suggest the clinical upper normal limit of hs-TNI should be lowered for COVID-19, in order to avoid negligence of heart injury for COVID-19 patients on admission. Our suggestion also agrees with the opinion, which was issued on *The Lancet* in 2018 [11], that reclassification of hs-TNI for acute coronary syndrome in emergency departments in order to improve clinical outcomes.

CK-MB is another sensitive heart injury indicator which can also reflect myocarditis and myocardial infarction. After acute myocardial infarction, CK-MB will begin to increase at 2-4 hours, peak at 12 hours, and return to baseline within 48-72 hours [12, 13]. In our study, we found CK-MB increase tended to occur in male patients and patients with current smoking. Approximately 10.1% COVID-19 patients had CK-MB exceeding clinical upper normal limit (24 U/L) on admission. High CK-MB on admission ($\geq$ 18 U/L), even within the clinical upper normal limit ($\leq$ 24 U/L), already was associated higher mortality. These results proved heart injury such as viral myocarditis or myocardial infarction indeed occurred in COVID-19 on admission and predicted adverse clinical outcomes.

LDH and α-HBDH are two kinds of myocardial enzymes. LDH and α-HBDH mainly

exist in myocardia and would be released into blood once myocardial injury.

Although LDH and α-HBDH increases are relatively less specific in heart injury, they

also play important helping roles in recognition of myocarditis or myocardial

infarction [14, 15]. In our study, we found increases of LDH and α-HBDH were more

likely to occur in older patients and patients with hypertension. Both high LDH and

α-HBDH on admission were associated with higher mortality. In addition, we found

high LDH and α-HBDH were associated with more acute respiratory symptoms such

as breathlessness, chest distress or pain, dyspnea or respiratory failure on admission.

This result also implied that the increases of LDH and α-HBDH might not be specific

due to heart injury. LDH and α-HBDH increases might not merely be induced by heart

injury, but also be induced by lung or other organs injury. Nevertheless, LDH level on

admission was significantly negatively correlated with survival days.

The potential mechanism for COVID-19-caused heart injury might be

virus-induced inflammatory storm. Inflammatory cells infiltration and inflammatory

cytokines release can directly lead to apoptosis or necrosis of myocardial cells [16,

17]. In our study, we found high levels of heart injury indicators were associated with

increased levels of inflammatory cells (WBC and neutrophils) and inflammatory

cytokines (IL-6 and CRP). Therefore, we speculated that COVID-19 infection would

cause heart injury such as myocarditis or myocardial infarction by inducing

inflammatory cells infiltration and inflammatory cytokines storm. Early and special

anti-inflammatory treatments should be undertaken by cardiologists to protect

myocardium [18]. Another potential mechanism for COVID-19-caused heart injury might be angiotensin-converting enzyme 2 (ACE2)–mediated direct injury to heart. ACE2 as a human cell receptor had a strong binding affinity to the Spike protein of 2019-nCoV, namely Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [19]. Recent study reported ACE2 is highly expressed in heart [20]. Therefore, SARS-CoV-2 of COVID-19 might directly attack heart by binding ACE2 on myocardial cells.

Some limitations existed in this study. First, we only assessed heart injury from the perspective of serum myocardial enzymes and protein. It would be better if echocardiography and electrocardiograph were also measured in this study. Secondly, it would be better if we could assess heart injury-specific mortality in the future study with a larger sample size. Thirdly, we have not been able to obtain myocardial tissues from COVID-19 patients. Thus we currently cannot directly observe myocardial injury from the golden standard of pathology. Although the first autopsy of COVID-19 patient was completed and pulmonary pathology was obtained on Feb 16, 2020 in Wuhan Jinyintan Hospital (China), it remains a long way to remind clinicians to focus on cardiac pathology for COVID-19 infection. Our present results also can remind pathologists to pay attention to cardiac pathology in the future, especially for those deceased COVID-19 patients who had high heart injury indicators on admission.

Conclusions

In summary, heart injury signs arise in COVID-19 on admission and would be associated with subsequently higher and earlier mortality. COVID-19 virus might attack heart via inducing inflammatory storm or attack heart directly. Clinicians must beware of heart injury indicators for COVID-19 patients, especially for those with older age, hypertension and current smoking. In order to maximally prevent or rescue heart injury-related mortality in COVID-19, cardiologists must participate in early and special managements for patients with COVID-19.

Conflicts of Interest

All authors declared that they have no Conflicts of Interest.

All authors have seen and approved the manuscript.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon appropriate request.

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Table 1, Clinical and laboratory characteristics of the enrolled patients (n=188).

Parameters		All patients
Age (years)	Mean ± SD	51.9± 14.26
	Median (25th and 75th percentile)	51 (43~60)
Male		119 (63.3%)
Huanan seafood market exposure		92 (48.9%)
Infection by family members		15 (8.0%)
Current smoking		17 (9.0%)
Comorbidity [a]		64 (34.0%)
	Hypertension	38 (20.2%)
	Diabetes	20 (10.6%)
Initial symptoms and signs [b]		
	Fever	174 (92.6%)
	Highest temperature (℃) (n=156)	38.73± 0.67
	Cough	157 (83.5%)
	Sputum	74 (39.4%)
	Breathlessness	72 (38.3%)
	Chest distress or pain	63 (33.5%)
	Fatigue or myalgia	61 (32.5%)
	Dyspnea	24 (12.8%)
Days from symptoms/signs to admission		9 (7-12)
Vital signs on admission		
	Temperature (℃)	36.91 ± 0.76
	Heart rate (beats/min)	88 (82~98)
	Respiratory rate (breaths/min)	20 (20~23.75)
	Systolic pressure (mmHg)	122 (115~134.8)
	Diastolic pressure (mmHg)	75 (75~85)
Complications on admission		
	Respiratory failure	20 (10.6%)
	ARDS or sepsis	6 (3.2%)
hs-TnI (pg/mL)	Median (25th and 75th percentile)	3.65 (1.3~9.425)
	33th and 67th percentile	2~6.126
	> 28 pg/mL (clinical upper normal limit)	21 (11.2%)
LDH (U/L)	Median (25th and 75th percentile)	308.5 (233.3~389.8)
	33th and 67th percentile	253.2~354.5
	> 250 U/L (clinical upper normal limit)	129 (68.6%)
α-HBDH (n=173) (U/L)	Median (25th and 75th percentile)	255 (198.5~337)
	33th and 67th percentile	215.8~305
	> 182 U/L (clinical upper normal limit)	143 (76.1%)

CK (U/L)	Median (25th and 75th percentile)	83 (46.25~159.5)
	33th and 67th percentile	53.74~123.6
	> 310 U/L (clinical upper normal limit)	21 (11.2%)
CK-MB (U/L)	Median (25th and 75th percentile)	15 (12~20)
	33th and 67th percentile	13~18
	> 24 U/L (clinical upper normal limit)	19 (10.1%)
Drug therapy		
	Antibiotics	185 (98.4%)
	Antiviral drugs	158 (84.0%)
	Corticosteroids	59 (31.4%)
Transfer to ICU		50 (26.6%)
Cured or deceased		
	Cured and discharged	145 (77.1%)
	Length of stay (days) for cured patients	12 (9-14)
	Deceased in hospital	43 (22.9%)
	Length of stay (days) for deceased patients (survival days)	7 (4-11)

[a] Besides hypertension and diabetes, other comorbidity included chronic liver disease (9 cases), coronary heart disease (6 cases), cerebrovascular disease (6 cases), Parkinson's disease (3 cases), rheumatoid disease (3 cases), chronic kidney disease (3 cases), thyroid disease (2 cases), stomach disease (3 cases), chronic obstructive pulmonary disease (2 cases) and pulmonary tuberculosis (3 cases).

[b] Other symptoms and signs included headache (12 cases), nasal obstruction or nasal discharge (8 cases), nausea and vomiting (7 cases), dizziness (6 cases), pharyngalgia (6 cases) and diarrhea (2 cases).

Continuous data were presented by mean ± standard deviation (SD), median (25th to 75th percentile) or 33th to 67th percentile.

Categorical data were presented by number with percentage.

Abbreviations: ARDS: acute respiratory distress syndrome; hsTnI: High-sensitivity troponin I; LDH: Lactic dehydrogenase; α-HBDH: α-hydroxybutyrate dehydrogenase; CK: Creatine kinase; CK-MB: creatine kinase-MB; ICU: intensive care unit.

Table 2, Clinical characteristics and outcomes between patients with different hs-TnI levels.

Parameters	Low hs-TnI group	Moderate hs-TnI group	High hs-TnI group
Age (years)	43.57 ± 11.99	50.76 ± 11.11 #	61.19 ± 13.98 * §
Male	56.7% (34/60)	69.7% (46/66)	62.9% (39/62)
Current smoking	10.0% (6/60)	10.6% (7/66)	6.5% (4/62)
Comorbidity	23.3% (14/60)	27.3% (18/66)	51.6% (32/62) * §
Hypertension	11.7% (7/60)	15.2% (10/66)	33.9% (21/62) * §
Diabetes	3.3% (2/60)	7.6% (5/66)	21.0% (13/62) §
Initial symptoms and signs			
Fever	95.0% (57/60)	93.9% (62/66)	88.7% (55/62)
Highest temperature (℃)	38.77 ± 0.71	38.66 ± 0.56	38.78 ± 0.75
Breathlessness	30.0% (18/60)	37.9% (25/66)	46.8% (29/62)
Chest distress or pain	33.3% (20/60)	28.8% (19/66)	38.7% (24/62)
Fatigue or myalgia	30.0% (18/60)	36.4% (24/66)	30.6% (19/62)
Dyspnea	10.0% (6/60)	12.1% (8/66)	16.1% (10/62)
Respiratory failure, ARDS or sepsis	13.3% (8/60)	10.6% (7/66)	17.7% (11/62)
Vital signs on admission			
Heart rate (beats/min)	85.5 (80.5~94)	87 (82~98)	89.5 (82~98)
Systolic pressure (mmHg)	119 (112~130.3)	119.5 (115~129.5)	130 (118.3~143) §
Diastolic pressure (mmHg)	76 (72.75~85)	75 (75~83)	77 (72~87)
Inflammatory and immune indexes			
WBC (×10^9/L)	6.04 (4.21~9.60)	5.77 (3.84~8.65)	5.72 (3.73~9.25)
Neutrophil percentage (%)	73.4 (61.28~84.7)	75.2 (57.8~83.88)	80.55 (70~89.93) *
Lymphocytes percentage (%)	18.6 (9.3~31.85)	16.5 (9.3~32.53)	12.95 (5.68~23.2) * §
Monocytes percentage (%)	5.7 (4.2~7.4)	6.3 (4.78~8.13)	4.75 (3.15~6.58) *
IL-6 (pg/mL)	6.02 (5.21~7.82)	6.2 (5.20~7.48)	8.92 (6.9~13.4) * §
CRP (mg/L)	22.6 (6.5~46.15)	37.2 (11.3~80.5)	55.3 (25.65~108.2) §
PCT ≥ 0.05 ng/mL	31.7% (19/60)	36.4% (24/66)	64.5% (40/62) * §
ESR (mm/h)	49 (39.75~65.25)	49 (42.18~69)	56.3 (39.5~68.15)
T cells count (/uL)	737 (544~1156)	628 (468~846)	575 (347.8~782.8) §
CD4+ T cells count (/uL)	428 (291.5~750.5)	362 (283~572)	337.5 (166.3~452.3) §
CD8+ T cells count (/uL)	311 (162.5~421.5)	236 (163~349)	231.5 (123~290.5) §
Outcomes			
Transfer to ICU	15.0% (9/60)	21.2% (14/66)	43.5% (27/62) * §
Mortality	10.0% (6/60)	9.1% (6/66)	50% (31/62) * §
Days from admission to death	11 (4.75~11.75)	8.5 (5.75~14.25)	7 (4~11)

Low hs-TnI group (n=60): hs-TnI < 2 pg/mL; Moderate hs-TnI group (n=66): 2 ≤ hs-TnI < 6.126 pg/mL; High hs-TnI group (n=62): hs-TnI ≥ 6.126 pg/mL.

Statistically significant for Moderate hs-TnI group vs. Low hs-TnI group (P<0.05).

* Statistically significant for High hs-TnI group vs. Moderate hs-TnI group (P<0.05).

§ Statistically significant for High hs-TnI group vs. Low hs-TnI group (P<0.05).

Continuous data were presented by mean ± standard deviation (SD) or median (25th to 75th percentile). Categorical data were presented by percentage with number.

Abbreviations: hsTnI: High-sensitivity troponin I; ARDS: acute respiratory distress syndrome; WBC: white blood cells; IL-6: interleukin-6; CRP: C-reaction protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate; ICU: intensive care unit.

Table 3, Clinical characteristics and outcomes between patients with different CK-MB levels.

Parameters	Low CK-MB group	Moderate CK-MB group	High CK-MB group
Age (years)	50.15 ± 13.54	51.19 ± 13.33	54.11 ± 15.77
Male	41.7% (20/48)	67.5% (52/77) [#]	74.6% (47/63) [§]
Current smoking	0.0% (0/48)	9.1% (7/77)	15.9% (10/63) [§]
Comorbidity	29.2% (14/48)	31.2% (24/77)	41.3% (26/63)
Hypertension	12.5% (6/48)	18.2% (14/77)	28.6% (18/63)
Diabetes	4.2% (2/48)	10.4% (8/77)	15.9% (10/63)
Initial symptoms and signs			
Fever	85.4% (41/48)	93.5% (72/77)	96.8% (61/63)
Highest temperature (℃)	38.61 ± 0.79	38.71 ± 0.56	38.85 ± 0.71
Breathlessness	33.3% (16/48)	32.5% (25/77)	49.2% (31/63)
Chest distress or pain	33.3% (16/48)	29.9% (23/77)	38.1% (24/63)
Fatigue or myalgia	29.2% (14/48)	33.8% (26/77)	33.3% (21/63)
Dyspnea	10.4% (5/48)	13.0% (10/77)	14.3% (9/63)
Respiratory failure, ARDS or sepsis	12.5% (6/48)	15.6% (12/77)	12.7% (8/63)
Vital signs on admission			
Heart rate (beats/min)	87 (82~97)	88 (82~98)	86 (82~96)
Systolic pressure (mmHg)	119.5 (108.5~131)	119 (116~133)	123 (115~140)
Diastolic pressure (mmHg)	75 (72~87)	75 (75~83.5)	75 (75~87)
Inflammatory and immune indexes			
WBC (×10^9/L)	5.25 (3.58~6.72)	5.92 (3.74~8.5)	7.83 (4.45~10.76) [§]
Neutrophil percentage (%)	70.8 (59.03~82.6)	74.7 (60.6~85.8)	82 (68.7~89.6) * [§]
Lymphocytes percentage (%)	21 (10.75~30.38)	16.8 (9.3~32.15)	11 (6.4~23.2) * [§]
Monocytes percentage (%)	5.95 (4.53~7.35)	5.7 (4.2~7.4)	4.9 (3.2~7.4)
IL-6 (pg/mL)	6.76 (5.34~10.75)	7.36 (5.39~8.93)	7.4 (5.5~10.42)
CRP (mg/L)	26.15 (5.15~69.18)	34.95 (10.1~76.18)	51.7 (24.6~90.8) [§]
PCT ≥ 0.05 ng/mL	31.3% (15/48)	42.9% (33/77)	55.6% (35/63) [§]
ESR (mm/h)	52.7 (41.93~65)	49 (39~70)	49 (37.8~66)
T cells count (/uL)	660 (547~975)	628 (453~959)	587.5 (366.5~846)
CD4+ T cells count (/uL)	390 (345~578)	382 (270~652)	291.5 (194~523)
CD8+ T cells count (/uL)	239 (171~323)	277 (154~355)	231 (134.5~353.5)
Outcomes			
Transfer to ICU	18.8% (9/48)	18.2% (14/77)	42.9% (27/63) * [§]
Mortality	18.8% (9/48)	15.6% (12/77)	34.9% (22/63) *
Days from admission to death	7 (5~15.5)	11 (3.25~13.75)	7 (4~8.5)

Low CK-MB group (n=48): CK-MB < 13 U/L; Moderate CK-MB group (n=77): 13 ≤ CK-MB < 18 U/L; High CK-MB group (n=63): CK-MB ≥18 U/L.

[#] Statistically significant for Moderate CK-MB group vs. Low CK-MB group (P<0.05).

* Statistically significant for High CK-MB group vs. Moderate CK-MB group (P<0.05).

§ Statistically significant for High CK-MB group vs. Low CK-MB group (P<0.05).

Continuous data were presented by mean ± standard deviation (SD) or median (25th to 75th percentile). Categorical data were presented by percentage with number.

Abbreviations: CK-MB: creatine kinase-MB; ARDS: acute respiratory distress syndrome; WBC: white blood cells; IL-6: interleukin-6; CRP: C-reaction protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate; ICU: intensive care unit.

Table 4, Clinical characteristics and outcomes between patients with different LDH levels.

Parameters	Low LDH group	Moderate LDH group	High LDH group
Age (years)	46.97 ± 11.2	50.22 ± 13.54	58.58 ± 15.35 * §
Male	51.6% (32/62)	67.2% (43/64)	71.0% (44/62)
Current smoking	8.1% (5/62)	7.8% (5/64)	11.3% (7/62)
Comorbidity	27.4% (17/62)	31.3% (20/64)	43.5% (27/62)
Hypertension	9.7% (6/62)	18.8% (12/64)	32.3% (20/62) §
Diabetes	4.8% (3/62)	9.4% (6/64)	17.7% (11/62)
Initial symptoms and signs			
Fever	91.9% (57/62)	92.2% (59/64)	93.5% (58/62)
Highest temperature (℃)	38.53 ± 0.69	38.76 ± 0.58	38.9 ± 0.70
Breathlessness	22.6% (14/62)	29.7% (19/64)	62.9% (39/62) * §
Chest distress or pain	17.7% (11/62)	28.1% (18/64)	54.8% (34/62) * §
Fatigue or myalgia	30.6% (19/62)	34.4% (22/64)	32.3% (20/62)
Dyspnea	4.8% (3/62)	12.5% (8/64)	21.0% (13/62) §
Respiratory failure, ARDS or sepsis	4.8% (3/62)	12.5% (8/64)	24.2% (15/62) §
Vital signs on admission			
Heart rate (beats/min)	87.5 (82~98)	88 (82~96.75)	87 (82~98)
Systolic pressure (mmHg)	119 (115~127.3)	119 (112.5~129)	132.5 (119~144.3) * §
Diastolic pressure (mmHg)	75 (75~85.5)	76 (75~84)	77 (72~87)
Inflammatory and immune indexes			
WBC (×10^9/L)	4.81 (3.37~6.91)	5.81 (3.59~8.27)	8.07 (5.12~11.02) * §
Neutrophil percentage (%)	63.25 (54.65~76.03)	79.4 (68.33~83.75) #	87.25 (74.03~91.88) * §
Lymphocytes percentage (%)	27.8 (17.25~35.43)	14.95 (10.63~23.35) #	8.6 (5.28~17.95) * §
Monocytes percentage (%)	6.85 (5.58~8.4)	5.65 (4.65~7.1)	3.55 (2.38~5.55) * §
IL-6 (pg/mL)	5.46 (4.94~7.66)	6.53 (5.52~7.47)	8.63 (6.32~12.88) * §
CRP (mg/L)	8.45 (2.8~28.45)	46 (22.5~97.2) #	64.7 (34.6~107.8) §
PCT ≥ 0.05 ng/mL	17.7% (11/62)	46.9% (30/64) #	67.7% (42/62) §
ESR (mm/h)	45 (35.85~62.5)	48 (36.3~65)	61 (43~70.5) §
T cells count (/uL)	703 (525~1030)	633 (467~882)	458.5 (353.8~728.3) §
CD4+ T cells count (/uL)	428 (334~736)	342 (261~501)	287.5 (148.8~442) §
CD8+ T cells count (/uL)	236 (169.5~376.5)	278 (157~368)	184.5 (98.5~295)
Outcomes			
Transfer to ICU	6.5% (4/62)	17.2% (11/64)	56.5% (35/62) * §
Mortality	3.2% (2/62)	12.5% (8/64)	53.2% (33/62) * §
Days from admission to death	11 (11~11)	11 (4.5~21.5)	7 (4~10)

Low LDH group (n=62): LDH < 253.2 U/L; Moderate LDH group (n=64): 253.2 ≤ LDH < 354.5 U/L; High LDH group (n=62): LDH ≥354.5 U/L.

Statistically significant for Moderate LDH group vs. Low LDH group (P<0.05).

* Statistically significant for High LDH group vs. Moderate LDH group (P<0.05).

§ Statistically significant for High LDH group vs. Low LDH group (P<0.05).

Continuous data were presented by mean ± standard deviation (SD) or median (25th to 75th percentile). Categorical data were presented by percentage with number.

Abbreviations: LDH: lactic dehydrogenase; ARDS: acute respiratory distress syndrome; WBC: white blood cells; IL-6: interleukin-6; CRP: C-reaction protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate; ICU: intensive care unit.

Table 5, Clinical characteristics and outcomes between patients with different α-HBDH levels.

Parameters	Low α-HBDH group	Moderate α-HBDH group	High α-HBDH group
Age (years)	46.98 ± 11.28	50.28 ± 15.47	59.22 ± 13.85 * §
Male	54.4% (31/57)	62.1% (36/58)	74.1% (43/58)
Current smoking	5.3% (3/57)	10.3% (6/58)	8.6% (5/58)
Comorbidity	24.6% (14/57)	34.5% (20/58)	46.6% (27/58) §
Hypertension	7.0% (4/57)	24.1% (14/58) #	32.8% (19/58) §
Diabetes	3.5% (2/57)	10.3% (6/58)	17.2% (10/58)
Initial symptoms and signs			
Fever	91.2% (52/57)	93.1% (54/58)	94.8% (55/58)
Highest temperature (℃)	38.63 ± 0.67	38.68 ± 0.67	38.93 ± 0.68
Breathlessness	26.3% (15/57)	22.4% (13/58)	63.8% (37/58) * §
Chest distress or pain	17.5% (10/57)	27.6% (16/58)	55.2% (32/58) * §
Fatigue or myalgia	21.1% (12/57)	37.9% (22/58)	32.8% (19/58)
Dyspnea	5.3% (3/57)	12.1% (7/58)	22.4% (13/58) §
Respiratory failure, ARDS or sepsis	5.3% (3/57)	10.3% (6/58)	20.7% (12/58) §
Vital signs on admission			
Heart rate (beats/min)	87 (81.5~98)	88 (82~98)	88 (82~98)
Systolic pressure (mmHg)	119 (113.5~125.5)	119 (115~129.5)	131.5 (119~143) * §
Diastolic pressure (mmHg)	75 (73.5~84.5)	75 (75~83)	77 (73.5~87)
Inflammatory and immune indexes			
WBC (×10^9/L)	4.84 (3.42~6.27)	5.95 (3.73~8.79)	7.90 (4.50~10.32) §
Neutrophil percentage (%)	66.6 (55.85~76.05)	78.95 (64.73~85.03) #	85.8 (70.55~90.53) * §
Lymphocytes percentage (%)	27.5 (15.7~35.2)	15.05 (8.63~26.2) #	9.15 (5.55~22.35) §
Monocytes percentage (%)	6.8 (5.5~8.3)	5.7 (4.68~7.75)	3.8 (2.53~5.88) * §
IL-6 (pg/mL)	5.67 (5.29~7.88)	6.06 (5.30~7.42)	8.83 (7.32~13.44) * §
CRP (mg/L)	8.2 (3.05~41.35)	33.1 (16.1~71.15) #	67.9 (37.5~112.2) * §
PCT ≥ 0.05 ng/mL	28.1% (16/57)	37.9% (22/58)	69.0% (40/58) §
ESR (mm/h)	44 (30.6~63.5)	52 (41.8~71)	57.15 (41.9~68.48)
T cells count (/uL)	771 (563~1030)	620 (385.3~823.5) #	470.5 (366.5~793.5) §
CD4+ T cells count (/uL)	434.5 (355.3~743.8)	328 (218~490.8) #	286.5 (164.5~487) §
CD8+ T cells count (/uL)	255.5 (196.3~421.3)	234.5 (154~357.3)	230 (118.8~325.8)
Outcomes			
Transfer to ICU	1.8% (1/57)	17.2% (10/58) #	48.3% (28/58) * §
Mortality	3.5% (2/57)	15.5% (9/58)	53.4% (31/58) * §
Days from admission to death	8.5 (6~11)	11 (4~19)	7 (4~10)

Low α-HBDH group (n=57): α-HBDH < 215.8 U/L; Moderate α-HBDH group (n=58): 215.8 ≤ α-HBDH < 305 U/L; High α-HBDH group (n=58): α-HBDH ≥305 U/L.

Statistically significant for Moderate α-HBDH group vs. Low α-HBDH group (P<0.05).

* Statistically significant for High α-HBDH group vs. Moderate α-HBDH group (P<0.05).

§ Statistically significant for High α-HBDH group vs. Low α-HBDH group (P<0.05).

Continuous data were presented by mean ± standard deviation (SD) or median (25th to 75th percentile). Categorical data were presented by percentage with number.

Abbreviations: α-HBDH: α-hydroxybutyrate dehydrogenase; ARDS: acute respiratory distress syndrome; WBC: white blood cells; IL-6: interleukin-6; CRP: C-reaction protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate; ICU: intensive care unit.
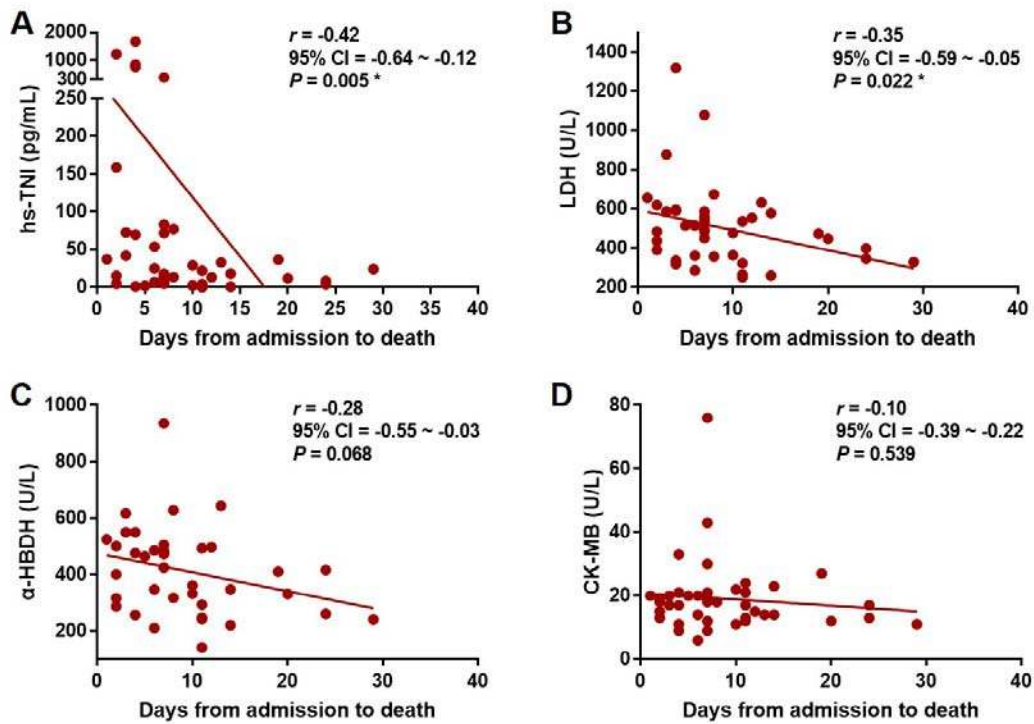
Figure 1, Correlations of heart injury indicators with survival days for deceased patients. A: Correlation of hs-TNI with survival days; B: Correlation of LDH with survival days; C: Correlation of α-HBDH with survival days; D: Correlation of CK-MB with survival days.

* Statistically significant.

Supplementary material

Supplementary table 1, Mortality between patients with different CK levels.

	Low CK group	Moderate CK group	High CK group	P
Mortality	17.7% (11/62)	32.8% (21/64)	17.7% (11/62)	0.066

CK: Creatine kinase.