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Cardiac injuries in patients with coronavirus disease 2019: Not to be ignored

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ABSTRACT

Objective: To describe the clinical features of coronavirus disease 2019 (COVID-19).
Methods: We recruited 73 patients with COVID-19 [49 men and 24 women; average age: 58.36 years (SD: 14.31)] admitted to the intensive care unit of Wuhan Jinyintan Hospital from December 30, 2019 to February 16, 2020. Demographics, underlying diseases, and laboratory test results on admission were collected and analyzed. Data were compared between survivors and non-survivors.
Results: The non-survivors were older (65.46 [SD 9.74]*vs* 46.23 [12.01]) and were more likely to have chronic medical illnesses. Non-survivors tend to develop more severe lymphopenia, with higher C-reactive protein, interleukin-6, D-dimer, and hs-Troponin I(hs-TnI) levels. Patients with elevated hs-TnI levels on admission had shorter duration from symptom onset to death. Increased hs-TnI level was related to dismal prognosis. Death risk increased by 20.8% when the hs-TnI level increased by one unit. After adjusting for inflammatory or coagulation index, the independent predictive relationship between hs-TnI and death disappeared.
Conclusions: Cardiac injury may occur at the early stage of COVID-19, which is associated with high mortality. Inflammatory factor cascade and coagulation abnormality may be the potential mechanisms of COVID-19 combined with cardiac injury.

Introduction

The outbreak of the viral pneumonia caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), occurred in Wuhan, China in December 2019, and spread rapidly worldwide(Wuhan Municipal Health Commission, 2020; WHO, 2020a; Holshue et al., 2020).The illness progression in some patients was rapid. In April 27, 2020, the cumulative number of patients with infections worldwide reached 2 878 196; of these, 198 668 patients have died (WHO, 2020b). In January 30, 2020, the World Health Organization issued a global warning about the highly contagious disease (WHO, 2020c), which was named as coronavirus disease 2019 (COVID-19) in February 11, 2020(WHO, 2020d). However, there have been a few studies on the clinical characteristics of the mortality cases due to the small sample size. To understand the clinical characteristics of COVID-9, we aimed to

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analyze the clinical features of 73 patients diagnosed with COVID-19.

Methods

Study population

This retrospective study analyzed 73 patients with COVID-19 who were admitted to the intensive care unit (ICU) of Wuhan Jinyintan Hospital from December 30, 2019 to February 16, 2020. The hospital specializes on infectious diseases and was prescribed by the Chinese government as one of the first designated treatment units for patients with the disease. The diagnosis of confirmed and clinical cases was made following the guideline of Diagnosis and Treatment of Novel Coronavirus Pneumonia (Trial Version 5) (National Health Commission of the People's Republic of China, 2020). This study was approved by the Ethics Committee of Wuhan Jinyintan Hospital (KY-2020-28.01), and all relevant personnel waived the requirement for obtaining patients' informed consent due to the particularity of the disease outbreak.

Data collection

This retrospective analysis was based on the case reports, nursing records, laboratory test results, and imaging findings of the patients. The patients' data on admission, including demographics, underlying diseases, and laboratory test results were collected. Two experienced clinicians reviewed and summarized the data. The patients were categorized into the non-survivors and survivors. Cardiac injury was defined as blood levels of cardiac biomarkers [hs-Troponin I (hs-TnI] above the 99th percentile of the upper reference limit, regardless of new abnormalities in electrocardiography and echocardiography.

Statistical analysis

We presented the continuous measurements with normal distributions as mean (standard deviation [SD]), whereas those that without normal distributions were expressed as median (interquartile range [IQR]). Categorical variables were described as frequency rates and percentages (%). For the laboratory test results, we also evaluated whether the data were outside the normal range. SPSS (version 24.0, IBM Co., Armonk, NY, USA) was used for all analyses.First,we compared the clinical and laboratory data between the non-survivors and survivors.Then the non-survivors were divided into two groups based on cardiac injury and compared the course-related data.The Mann–Whitney U test or Student's t test was used for continuous variables, and the Chi-squared test was used for categorical variables. To explore the relationship between cardiac injury and prognosis of COVID-19, multivariable analysis was conducted using logistic regression models with identified factors and previously recognized risk factors. Model 1 included sex and age as covariates. Model 2 was adjusted by Model 1 variables plus days from onset to admission. Further, CK-MB + CVD history (Model 3), CRP + IL-6 (Model 4),PT + D-dimer (Model 5) were entered in Model 2 as a covariate respectively.A P value <.05 indicated statistical significance.

Results

Demographics

Among the 73 patients, 49 were men and 24 were women, with an average age of 58.36 years (SD 14.31), ranging from 24 to 79 years. Many patients have chronic medical illnesses, including hypertension (32.88%), cardiovascular and cerebrovascular diseases (9.59%), diabetes (16.44%). Compared with survivors, the non-survivors were older (65.46 [SD 9.74] *vs* 46.23 [12.01]) and were more likely to have chronic medical illnesses. The median time from symptom onset to hospital was 10 days(IQR 8-12) and 8 days (IQR 7-10) in the non-survivors and survivors, respectively (Table 1).

Laboratory findings

Results of routine blood and biochemical examinations as well as inflammatory markers on admission of the patients were collected. On admission, most patients had marked lymphopenia, but non-survivors tend to develop more severe lymphopenia. C-reactive protein (CRP) and interleukin-6 (IL-6) levels were higher in non-survivors than in survivors. In our cohort, the level of D-dimer increased in 28 (38.36%) patients, and the level of D-dimer was higher in non-survivors than in survivors(1.51[0.80-7.18] *vs* 0.52[0.31-1.12]). In the non-survivor group, the proportion of patients with hs-TnI level above the normal range was 25.53% (n = 12), which was significantly higher than that of the survivor group. Liver and kidney injuries on admission were not significantly different between the two groups (Table 2).

Cardiac injury markers predicted poor prognosis

On admission, the level of hs-TnI increased in many patients. The level of hs-TnI was 16.6(10.1-40.8) pg/mL in non-survivors, which was higher than that of the survivors. Besides, hs-TnI levels

Table 1
Demographics of 73 patients with COVID-19.

	All patients (n=73)	Non-survivors (n=47)	Survivors (n=26)	
Age, years				
Mean (standard deviation)	58.36 ± 14.31	65.46 ± 9.74	46.23 ± 12.01	<0.001
Range	24-79	24-79	26-79	
≤44	15(19.18%)	2(4.26%)	12(46.15%)	
45-59	20(27.40%)	8(17.02%)	12(46.15%)	
60-74	30(41.10%)	29(61.70%)	1(3.85%)	
≥75	9(12.33%)	8(17.02%)	1(3.85%)	
Sex				
Female	24(32.88%)	15(31.91%)	9(34.62%)	0.814
Male	49(67.12%)	32(68.09%)	17(65.38%)	
Days from symptom onset to admission, days	10.00(7.00-12.00)	10.00(8.00-12.00)	8.00(7.00-10.00)	0.019
Chronic medical illness				
Hypertension	24(32.88%)	21(44.68%)	3(11.54%)	0.004
Cardiovascular and cerebrovascular diseases	7(9.59%)	7(14.89%)	0(0%)	0.010
Endocrine system disease	12(16.44%)	10(21.28%)	2(7.69%)	0.115

Values are numbers (percentages) or median (interquartile range) unless stated otherwise. Percentages do not total up to 100% owing to missing data.

Table 2
Laboratory findings of patients with COVID-19.

	Non-survivors (n=47)	Survivors (n=26)	P value
Leucocytes (× 10⁹ per L; normal range 3. 5–9.5×10⁹ per L)	7.57(4.99-10.76)	6.16(5.09-10.49)	0.607
Neutrophils (× 10⁹ per L; normal range 1.8–6.3× 10⁹ per L)	6.41(4.30-9.68)	4.96(3.03-8.64)	0.225
Lymphocytes (× 10⁹ per L; normal range 1.1–3.2× 10⁹ per L)	0.59(0.43-0.90)	0.98(0.29-1.30)	0.001
Platelets (×10⁹ per L; normal range 125.0–350.0×10⁹ per L)	168(126-211)	204(149-268)	0.054
Prothrombin time (s; normal range 10.5–13.5s)	11.80(10.9-12.93)	11.1(10.25-12.05)	0.016
D-dimer (μg/L; normal range 0.0–1.5μg/L)	1.51(0.80-7.18)	0.52(0.31-1.12)	0.000
ALT (U/L; normal range 7-40 U/L)	32.0(20-48)	27.5(19.5-38.5)	0.454
AST (U/L; normal range 13–35 U/L)	38(32-59)	31.5(24.0-43.5)	0.030
Serum creatinine (mol/L; normal range 57–111 mol/L)	74.4(64.0-94.3)	77.0(61.1-91.9)	0.612
Blood urea nitrogen (mmol/L; normal range 3.6–9.5mmol/L)	6.0(4.8-7.6)	4.70(3.4-6.8)	0.014
hsTroponin I (U/L; normal range 0-28 U/L)	16.6(10.1-40.8)	3.5(1.8-4.1)	0.000
CK-MB (U/L; normal range 0-24 U/L)	17(14.8-22.0)	14(12.0-19.3)	0.038
LDH (U/L; normal range 120-250 U/L)	449(315.5-612.3)	281(215.7-337.5)	0.00
Myoglobin (ng/mL; normal range 0.0–146,9ng/mL)	96(57.0-168.5)	41(27.7-76.4)	0.003
C-reactive protein (mg/L; normal range 0.0–5.0mg/L)	118.2(75.0-160.0)	52.1(17.0-80.6)	0.00
Interleukin-6 (pg/mL; normal range 0.0–7.0pg/mL)	9.1(7.0-13.1)	4.9(4.0-6.3)	0.00

Values are numbers (percentages) or median (interquartile range) unless stated otherwise. Percentages do not total 100% owing to missing data.
COVID-19, coronavirus disease 2019; CK-MB, creatinine kinase-MB; AST, aspartate aminotransferase

increased more markedly with increasing age. 40 non-survivors had test result of hs-TnI, they were divided into two groups based on cardiac injury, Further analysis revealed that non-survivors with elevated hs-TnI levels on admission had shorter duration from symptom onset to death, and TnI elevation was related to the dismal prognosis. Typically, the death risk increased by 20.8% when the hs-TnI levels increased by one unit. Adjusted for sex,age and days from onset to admission or CK-MB + CVD, hs-TnI was still the independent predictive factor for death.However, After adjusting for inflammatory index or coagulation index, the independent predictive relationship between hs-TnI and death disappeared (Tables 3 and 4 and Fig. 1).

Discussion

COVID-19 is an infectious disease that has not been comprehensively understood so far. Therefore, it is of great clinical significance to explore the clinical features and factors influencing prognosis of COVID-19 patients. However, studies on cases with severe COVID-19 are few at present. This study enrolled COVID-19 patients, including 47 non-survivors and 26 survivors, admitted to the ICU. According to our results, older patients with concurrent chronic diseases have an increased mortality risk, which was consistent with the results of Chen et al.(2020). The mortality of critically ill COVID-19 patients is high, but its mechanism is not clear at present, and it might be related to the virus-induced acute lung injury, inflammatory factor storm. We collected the laboratory results of patients on admission and found that 29 (61.7%) patients in the non-survivor group had elevated IL-6 levels on admission, suggesting the presence of severe inflammatory response in these patients. Some studies reported that the risk of respiratory failure in patients with IL-6 level >80 pg/ml increases 22-folds compared with the patients with low IL-6 levels (Herold et al., 2020). Actemra, an IL-6 antagonist, is verified

Table 4
Odds ratio for the prognosis of COVID-19.

	hs-Troponin I	P value
Unadjusted	1.208(1.077-1.355)	0.001
Model 1	1.131(1.008-1.269)	0.036
Model 2	1.126(1.002-1.264)	0.045
Model 3	1.129(1.001-1.273)	0.047
Model 4	1.10(0.958-1.263)	0.175
Model 5	1.209(0.991-1.474)	0.061

Model 1: Adjusted for sex and age
Model 2: Model 1+days from onset to admission
Model 3: Model 2+CK-MB+CVD history
Model 4: Model 2 +CRP+IL-6
Model 5: Model 2 + PT+D-dimer
COVID-19, coronavirus disease 2019; CK-MB, creatinine kinase-MB; CVD, cardiovascular disease; IL-6, interleukin-6; PT, prothrombin time;

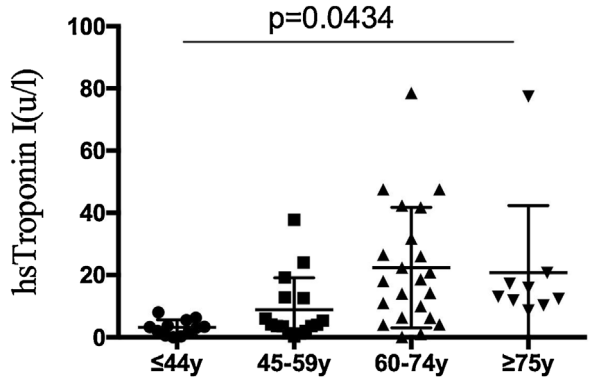

Fig. 1. Relationship between age and hs-Troponin I in patients with coronavirus disease 2019 (COVID-19)

Table 3
The course of COVID-19 in patients grouped by serum hs-Troponin I levels at admission to the general ward.

	Increased group (N=12)	Normal group (N=28)	P value
Days from onset to admission	12(10.3-12.8)	10(8.0-12.8)	0.213
Days from admission to ICU	1.1(1-3.8)	6(3-10)	0.000
Days in ICU	4(2-8.75)	5(2-9)	0.652
Days from onset to death	18.5(14.5-21.1)	22.5(19-29.8)	0.016

Values are median (interquartile range) unless stated otherwise. *P* values indicate differences between the increased and normal groups. $P < .05$ was considered statistically significant
COVID-19, coronavirus disease 2019; ICU, intensive care unit

to block the inflammatory factor cascade to prevent the progression to severe and critical conditions and to reduce the mortality risk. Similarly, there was also a marked difference in the CRP level between non-survivors and survivors, suggesting that severe inflammatory response might be one of the causes of death.

The lung is the major target organ of COVID-19, but severe cases are mostly combined with multiple organ dysfunction. Wang et al. (2020) discovered that approximately 7.2% of patients had concurrent cardiac injury, whereas the incidence rate of cardiac injury was even higher among ICU patients, which was approximately 22.2%. According to a study enrolling 416 subjects, the incidence rate of cardiac injury is approximately 19.7%, and concurrent cardiac injury is an independent risk factor of death. Our study discovered that the level of hs-TnI increased in many patients on admission, indicating that cardiac injury occurred in the early stage of the disease.The incidence rate of cardiac injury among patients at admission was 16.44%, with the non-survivors having an incidence rate of as high as 25.53%. In addition, no obvious liver or kidney dysfunction was detected, revealing that severe COVID-19 patients might develop cardiac injury at the early stage of the disease, and that the heart might be the first affected extrapulmonary organ. Moreover, we found that the incidence rate of cardiac injury increased with increasing age. Further analysis revealed that the elevated hs-TnI levels was closely correlated with the prognosis andmortality risk of COVID-19 patients. Specifically, the mortality risk increased by 20.8% when the hs-TnI level increased by 1 unit. Patients with elevated hs-TnI levels on admission had a shorter duration from symptom onset to ICU admission for further rescue interventions and shorter overall course of disease. At present, the mechanism of cardiac injury in COVID-19 patients remains unclear. Both, the novel SARS-CoV-2 and SARS virus in 2003 belong to the β coronavirus, and ACE2 has been verified as the common pathogenic target. ACE2 is extensively expressed in myocardial cells, cardiac fibroblasts, and coronary artery endothelial cells; therefore, SARS-CoV-2 may act on ACE2 to induce myocardial damage. Furthermore, the recently published autopsy results of COVID-19 patients demonstrated the presence of SARS-CoV-2 particles in the myocardial interstitium (Tavazzi et al., 2020). Shi et al.(2020) discovered that COVID-19 patients with concurrent myocardial damage had markedly elevated inflammatory index levels, and myocardial damage was considered to be related to the inflammatory response. Zheng et al. (2020) found that the D-dimer level of >0.5 μg/L was associated with a poor prognosis in COVID-19 patients, and the possible mechanism could be increased production of pro-inflammatory factors in COVID-19 patients, which aggravated the formation of atherosclerotic plaques and resulted in plaque rupture caused by local inflammation, pro-coagulant factors, and hemodynamic changes, thereby inducing thrombosis and myocardial infarction. Our data showed that the elevated troponin level was related to a poor prognosis, but after adjusting for inflammatory factors and coagulation indexes, the independent predictive relationship between hs-TnI and death in the multivariate analysis disappeared, revealing that cardiac injury might be related to the inflammatory response and abnormal coagulation function, which was consistent with previous research results. The abovementioned findings reveal that the heart is the potential target of SARS-CoV-2, which is associated with the severe course of the disease; thus, early monitoring and assessment of cardiac injury should be conducted as soon as possible while paying attention to the pulmonary injury.

This study has some limitations. First, the sample size was small. Second, only the assay indexes upon admission were examined, whereas the dynamic changes in these indexes were not observed. Therefore, larger studies are warranted to further determine the clinical features of COVID-19 patients.

Conclusion

Cardiac injury may occur at the early stage of COVID-19, which is associated with high mortality. Inflammatory factor cascade and coagulation abnormality may be the potential mechanisms of COVID-19 combined with cardiac injury.

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Conflict of interest

The authors declare no conflicts of interest.

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