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

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\textbf{A B S T R A C T}

Objective: To describe the clinical features of coronavirus disease 2019 (COVID-19).

\textbf{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.

\textbf{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.

\textbf{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.

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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\cite{2020WuhanMUC}. 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\cite{WHO2020b}. In January 30, 2020, the World Health Organization issued a global warning about the highly contagious disease\cite{WHO2020c}, which was named as coronavirus disease 2019 (COVID-19) in February 11, 2020\cite{WHO2020d}. 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...
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 physicians 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 of 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 (151.51[80.78–718] 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         | 58.36 ± 14.31        | 65.46 ± 9.74     | 46.23 ± 12.01 |
| Mean (standard deviation) | <0.001               |                  |
| Range              | 24–79                | 24–79            | 26–79          |
| ≤44                | 15(19.18%)           | 2(4.62%)         | 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                |                      |                  |                |
| Male               | 24(32.88%)           | 15(31.91%)       | 9(34.62%)      |
| Female             | 49(67.12%)           | 32(68.09%)       | 17(65.38%)     |
| Days from symptom onset to admission, days |          |                  |                |
| Chronic medical illness |                  |                  |                |
| Hypertension       | 24(32.88%)           | 21(44.68%)       | 3(11.54%)      |
| Cardiovascular and cerebrovascular diseases |          |                  |                |
| Endocrine system disease |            |                  |                |
| Values are numbers (percentages) or median (interquartile range) unless stated otherwise. Percentages do not total up to 100% owing to missing data. |
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 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 10.5–11.5s) | 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(0.8-7.18) | 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(24-43.5) | 0.030 |
| Serum creatinine (mol/l; normal range 57–111 mol/L) | 74.6(4.6-94.3) | 77.0(61.1-91.9) | 0.612 |
| Blood urea nitrogen (mmol/L; normal range 3.6–9.5mmol/L) | 6.0(4.8-7.61) | 4.7(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(215.7-317.5) | 0.00 |
| Myoglobin (ng/mL; normal range 0.0–146.9ng/mL) | 96(570.1–168.5) | 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(170-80.6) | 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

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 | 11.5(1.3-8.3) | 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

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                |              | 1.100(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)
to block the inflammatory factor cascade to prevent the progress
ion 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 approxi-
mately 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 23.53%. 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 and mortality 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 pathogenetic 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 demon-
strated 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 multivari-
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
above-mentioned 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
cogulation abnormality may be the potential mechanisms of
COVID-19 combined with cardiac injury.

Funding

This study was supported by “the Fundamental Research Funds
for the Central Universities (WK9110000377)”.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgment

We thank Prof Jilong Shen provided language help during the
research. We thank all the medical staff were involved in treating
the patients and all patients and their families involved in the
study.

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