Yong Feng ORCID iD: 0000-0003-1590-0186

Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China

Huan Han[1], Linlin Xie[2], Rui Liu[1], Jie Yang[1], Fang Liu[3,4], Kailang Wu[3], Lang Chen[2], Wei Hou[2], Yong Feng[2*], Chengliang Zhu[1*]

[1] Dept. of Clinical Laboratory, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, China.

[2] State Key Laboratory of Virology, School of Basic Medical Sciences, Wuhan University, Wuhan 430071, Hubei, China.

[3] State Key Laboratory of Virology, College of Life Sciences of Wuhan University, Wuhan 430072, Hubei, China.

[4] Wuhan Institute of Biotechnology, Wuhan 430075, Hubei, China.

*Correspondence: Yong Feng (email: yongfeng@whu.edu.cn) and Chengliang Zhu (xinchengzhu@163.com).

Abstact

An outbreak of SARS-CoV-2 epidemic spreads rapidly worldwide. SARS-CoV-2 infection caused mildly to seriously and fatally respiratory, enteric, cardiovascular, and neurological diseases. In this study, we detected and analyzed

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jmv.25809.

the main laboratory indicators related to heart injury, CK-MB, MYO, ultra-TnI and NT-proBNP, in 273 COVID-19 patients and investigated the correlation between heart injury and severity of the disease. It was found that higher concentration in venous blood of CK-MB, MYO, ultra-TnI and NT-proBNP were associated with the severity and case-fatality rate of COVID-19. Careful monitoring of the myocardiac enzyme profiles is of great importance in reducing the complications and mortality in COVID-19 patients.

Keywords: COVID-19; laboratory indicators; heart injury; disease severity

Introduction

Since December, 2019, an outbreak of pneumonia caused by a novel coronavirus (SARS-CoV-2) has raised intense attention in Wuhan, Hubei province, China.[1-3] This disease, named COVID-19 by World Health Organization (WHO), spreads rapidly around the country and worldwide.

Coronaviruses can infect a variety of livestock, poultry, and humans, in which they can cause respiratory, enteric, cardiovascular, and neurological diseases.[4-7] SARS-CoV-2 appears to have greater infectivity and a lower case fatality rate (CFR) as compared to severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome coronavirus (MERS).[8] So far, a few patients with SARS-CoV-2 have developed severe pneumonia, pulmonary oedema, acute respiratory distress syndrome (ARDS), or multiple organ failure and died. According to a summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention, the overall case-fatality rate was 2.3% (1023 deaths among 44 672 confirmed cases).[9] No deaths were reported among mild and severe cases. The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions, 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension,

and 5.6% for cancer. Therefore, to lower the CFR in COVID-19 patients, much attention have to be paid on heart injury and its clinical performance.

At present, information regarding the clinical features of pneumonia caused by SARS-CoV-2 is scarce.[3, 10, 11] In this study, we analyzed the main laboratory indicators of heart injury in COVID-19 patients and investigated the correlation between heart injury and severity of the disease.

Methods

Patients

For this retrospective, single-centre study, we recruited 273 patients from Jan 1 to Feb 18, 2020, at Renmin Hospital of Wuhan University, China. All patients were diagnosed as having SARS-CoV-2 infection according to WHO interim guidance. This study was approved by the Ethics Committee of the Renmin Hospital of Wuhan University.

According to the relevant diagnostic criteria, patients were divided into three groups: mild (198 cases), severe (60 cases) and critical (15 cases). The required conditions must be met for mild cases was the positive SARS-CoV-2 RNA nucleic acid test (NAT) by RT-PCR, fever or other respiratory symptoms and the typical CT image abnormities of viral pneumonia are optional.[12] Severe cases additionally met at least one of the following conditions: (1) Shortness of breath, RR≥30 times/min, (2) Oxygen saturation (Resting state) ≤93%, or (3) PaO2/FiO2 ≤300mmHg. Critical cases need to met at least one of the extra following conditions: (1) Respiratory failure that need to receive mechanical ventilation; (2) Shock and (3) Multiple organ failure that need to be transferred to the intensive care unit (ICU).[11]

Blood test

We collected data of the first detection of heart injury laboratory parameters in these 273 COVID-19 patients on admission. All patients were collected 3 ml of venous blood into procoagulant tubes and EDTA-K2 anticoagulant tubes respectively in the early morning, then centrifuged at 3000 rpm for 10 min to separate serum and plasma. The levels of CK-MB, MYO, ultra-TnI in the serum were measured using standard assay kit and Siemens ADVIA CENTAUR XP automatic chemiluminescence immunoassay analyzer, and the level of NT-pro BNP in the plasma was measured by the CobasE601 immunoanalyzer for all patients according to the manufacturer's instructions.

Statistical analysis

SPSS 25.0 was used for statistical analysis. Measurement data were expressed as P50 (P25~P75). Count data were analyzed by Chi-square test or Fisher exact probability method. The measurement data are compared by Kruskal-Wallis test. Differences between groups were analyzed. $P < 0.05$ was considered as statistically significant.

Results

273 COVID-19 patients on admission from Jan 1 to Feb 18, 2020, were included in this study. According to the relevant diagnostic criteria, patients were divided into three groups: mild (198 cases), severe (60 cases) and critical (15 cases). There was no significant difference in gender and age among three groups in this study (Table 1).

The blood tests of patients on admission showed most patients had normal levels of creatine kinase isoenzyme-MB **(**CK-MB**)**, myohe-moglobin **(**MYO**),** cardiac troponin I (ultra-TnI) and N-terminal pro-brain natriuretic peptide (NT-

proBNP). Several were above the normal range: CK-MB were above the normal range (0-5 ng/mL) in 10 (10/273) patients, MYO were above the normal range (0-110 μg/L) in 29 (29/273) patients, ultra-TnI were above the normal range (0-0.04 ng/mL) in 27 (27/273) patients and NT-proBNP were above the normal range (0-900 pg/mL) in 34 (34/273) patients. These data together indicated that some COVID-19 patients developed acute cardiac injury.

Next, the changes of these indicators of the three groups were compared and analyzed, as well as their relationship with the clinical classification of the disease, as shown in Figure 1 and Table 2. The positive rate of CK-MB had no difference between the mild, severe and critical groups. While the positive rate of MYO, ultra-TnI and NT-proBNP is higher in severe cases and critical cases as compared to mild cases, the differences among the groups were statistically significant ($P<0.05$). After a pairwise comparison by Bonferroni correction, it was observed that the levels of NT-proBNP and MYO were significant increased in severe cases and critical cases compared to mild cases ($P<0.0167$), but no difference between severe cases and critical cases ($P>0.0167$). The increase of ultra-TnI only showed significantly difference between the mild cases and severe cases ($P<0.0167$), while there was no difference between mild cases and critical cases, severe cases and critical cases ($P>0.0167$). Thus, the increased concentration in venous blood of MYO, ultra-TnI and NT-proBNP were associated with the severity of COVID-19.

Till March 23, the overall case-fatality rate (CFR) was 8.79% (24 deaths among 273 cases) (Table 3). The CFR was 22.81% (13 deaths among 57 cases) in the Abnormal parameters group, which was much higher than the CFR (5.09% as 11 deaths among 216 cases) in the Normal parameters group. Notably, for those

severe cases and critical cases, the CFRs were 42.31 and 33.33% respectively in those who had abnormal myocardial parameters.

Then we analyzed this four heart injury parameters between the death (n=24) and alive (246 recovered and 3 still in hospital at severe situation). All four parameters were significantly higher in the death than in the alive group ($p<0.001$) (Figure 2).

Discussion

Viral pathogenicity is a well-known risk factor in chronic cardiovascular disease, a general consequence of the imbalance between infection-induced increased metabolic demand and reduced cardiac reserve. In all influenza pandemics other than the 1918 flu, cardiovascular events surpassed all other causes of mortality, including superimposed pneumonia.[13] Both SARS and MERS have been linked to acute myocarditis, acute myocardial infarction, and rapid-onset heart failure.[14, 15] Since the emergence of 2019 n-CoV, numerous studies have been carried out on the clinical features of the disease.[16] In a recent case report on 138 hospitalized COVID-19 patients, 7.2% developed acute cardiac injury.[11] In this study, we confirmed the heart injury association with SARS-CoV-2 infection, and analyzed correlation between heart injury and severity of COVID-19.

We divided the patients into three groups: mild, severe and critical, according to the relevant diagnostic criteria, and detected the concentration in venous blood of CK-MB, MYO, ultra-TnI and NT-proBNP. We found that a portion of patients showed elevated levels of CK-MB, MYO, ultra-TnI and NT-proBNP, indicating heart injury caused by SARS-CoV-2 infection, or a portion of patients with preexisting comorbid conditions, perticularly with cardiovascular disease, were sensitive to SARS-CoV-2 infection. Moreover, there were statistically significant

differences in the level and positive rate of MYO, ultra-TnI and NT-proBNP among the three groups. The increased concentration in venous blood of MYO, ultra-TnI and NT-proBNP is expected to predict the severity of the COVID-19.

The much higher CFR in the Abnormal parameters group than in the Normal parameters group indicated a higher fatality risk that associated with abnormal myocardial parameters. However, the CFR in this study is higher than the CFR in others reports, which might due to the irregular period in the early Febuary when there were a short of medical sevices for the dramatically increased infection cases.

In conclusion, the higher concentration in venous blood of CK-MB, MYO, ultra-TnI and NT-proBNP were associated with the severity and case-fatality rate of COVID-19. Therefore, careful monitoring of the myocardiac enzyme profiles is of great importance in reducing the complications and mortality in COVID-19 patients.

Acknowledgement

This work was supported by the National Mega Project on Major Infectious Disease Prevention under Grant 2017ZX10103005 (to K.L.W), the National Natural Science Foundation of China (81672079 to C.L.Z, 81471940 to Y.F), and the Open Research Program of the State Key Laboratory of Virology of China (2020KF001 to C.L.Z).

Conflict of interest

The authors declare that there are no conflict of interests.

Authors' contributions

Y.F and L.C conceived and designed this investigation. L.C and W.H helped to design the scheme of the investigation. H.H and R.L collected the original data. L.X analyzed the data. J.Y, F.L, and KL contributed to interpretation of the data. L.X, Y.F and L.C contributed to writing of the paper. H.H and L.X contributed equally to this study.

References

1. Lu H, Stratton CW, Tang Y-W. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *Journal of medical virology.* 2020;92(4):401-402.

2. Hui DS, I Azhar E, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases.* 2020;91:264-266.

3. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England journal of medicine.* 2020;382(8):727-733.

4. Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology.* 2018;23(2):130-137.

5. Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *The New England journal of medicine.* 2003;348(20):1967-1976.

6. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *The New England journal of medicine.* 2012;367(19):1814-1820.

7. Weiss SR, Leibowitz JL. Coronavirus pathogenesis. *Advances in virus research.* 2011;81:85-164.

8. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med.* Jan 29 2020.

9. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA.* Feb 24 2020.

10. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet.* 2020;395(10223):507-513.

11. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA.* 02/07 2020.

12. Liu R, Han H, Liu F, et al. Positive rate of RT-PCR detection of SARS-CoV-2 infection in 4880 cases from one hospital in Wuhan, China, from Jan to Feb 2020. *Clin Chim Acta.* Mar 7 2020;505:172-175.

13. Madjid M, Casscells SW. Of birds and men: cardiologists' role in influenza pandemics. *The Lancet.* 2004;364(9442):1309.

14. Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet (London, England).* 2003;361(9371):1767-1772.

15. Alhogbani T. Acute myocarditis associated with novel Middle east respiratory syndrome coronavirus. *Annals of Saudi medicine.* Jan-Feb 2016;36(1):78-80.

16. Li LQ, Huang T, Wang YQ, et al. 2019 novel coronavirus patients' clinical characteristics, discharge rate and fatality rate of meta-analysis. *J Med Virol.* Mar 12 2020.

Figures

Fig. 1. Levels of CK-MB, MYO, ultra-TnI and NT-proBNP of the three COVID-19 patients groups were compared and analyzed. According to the relevant diagnostic criteria, patients were divided into three groups: mild (n=198), severe (n=60) and critical (n=15). ***p<0.001.

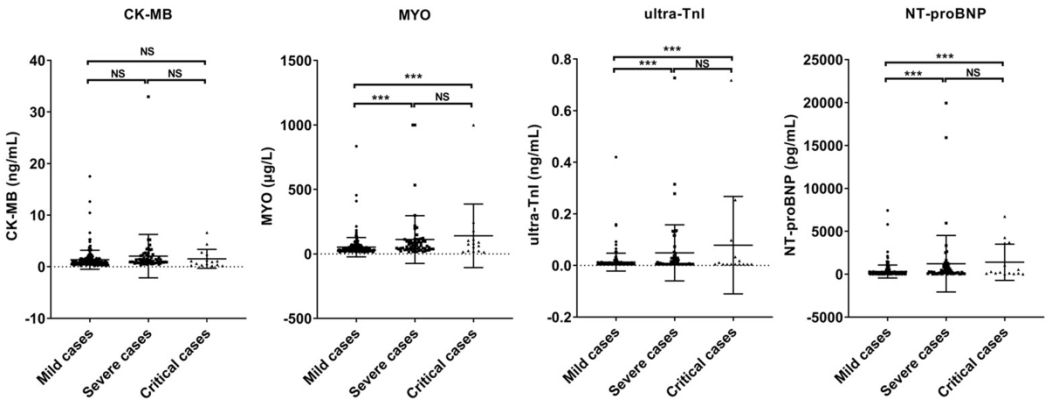
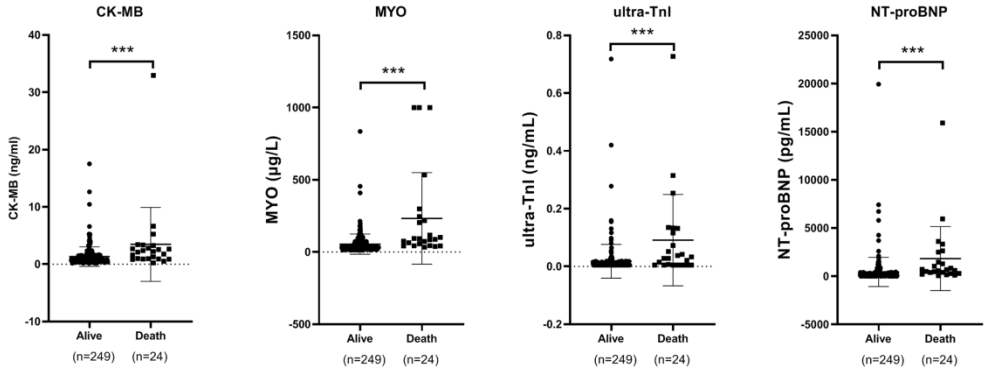


Fig. 2. **Levels of CK-MB, MYO, ultra-TnI and NT-proBNP were compared and analyzed between death and alive COVID-19 patients.** Till March 23, twenty-four patients died among 273 cases. 246 recovered and 3 still in hospital at severe situation (249 alive in total). ***p<0.001.



Tables.

Table 1. Gender and age characteristics of COVID-19 patients in this study

	Mild cases (n=198)	Severe cases (n=60)	Critical cases (n=15)
Age, years	58.95±10.80	58.97±14.38	57.27±17.25
Sex			
Men	71	21	5
Women	127	39	10

Table 2. Levels of CK-MB, MYO, ultra-TnI and NT-proBNP in COCID-19 patients in this study

	Mild cases (n=198)	Severe cases (n=60)	Critical cases (n=15)
CK-MB (ng/ml)	0.91 (0.61~1.41)	1.10 (0.76~2.12)	0.97(0.32~2.37)
⩽5	192 (96.97%)	57 (95.00%)	14 (93.33%)
>5	6 (3.03%)	3 (5.00%) ^{NS}	1 (6.67%)^{NS}

MYO (μg/L)	34.66 (26.46~54.54)	57.73 (37.43~100.71)	75.34 (23.24~112.47)
⩽110	187 (94.44%)	46 (76.67%)	11 (73.33%)
>110	11 (5.56%)	14 (23.33%) [a]	4 (26.67%) [a]
ultra-TnI (ng/ml)	0.01 (0.01~0.01)	0.01 (0.01~0.04)	0.01 (0.01~0.03)
⩽0.04	188 (94.95%)	46 (76.67%)	12 (80.00%)
>0.04	10 (5.05%)	14 (23.33%) [a]	3 (20.00%)
NT-proBNP (pg/ml)	113.65 (45.92~274.23)	290.85 (106.13~958.98)	224.50 (91.73~3615)
⩽900	184 (92.93%)	45 (75.00%)	10 (66.67%)
>900	14 (7.07%)	15 (25.00%) [a]	5 (33.33%) [a]

NS means no significant. [a] is compared with wild cases, P<0.05.

Table 3. Case-fatality rate of COVID-19 patients in this study

	Total			
	Mild	Severe	Critical	Total
Cases	198	60	15	273
Death	2[a]	19	3	24
CFR	1.01% [a]	31.67%	20.00%	8.79%
	Normal parameters group[b]			
Cases	173	34	9	216
Death	2	8	1	11
CFR	1.16%	23.53%	11.11%	5.09%
	Abnormal parameters group[c]			
Cases	25	26	6	57
Death	0	11	2	13
CFR	0	42.31%	33.33%	22.81%

[a] 2 mild cases on admission progressed to severe and died. [b] Normal parameters were defined as CK-MB in the range of 0-5 ng/mL; **MYO,** 0-110 μg/L; ultra-TnI, 0-0.04 ng/mL; **NT-proBNP,** 0-900 pg/mL. [c] Abnormal parameters were defined as parameters above the normal range.