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Joint predictive value of cTnI and NT-proBNP on mortality in patients with coronavirus disease 2019: A retrospective research in Wuhan, China

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ABSTRACT

Background and Objectives: The pandemic of coronavirus disease 2019 (COVID-19) remains to be the biggest public threat all over the world. Because of the rapid deterioration in some patients, markers that could predict poor clinical outcomes are urgently required. This study was to evaluate the predictive values of cardiac injury parameters, including cardiac troponin I (cTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, on mortality in COVID-19 patients. **Methods**: COVID-19 patients in Zhongfaxincheng branch of Tongji Hospital (Wuhan, China) from February 8–28, 2020, were enrolled in this study. We followed up the patients for 30 days after admission. **Results**: A total of 134 patients were included in the study. Multivariate Cox regression showed that 1) patients with elevated cTnI levels had a higher risk of death (hazard ratio [HR] 7.33, 95% confidence interval [CI] 2.56–21.00) than patients with normal cTnI levels; 2) patients with elevated NT-proBNP levels had a higher risk of death (HR 27.88, 95% CI 3.55–218.78) than patients with normal NT-proBNP levels; 3) patients with both elevated cTnI and NT-proBNP levels had a significantly higher risk of death (HR 53.87, 95% CI 6.31–459.91, $P < 0.001$) compared to patients without elevated cTnI or NT-proBNP levels; 4) the progressions of cTnI and NT-proBNP levels were also correlated with death (HR 12.70, 95% CI 3.94–40.88, $P < 0.001$ and HR 51.09, 95% CI 5.82–448.26, $P < 0.001$). **Conclusions**: In COVID-19 patients, cTnI and NT-proBNP levels could be monitored to identify patients at a high risk of death in their later course of disease.

Key words: coronavirus disease 2019, cTnI, NT-proBNP, cardiac injury, predictive

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INTRODUCTION

Since its first outbreak in Wuhan, China, the pandemic of coronavirus disease 2019 (COVID-19) has spread to 215 countries, attached to more than 135 million people, and led to more than 2.9 million deaths. It is still the biggest public health threat all over the world. Compared to previous diseases caused by the coronavirus, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), COVID-19 is characterized by a higher infection rate and a lower death rate.[1] However, given the huge number of infected patients, identifying the high-risk patients and giving them more attention is the priority for clinicians to improve the patients' outcomes.

A big challenge for reducing case fatality rate is the unpredictable progression of the disease. Patients may present as stable in the early stage and then undergo dramatic exacerbation in the later stage or even in the process of recovery. So, identifying individuals' characters that could predict poor outcomes has been the priority for investigators. Several clinical characters, such as old age, concomitant cardiovascular or respiratory diseases, diabetes, and cancer, have been proposed to be related with poor clinical outcomes.[2, 3]

Laboratory abnormalities, including elevated markers of inflammation, coagulation disorder, and cardiac injury, have also been correlated with disease severity. [2, 4] Among the laboratory abnormalities, parameters indicating cardiac injury have aroused most research interests. Cardiac troponin I (cTnI) is a sensitive indicator for cardiomyocyte injury, and it was reported that 20–30% of patients with COVID-19 had increased cTnI levels,[5] and nonsurvivors or critically ill patients had a higher rate of cTnI elevation than survivors or mild cases.[2, 4,6,7] Several studies have shown the association between the cardiac injury markers and worse clinical outcomes, including death.[2,8] N-terminal pro-B-type natriuretic peptide (NT-proBNP) is another parameter indicating cardiac injury, and it has been used as a sensitive indicator of heart function insufficiency. In a recent report of hospitalized Chinese COVID-19 patients, 52% of nonsurvivors suffered heart failure, compared to 12% of the survivors.[2] Recent studies have also shown the association of elevated NT-proBNP levels with poor outcomes in COVID-19 patients.[9]

Though both cTnI and NT-proBNP levels have been reported to be associated with poor clinical outcomes in COVID-19 patients, no study has tried to explore the joint predictive value of the two parameters. Therefore, in this retrospective, single-center study, we investigated the associations of cTnI levels, NT-proBNP levels, as well as their joint effects on mortality in patients with COVID-19. Moreover, we explored the effect of the progression of cTnI and NT-proBNP levels on mortality in our patients.

METHODS

Study participants

In early February 2020, a medical team from Peking University First Hospital, Peking University People's Hospital, and Peking University Third Hospital was sent to Wuhan to support local treatment of COVID-19 patients. They were assigned to treat severe and critically ill patients in Zhongfaxincheng branch of Tongji Hospital (Wuhan, China). From February 8–28, 2020, 138 patients were transferred to their wards. All patients were diagnosed with COVID-19 in accordance with the criteria of WHO interim guidance.[10] Among them, three patients had no record of cTnI and one patient had no record of NT-proBNP. Thus, we enrolled 134 participants in this study. A flowchart of screening and enrollment of the patients is shown in Figure 1. The study was approved by the Ethics Committees of Peking University First Hospital (number 2020-236).

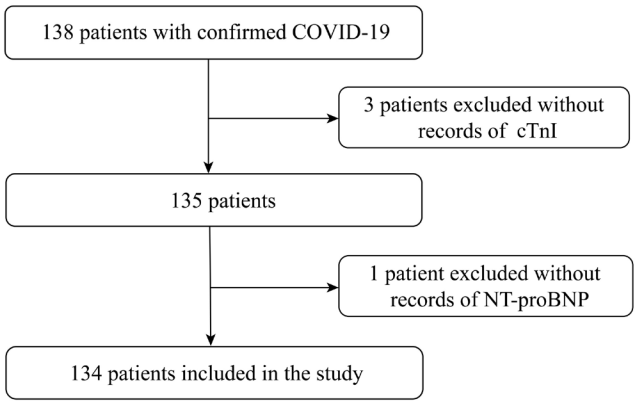

Figure 1. Flowchart of screening and enrollment of patients. COVID-19: coronavirus disease 2019; cTnI: cardiac troponin I; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

Data collection

Demographic characteristics (age and sex), symptoms, medical history, laboratory results, treatments, and clinical outcomes were collected from electronic medical records and reviewed by a team of trained physicians.

CTnI levels were measured using the chemiluminescent immunoassay method (Abbott, Chicago, USA), and NT-proBNP levels were measured using the electrical chemiluminescent immunoassay method (Roche, Basel, Switzerland). According to the test manual and reagent instructions of Tongji Hospital, the normal reference range of cTnI uses the 99th percentile of healthy people as the upper limit, which is ≤ 26.2 ng/L. The normal reference range of NT-proBNP is 5.0–97.3 ng/L for 18–44 years of age, 5.0–121.0 ng/L for 45–54 years of age, 5.0–198.0 ng/L for 55–64 years of age, 5.0–285.0 ng/L for 65–74 years of age, and 5.0–526.0 ng/L for ≥ 75 years of age. cTnI elevation was defined as the highest blood level of cTnI above the 99th percentile reference limit, and NT-proBNP elevation was defined as the highest blood NT-proBNP level above the normal range of related age. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[11]

Severity of the disease was staged according to the Diagnosis and Treatment Plan for COVID-19 (Tentative, the seventh version) issued by the National Health Committee of the People's Republic of China. A severe case was defined as

having one of the following: (1) respiratory rate > 30/min, (2) pulse oxygen saturation (SpO_2) ≤ 93%, and (3) arterial oxygen pressure (PaO_2)/fraction of inspired oxygen (FiO_2) ratio ≤ 300 mmHg. A critically ill case was defined as having at least one of the following criteria: shock, respiratory failure requiring mechanical ventilation, and extrapulmonary organ failure requiring intensive care. The clinical outcomes were defined as death and ventilator use within 30 days after admission.

Statistical analysis

Data are shown as mean ± standard deviation for continuous variables that were normally distributed, and as median and interquartile range (IQR) for continuous variables that were non-normally distributed. Categorical variables are expressed as number and proportion. Proportions were compared using the χ^2 test. Mean values were compared using the *t*-test when the data were normally distributed and the Kruskal–Wallis test when they were not.

Multivariate Cox regression was used to determine the association of cTnI levels, NT-proBNP levels, and their combined effects on death rate. The hazard ratio (HR) and 95% confidence interval (CI) are shown to indicate the effect. Survival curve was plotted using the Kaplan–Meier method and compared among different groups of patients using the log-rank test. All analyses were considered statistically significant at $P < 0.05$. All statistical analyses were performed with EmpowerStats (http://www.empowerstats.com/en/index.html) and R-Project (https://www.r-project.org/, version 3.4.3).

RESULTS

Patients' characteristics and laboratory findings

Characteristics and laboratory results of the patients are summarized in Table 1. The mean age was 62.0 ± 14.6 years, and 50.8% (68/134) of the patients were men. Common symptoms such as fever (116/134, 86.6%), cough (112/134, 83.6%), sputum production (83/134, 62.0%), and shortness of breath (89/134, 66.4%) were observed in the patients. A total of 18.7% (25/134) of the patients experienced chest pain and 25.4% (34/134) had palpitation.

Mean/median levels of SpO_2, lymphocytes, and eGFR were significantly lower, whereas mean/median levels of white blood cell (WBC) count, high-sensitivity C-reactive protein (hsCRP), D-dimer, cTnI levels, NT-proBNP levels, and creatinine kinase isoenzyme-MB (CK-MB) were significantly higher in patients with cTnI elevation compared with those without. In patients with elevated NT-proBNP levels, mean/median levels of SpO_2, lymphocytes, and eGFR were significantly lower, and mean/median levels of WBC count, hsCRP, D-dimer, cTnI, NT-proBNP, and CK-MB were significantly higher compared with patients without.

Treatment and clinical outcomes

Table 2 shows the treatments and clinical outcomes for different groups of patients. In all the included patients, 22.4% (30/134) and 9.0% (12/134) of the patients received noninvasive ventilation and invasive ventilation, respectively. A total of 23.9% (32/134) of the patients used glucocorticoids, and 17.9% (24/134) received intravenous immunoglobulin therapy. A total of 9 (6.7%) patients required admission to the ICU. The overall mortality rate in our study was 18.7%. Patients with cTnI elevation had higher rates of glucocorticoid use (72.0% *vs.* 12.8%, $P < 0.001$), noninvasive ventilator use (80.0% *vs.* 9.2%, $P < 0.001$), invasive ventilator use (40.0% *vs.* 1.8%, $P < 0.001$), ICU admission (28.0% *vs.* 1.8%, $P < 0.001$), being critically ill (84.0% *vs.* 11.0%, $P < 0.001$), and death (68.0% *vs.* 7.3%, $P < 0.001$) than those with normal cTnI levels. Patients with elevated NT-proBNP levels had a significantly higher proportion of glucocorticoid use (46.7% *vs.* 5.4%, $P < 0.001$), noninvasive ventilator use (45.0% *vs.* 4.1%, $P < 0.001$), invasive ventilator use (18.3% *vs.* 1.4%, $P < 0.001$), ICU admission (13.3% *vs.* 1.4%, $P = 0.006$), being critically ill (50.0% *vs.* 4.1%, $P < 0.001$), and death (40.0% *vs.* 1.4%, $P < 0.001$) than those with normal NT-proBNP levels.

Associations of cTnI elevation and NT-proBNP elevation with death

The associations of cTnI levels, NT-proBNP levels, and their combined effect on the mortality rate were determined by multivariate Cox regression (Table 3). We adjusted for sex, age, history of hypertension, coronary heart disease, diabetes, chronic pulmonary disease, SpO_2, and eGFR in the regression model. We found that the risk of death increased by 633% (HR 7.33, 95% CI 2.56–21.00, $P < 0.001$) in patients with cTnI elevation compared with those without. Similarly, patients with elevated NT-proBNP levels had a greater risk of death (HR 27.88, 95% CI 3.55–218.78, $P = 0.002$) than those with normal NT-proBNP levels in multivariate Cox regression. To detect the joint effect of cTnI and NT-proBNP elevation, we divided the patients into three groups according to the incidence of cTnI and NT-proBNP elevation: group 1, patients without cTnI or NT-proBNP elevation; group 2, patients with either cTnI or NT-proBNP elevation; and group 3, patients with both cTnI and NT-proBNP elevation. Cox regression analysis showed that compared to group 1, group 2 had a higher risk of death (HR 15.08, 95% CI 1.82–124.99, $P = 0.012$), and group 3 had the highest risk of death (HR 53.87, 95% CI 6.31–459.91, $P < 0.001$). In addition, multivariate Cox regression analysis was done to detect the association of progression of cTnI and NT-proBNP levels during

Table 1: Baseline characteristics and laboratory results of 134 patients with COVID-19

Variables	All (n = 134)	cTnI elevated		P-value	NT-proBNP elevated		P-value
		No (n = 109)	Yes (n = 25)		No (n = 74)	Yes (n = 60)	
Age, years	62.0 ± 14.6	61.2 ± 14.8	65.5 ± 13.8	0.192	60.5 ± 14.1	63.9 ± 15.2	0.178
Male, %	68 (50.8%)	49 (45.0%)	19 (76.0%)	0.005	35 (47.3%)	33 (55.0%)	0.375
Signs and symptoms							
SpO_2 at admission, %	92.2 ± 7.3	93.9 ± 5.2	85.2 ± 10.5	< 0.001	94.2 ± 5.3	89.8 ± 8.6	< 0.001
SBP at admission, mmHg	133.5 ± 22.4	133.7 ± 22.1	132.9 ± 24.2	0.874	131.1 ± 18.5	136.6 ± 26.4	0.158
DBP at admission, mmHg	82.6 ± 14.8	82.2 ± 14.5	84.4 ± 16.4	0.511	81.7 ± 13.3	83.8 ± 16.6	0.409
Heart rate at admission, bpm	97.0 ± 18.0	95.6 ± 15.5	102.7 ± 25.8	0.078	95.7 ± 15.3	98.5 ± 20.9	0.373
Fever, %	116 (86.6%)	93 (85.3%)	23 (92.0%)	0.377	63 (85.1%)	53 (88.3%)	0.589
Cough, %	112 (83.6%)	90 (82.6%)	22 (88.0%)	0.509	59 (79.7%)	53 (88.3%)	0.181
Sputum production, %	83 (62.0%)	65 (60.0%)	18 (72.0%)	0.251	41 (55.4%)	42 (70.0%)	0.084
Shortness of breath, %	89 (66.4%)	71 (65.1%)	18 (72.0%)	0.512	44 (59.5%)	45 (75.0%)	0.058
Chest pain, %	25 (18.7%)	20 (18.3%)	5 (20.0%)	0.848	11 (14.9%)	14 (23.3%)	0.211
Palpitation, %	34 (25.4%)	30 (27.5%)	4 (16.0%)	0.232	18 (24.3%)	16 (26.7%)	0.757
Abdominal pain, %	25 (18.7%)	23 (21.1%)	2 (8.0%)	0.129	13 (17.6%)	12 (20.0%)	0.719
Fatigue, %	82 (61.2%)	69 (63.3%)	13 (52.0%)	0.296	46 (62.2%)	36 (60.0%)	0.798
Medical history							
Coronary heart disease, %	26 (19.4%)	21 (19.3%)	5 (20.0%)	0.933	14 (18.9%)	12 (20.0%)	0.875
Hypertension, %	62 (46.3%)	50 (45.9%)	12 (48.0%)	0.847	30 (40.5%)	32 (53.3%)	0.140
Chronic pulmonary disease, %	21 (15.7%)	15 (13.8%)	6 (24.0%)	0.204	10 (13.5%)	11 (18.3%)	0.445
Chronic kidney disease, %	9 (6.7%)	5 (4.6%)	4 (16.0%)	0.040	2 (2.7%)	7 (11.7%)	0.039
Diabetes, %	27 (20.1%)	20 (18.4%)	7 (28.0%)	0.278	15 (20.3%)	12 (20.0%)	0.969
Laboratory results							
WBC, $\times 10^9$/L	5.5 (4.4–7.7)	5.2 (4.3–6.6)	8.5 (6.8–13.33)	< 0.001	5.0 (4.2–5.8)	7.2 (5.0–10.6)	< 0.001
Lymphocytes, $\times 10^9$/L	0.9 (0.6–1.4)	1.0 (0.7–1.4)	0.6 (0.5–1.1)	0.010	1.1 (0.8–1.6)	0.8 (0.5–1.1)	< 0.001
Hemoglobin, g/L	124.1 ± 20.7	122.6 ± 16.8	130.7 ± 32.4	0.077	125.3 ± 12.9	122.7 ± 27.4	0.466
Platelets, $\times 10^9$/L	231.5 (159.3–291.8)	233.0 (165.0–291.0)	222.0 (138.0–295.0)	0.673	241.0 (168.0–291.0)	216.0 (147.0–292.8)	0.390
Creatinine, μmol/L	72.5 (58.0–91.0)	70.0 (57.0–87.0)	91.0 (69.0–105.0)	0.003	65.0 (55.0–1.8)	85.5 (66.0–99.0)	< 0.001
eGFR, ml/min/1.73^{m2}	78.2 (57.1–94.2)	82.3 (60.0–95.2)	59.6 (46.8–78.3)	0.003	85.5 (71.2–99.7)	61.1 (49.6–84.4)	< 0.001
hsCRP, mg/L	33.1 (6.2–81.0)	26.1 (5.3–57.9)	121.4 (40.2–210.1)	< 0.001	11.9 (3.5–40.6)	59.6 (27.2–142.6)	< 0.001
Procalcitonin, ng/mL	0.05 (0.03–0.14)	0.04 (0.03–0.10)	0.32 (0.12–0.57)	< 0.001	0.03 (0.02–0.08)	0.12 (0.05–0.36)	< 0.001
D-Dimer, μg/mL	1.2 (0.5–2.3)	1.0 (0.5–2.0)	2.6 (1.4–16.2)	< 0.001	0.7 (0.4–1.8)	1.7 (0.9–2.8)	< 0.001
cTnI, pg/mL	4.6 (2.2–10.3)	3.6 (1.9–7.2)	57.6 (11.2–234.8)	< 0.001	3.1 (1.9–5.4)	9.4 (4.1–26.4)	< 0.001
Myohemoglobin, μg/L	58.6 (37.8–129.1)	53.0 (35.5–90.9)	131.7 (60.5–247.4)	< 0.001	43.0 (32.0–73.1)	119.8 (52.8–175.1)	< 0.001
CK-MB, ng/mL	0.9 (0.4–1.7)	0.7 (0.4–1.4)	1.7 (1.1–5.4)	< 0.001	0.7 (0.4–1.3)	1.3 (0.6–2.4)	< 0.001
NT pro-BNP, pg/mL	180.0 (67.0–456.5)	142.0 (64.0–292.0)	852.0 (386.0–1658.0)	< 0.001	92.0 (56.8–179.8)	523.5 (291.5–1011.8)	< 0.001

SpO_2: pulse oxygen saturation; SBP: systolic blood pressure; DBP: diastolic blood pressure; WBC: white blood cell; eGFR: estimated glomerular filtration rate; hsCRP: high-sensitivity C-reactive protein; cTnI: cardiac troponin I; CK-MB: creatinine kinase isoenzyme-MB; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

Table 2: Treatments and clinical outcomes of 134 patients with COVID-19

Variable	*n* (%)	cTnI elevated		*P*-value	NT-proBNP elevated		*P*-value
		No (*n* = 109)	Yes (*n* = 25)		No (*n* = 74)	Yes (*n* = 60)	
Treatment							
Antiviral treatment, %	115 (85.8%)	95 (87.1%)	20 (80.0%)	0.355	61 (82.4%)	54 (90.0%)	0.212
Antibiotic treatment, %	63 (47.0%)	40 (36.7%)	23 (92.0%)	< 0.001	21 (28.4%)	42 (70.0%)	< 0.001
Intravenous immunoglobulin therapy, %	24 (17.9%)	16 (14.7%)	8 (32.0%)	0.042	6 (8.1%)	18 (30.0%)	0.001
Glucocorticoids, %	32 (23.9%)	14 (12.8%)	18 (72.0%)	< 0.001	4 (5.4%)	28 (46.7%)	< 0.001
Noninvasive ventilation, %	30 (22.4%)	10 (9.2%)	20 (80.0%)	< 0.001	3 (4.1%)	27 (45.0%)	< 0.001
Invasive mechanical ventilation, %	12 (9.0%)	2 (1.8%)	10 (40.0%)	< 0.001	1 (1.4%)	11 (18.3%)	< 0.001
Clinical outcomes							
ICU admission, %	9 (6.7%)	2 (1.8%)	7 (28.0%)	< 0.001	1 (1.4%)	8 (13.3%)	0.006
Critically ill, %	33 (24.6%)	12 (11.0%)	21 (84.0%)	< 0.001	3 (4.1%)	30 (50.0%)	< 0.001
Death, %	25 (18.7%)	8 (7.3%)	17 (68.0%)	< 0.001	1 (1.4%)	24 (40.0%)	< 0.001
Ventilator use, %	31 (23.1%)	10 (9.2%)	21 (84.0%)	< 0.001	3 (4.1%)	28 (46.7%)	< 0.001

cTnI: cardiac troponin I; NT-proBNP: N-terminal pro-B-type natriuretic peptide; ICU: intensive care unit.

Table 3: Multivariate Cox regression analysis on the association of elevated cTnI and NT-proBNP levels with death in COVID-19 patients

Death						
Variables			**Unadjusted**		**Adjusted***	
	n (%)	Death (%)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Elevated cTnI levels	25 (18.7%)	17 (68.0%)	12.94 (5.55–30.18)	< 0.001	7.33 (2.56–21.00)	< 0.001
Elevated NT-proBNP levels	60 (44.8%)	24 (40.0%)	36.62 (4.95–270.90)	< 0.001	27.88 (3.55–218.78)	0.002
Combined effect†						
Group 1	73 (54.5%)	1 (1.4%)	Reference		Reference	
Group 2	37 (27.6%)	7 (18.9%)	15.55 (1.91–126.45)	0.010	15.08 (1.82, 124.99)	0.012
Group 3	24 (17.9%)	17 (70.8%)	77.08 (10.22–581.35)	< 0.001	53.87 (6.31, 459.91)	< 0.001
P for trend				< 0.001		< 0.001

*Adjusted for gender, age, history of hypertension, coronary heart disease, diabetes, chronic pulmonary disease, pulse oxygen saturation, estimated glomerular filtration rate. †Group 1 stands for patients without elevated levels of cTnI or NT-proBNP. Group 2 stands for patients with elevated levels of cTnI or NT-proBNP. Group 3 stands for patients with elevated levels of cTnI and NT-proBNP. HR: hazard ratio; CI: confidence interval; cTnI: cardiac troponin I; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

hospitalization with death (Table 4). Compared to patients with normal cTnI levels during the whole hospital stay, the risk of death was the highest (HR 12.70, 95% CI 3.94–40.88, $P < 0.001$) in patients with normal cTnI levels at admission but developed cTnI elevation during hospitalization, after adjusting for sex, age, history of hypertension, coronary heart disease, diabetes, chronic pulmonary disease, SpO_2, and eGFR. Similarly, compared to patients with normal NT-proBNP levels during the whole hospital stay, the risk of death was the highest (HR 51.09, 95% CI 5.82–448.26, $P < 0.001$) in patients with normal NT-proBNP levels at admission but developed NT-proBNP elevation during hospitalization, after adjusting for sex, age, history of hypertension, coronary heart disease, diabetes, chronic pulmonary disease, SpO_2, and eGFR.

Kaplan–Meier curves (Figure 2) show that the rates of mortality increased in patients with cTnI and NT-proBNP elevation.

DISCUSSION

In this single-center retrospective study, we evaluated the predictive values of cTnI and NT-proBNP on mortality in 134 COVID-19 patients. The overall death rate was 18.7% (25 out of 134) in our study population. Both elevated levels of cTnI and NT-proBNP during hospital stay were significantly associated with an increased risk of death, after adjusting for gender, age, history of hypertension, coronary heart disease, diabetes, chronic pulmonary disease, SpO_2, and eGFR. Moreover, for the first time, we found that cTnI

Table 4: Multivariate Cox regression analysis on the association of progression of cTnI and NT-proBNP levels during hospitalization with death or ventilator use in COVID-19 patients

Death

Variables			Unadjusted		Adjusted*	
	n (%)	Death (%)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Progression of CTnI levels in hospitalization†						
Group 1	109 (81.3%)	8 (7.3%)	Reference		Reference	
Group 2	16 (11.9%)	9 (56.3%)	10.39 (3.99–27.07)	< 0.001	4.38 (1.25–15.33)	0.021
Group 3	9 (6.7%)	8 (88.9%)	17.96 (6.69–48.25)	< 0.001	12.70 (3.94–40.88)	< 0.001
P for trend				< 0.001		< 0.001
Progression of NT-proBNP levels in hospitalization†						
Group 1	74 (55.2%)	1 (1.4%)	Reference		Reference	
Group 2	48 (35.8%)	18 (37.5%)	34.03 (4.54–255.15)	< 0.001	21.51 (2.63–175.74)	0.013
Group 3	12 (9.0%)	6 (50.0%)	47.38 (5.70–393.82)	< 0.001	51.09 (5.82–448.26)	< 0.001
P for trend				< 0.001		< 0.001

*Adjusted for gender, age, history of hypertension, coronary heart disease, diabetes, chronic pulmonary disease, pulse oxygen saturation, estimated glomerular filtration rate. †Group 1 stands for patients without elevated levels of cTnI or NT-proBNP. Group 2 stands for patients with elevated levels of cTnI or NT-proBNP. Group 3 stands for patients with elevated levels of cTnI and NT-proBNP. HR: hazard ratio; CI: confidence interval; cTnI: cardiac troponin I; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

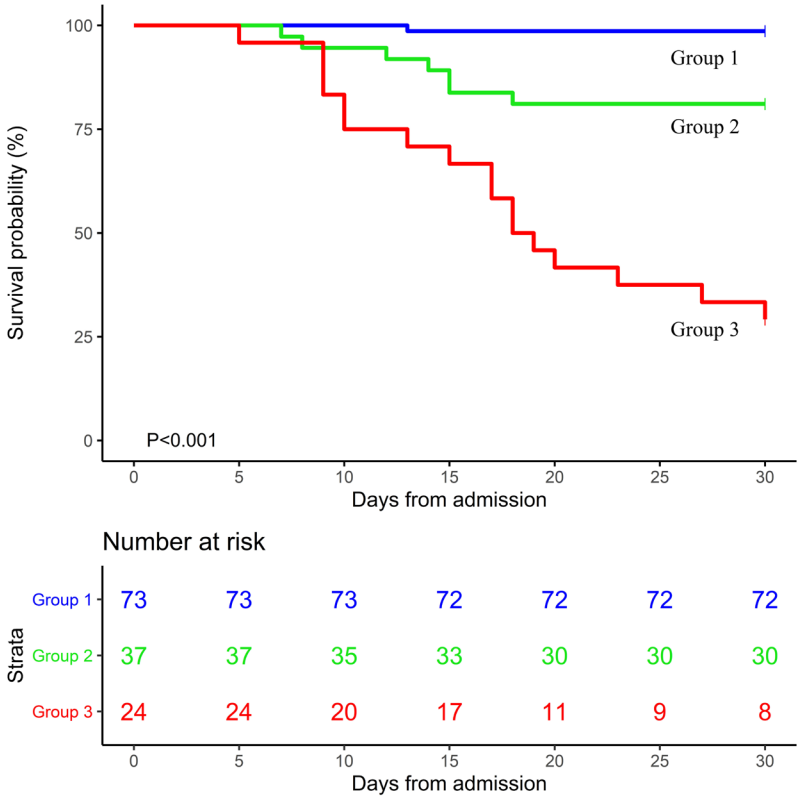

Figure 2: Kaplan–Meier curves of mortality according to the combined effect of elevated cTnI and NT-proBNP levels. Group 1 stands for patients without elevated levels of cTnI or NT-proBNP. Group 2 stands for patients with elevated levels of cTnI or NT-proBNP. Group 3 stands for patients with elevated levels of cTnI and NT-proBNP. cTnI: cardiac troponin I; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

and NT-proBNP had a joint effect on predicting death, and the progression of the two cardiac injury parameters could also predict death.

Prior to our study, several studies, including a meta-analysis, had addressed the predictive value of cTnI and NT-proBNP.[6, 9, 12-14] But based on those reported results, it is inconclusive whether the levels of cardiac injury parameters at admission were independently associated with death. One limitation of these studies is that most of them adjusted limited number of important covariates that could also influence the patients' outcomes. So, in our study, we included as much information as we were able to obtain, including age, gender, history of hypertension, coronary heart disease, diabetes, chronic pulmonary disease, SpO_2, and eGFR. After adjusting these important covariates, we found a very significant association between the two cardiac injury parameters and death in our study population.

To our knowledge, we are the first to show the joint predictive value of elevated cTnI and NT-proBNP levels on mortality in COVID-19 patients. A previous study showed that the combination of NT-proBNP and troponin I levels had higher prognostic utility in older patients with severe sepsis or septic shock in the ICU.[15] In our study, we found that the patients with both elevated cTnI and NT-proBNP levels had the highest risk of death. cTnI is a sensitive marker of cardiac injury, whereas NT-proBNP is a marker of heart insufficiency. Therefore, patients with elevated levels of both cTnI and NT-proBNP may have cardiac injury and dysfunction of the left and/or right ventricle. For these patients, the clinical prognosis may be worse because of severe cardiac injury and either poor or decompensated heart function after COVID-19 infection. These patients might be vulnerable to the excessive volume load during fluid resuscitation and would be less sensitive to vasopressors, which are the two vital treatments for sepsis shock caused by severe acute respiratory syndrome.

Another important contribution of our study is that we investigated the change of cardiac injury parameters and their effect in predicting death. Given the rapid deterioration of the disease in some patients,[16] baseline levels of cardiac injury may not be an optimal marker to predict future events. In the current study, we investigated the progression trend of these two parameters and found it to be independently associated with an increased risk of death. What can be translated from our findings to clinical use is that physicians need to monitor these parameters closely, and once their levels go up, they should consider more active therapy.

These findings are important for physicians to identify a potentially high-risk patient with COVID-19 in the early stage of this disease. Close monitoring of patients with elevated levels of cTnI and NT-proBNP may be required, which is crucial to reduce case fatality rate.

Mechanisms of cardiac injury are not fully understood. Several pathophysiological pathways have been proposed to explain the elevated parameters. Myocarditis might be an explanation of the cardiac injury through direct or indirect mechanisms.[17] Multiple autopsy findings showed the infiltration of macrophages and $CD4^+$ T lymphocytes in the myocardium of COVID-19 patients,[18-20] which was thought to be the outcome of the cytokine release syndrome.[21] Another case report demonstrated the presence of SARS-CoV-2 viral particles in cardiac macrophages, suggesting that cardiomyocytes can be directly infected by the virus.[22] Cardiac MRI showed that patients with severe COVID-19 had myocardial inflammation, edema, and/or diffuse myocardial fibrosis, which confirmed the incidence of myocarditis.[23,24] Another theory for the cardiac injury was microthrombi induced by endothelial injury.[25] Large thrombi, microangiopathy, and signs of disseminated intravascular coagulation were observed in severe cases of COVID-19.[26] A recent study showed that the most common pathological cause of myocyte necrosis is microthrombi.[27] Other explanations were type 1 and type 2 myocardial infarction. Inflammatory responses can directly affect atherosclerotic plaques and increase procoagulant and prothrombotic activity,[28] which could result in the acute coronary syndrome.[29] Oxygen supply–demand mismatch in severe and critically ill COVID-19 patients with hypoxia, acidosis, or hypotension can explain the type 2 myocardial infarction.[29]

LIMITATIONS

The major limitation of this study is that it is a retrospective study, and because of the small sample size and lack of some key clinical examinations, like ECG/echocardiogram, it was difficult to explore the underlying mechanism. Further large-scale prospective studies are warranted to confirm our discovery.

CONCLUSIONS

In conclusion, elevated cTnI and NT-proBNP levels have a joint effect in predicting death in COVID-19 patients. The progression of these two parameters needs to be monitored closely, since they could also predict death in these patients.

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Conflict of Interests

None.

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Authors Contributions

Haoyu Weng, Haichao Li, Yan Zhang, and Jianping Li designed the study. Fan Yang, Han Jin, Long Zhang, Shengcong Liu, Hongyu Yang, and Xizi Zheng were responsible for collecting data and establishing the database. Fangfang Fan, Zhihao Liu, Yuxi Li, and Tieci Yi did the data analysis. Haoyu Weng and Jianping Li wrote and revised the manuscript. All the authors approved the final version of the manuscript for publication. The manuscript has been read and approved by all the authors, and each author believes that the manuscript represents honest work.

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