Redefining NT-proBNP in predicting mortality of adult inpatients with COVID-19

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Abstract

NT-proBNP was much lower than the recommended threshold for heart failure in some adult COVID-19 inpatients with poor prognosis. NT-proBNP has different ranges of normal values for different age groups. NT-proBNP levels specific to age, defined as NT-proBNP ratio, were divided into quartiles and measured the hazard ratios (and 95% confidence intervals) for in-hospital death of COVID-19 patients. Higher NT-proBNP ratio was directly associated, in a dose-response manner, with a higher risk of all causes in-hospital death in the COVID-19 patients. Our study shows that NT-proBNP ratio is an independent predictor of the risk of in-hospital death of the adult patients with COVID-19. This implies that NT-proBNP levels specific to age in the COVID-19 patietns requires attention of healthcare workers.

Introduction

SARS-CoV-2 infection has been associated with cardiovascular implications including acute myocardial injury, myocarditis and arrhythmias[1–7]. Huang et al. reported that acute cardiac ischemia was presented in 12% of patients with COVID-19, showed by elevated levels of high-sensitive troponin I[8]. A retrospective, single-center case series of the 138 COVID-19 patients study reported that 16.7% patients had complications of acute cardiac damage and arrhythmia, respectively[9]. It was reported that 19.7% patients from a total of 416 cases with COVID-19 had cardiac injury with more adverse clinical outcomes compared to those without[10]. A recent review showed that up to 20%-30% of inpatients of COVID-19 have evidence of myocardial involvement[11].

Acute cardiac injury in COVID-19 patients is associated with higher morbidity and mortality. In a study enrolled 671 eligible hospitalized patients with severe COVID-19 from 1 January to 23 February 2020, 62 patients died who more often had heart damage than survivors (75.8% vs 9.7%, $p < 0.001$)[12]. An observational study among 187 patients with confirmed COVID-19, the mortality during hospitalization was 37.50% (6 of 16) for those without underlying CVD but elevated TnT levels and 69.44% (25 of 36) for those with underlying CVD and elevated TnT levels[13].

N-terminal pro-brain natriuretic peptide (NT-proBNP) increased significantly during the course of hospitalization in COVID-19 patients who ultimately died[13–16]. And some researcher concluded that NT-proBNP might be an independent risk factor for in-hospital death in patients with severe COVID-19[17]. They found that patients in high NT-proBNP (> 88.64 pg/ml) group had a significantly higher risk of death during the days of follow-up than the low group (NT-proBNP ≤ 88.64 pg/ml). However, the study did not consider that the normal reference range of NT-proBNP varies greatly among different age groups, it is not accurate to estimate the prognosis of COVID-19 only based on the absolute value of NT-proBNP.

In this report, we described the NT-proBNP ratio as measured NT-proBNP relative to the maximal normal values specific to age and the present study investigated the prognostic value of the NT-proBNP ratio and the association in the patients of COVID-19.

Results

Demographics and baseline characteristics

1089 eligible patients with available NT-proBNP were included and divided into quartiles according to ascending order of NT-proBNP ratio (Fig. 1). Participants with the highest NT-proBNP ratio were older and more likely to have a comorbidity of hypertension or coronary artery disease or chronic kidney disease, but less likely to be female, than participants with lower NT-proBNP ratio. Higher systolic blood pressure was more prevalent among those with greatest NT-proBNP ratio, who also had a elevated level of NT-proBNP, higher white-cell count, lower percentage of lymphocyte, lower monocyte count and more death. In contrast, other characteristics like body mass index, the blood routine items (lymphocyte count, monocyte%, neutrophil%, neutrophil count), renal functions (serum urea and creatinine, eGFR), and systematic inflammatory factors (high-sensitive C-reactive protein, procalcitonin) had no significance between the four groups (Table 1, Supplyment 1).

Table 1

Demographic and clinical characteristics of the patients at baseline[a].

	Quartile 1(N = 271)	Quartile 2(N = 270)	Quartile 3(N = 275)	Quartile 4(N = 273)	*P* value
Characteristics	**(0.003 ~ 0.053)**	**(0.054 ~ 0.131)**	**(0.132 ~ 0.371)**	**(0.376 ~ 77.778)**	
Age, median [IQR]-yr	54.00 [41.00,60.00]	62.00 [51.00, 69.00]	66.00 [56.50, 73.50]	67.00 [61.00, 74.00]	< 0.001***
Female sex, no. (%)	108 (39.90)	151 (55.90)	151 (54.90)	124 (45.40)	< 0.001***
Heart rate, median [IQR]	92.00 [80.50, 103.00]	90.00 [80.00, 100.00]	87.00 [79.00, 100.00]	89.00 [78.00, 104.50]	0.013*
Systolic blood pressure (mmHg), median [IQR]	128.00 [117.00, 139.00]	131.00 [119.00, 145.00]	129.00 [115.00, 142.75]	135.00 [120.25, 149.00]	< 0.001***
Diastolic blood pressure (mmHg), median [IQR]	82.00 [75.75, 90.00]	81.00 [74.00, 90.00]	79.00 [71.00, 87.00]	80.00 [71.00, 88.00]	0.010*
Mean arterial pressure (mmHg), median [IQR]	44.00 [37.00, 53.00]	50.00 [40.75, 60.00]	49.50 [40.00, 60.00]	54.00 [44.00, 66.00]	< 0.001***
Hypertension, no. (%)	52 (19.30)	78 (28.90)	92 (33.60)	109 (40.20)	< 0.001***
Coronary artery disease, no. (%)	5 (1.84)	17 (6.30)	28 (10.18)	29(10.62)	< 0.001***
Chronic kidney disease, no. (%)	0(0.00)	1 (0.37)	2 (0.73)	7 (2.56)	0.037*
White-cell count ($\times 10^9$/L), median [IQR]	5.73 [4.64, 7.15]	5.40 [4.31, 7.18]	5.72 [4.46, 7.20]	7.10 [5.15,10.55]	< 0.001***
Lymphocyte (%), median [IQR]	21.60 [14.40, 29.10]	22.00 [13.60, 30.20]	21.20 [13.40, 29.60]	16.60 [8.80, 25.08]	< 0.001***
<20%, no. (%)	120 (44.60)	123 (45.90)	118 (43.20)	154 (57.00)	0.005**
Monocyte count ($\times 10^9$/L), median [IQR]	0.51 [0.38, 0.66]	0.45 [0.34, 0.59]	0.48 [0.37, 0.64]	0.47 [0.35, 0.58]	0.015*

[a]The values shown are based on available data. IQR denotes interquartile range. *P< 0.05, **P< 0.01, ***P< 0.001.

	Quartile 1(N = 271)	Quartile 2(N = 270)	Quartile 3(N = 275)	Quartile 4(N = 273)	*P* value
NT-proBNP (pg/ml), median [IQR]	19.00 [9.50, 31.00]	70.00 [53.00, 98.00]	186.00 [138.00, 276.00]	827.00 [504.00, 1817.00]	< 0.001***
NT-proBNP ratio, median [IQR]	0.03 [0.02, 0.04]	0.08 [0.06, 0.11]	0.20 [0.16, 0.27]	0.80 [0.53, 1.67]	< 0.001***
In-hospital Death, no. (%)	1 (0.40)	10 (3.70)	20 (7.30)	84 (30.80)	< 0.001***

[a]The values shown are based on available data. IQR denotes interquartile range. *P< 0.05, **P< 0.01, ***P< 0.001.

Receiver operator characteristic (ROC) curve of NT-proBNP ratio for prediction in-hospital death

Receiver operator characteristic (ROC) curve were showed in Fig. 2 to analyze the prognostic value of NT-proBNP and NT-proBNP ratio for prediction in-hospital death with sensitivity and specificity (NT-proBNP, sensitivity 89.47% and specificity 69.64%; NT-proBNP ratio, sensitivity 76.52% and specificity 77.93%). The area under the curve (AUC) for in-hospital death of NT-proBNP and NT-proBNP ratio were 0.868 (95% CI 0.838–0.898, P< 0.0001) (Fig. 2A) and 0.850 (95% CI 0.815–0.884, P< 0.0001) (Fig. 2B). The cutoff point of NT-proBNP and NT-proBNP ratio for prediction in-hospital death were 202.500 (Fig. 2A) and 0.316 (Fig. 2B), respectively. NT-proBNP ratio had a lower sensitivity but higher specificity than NT-proBNP.

Cumulative survival curves of NT-proBNP and NT-proBNP ratio for prediction in-hospital death

All the patients in our research were divided into quartiles according to ascending order of the NT-proBNP ratio. To make this a fair comparison, we also divided all the parcipants in this study into quartiles according to ascending order of NT-proBNP. Cumulative survival curves of NT-proBNP and NT-proBNP ratio for the prediction of in-hospital death were showed in Fig. 3A and Fig. 3B.

Results of univariate and multivariate Cox proportional hazards analyses of in-hospital death

The incidence of in-hospital death was determined for overall and the quartiles of NT-proBNP and NT-proBNP ratio in the COVID-19 patients. The univariate analysis for overall showed that both absoulte value of NT-proBNP (the unadjusted hazard ratio and 95% confidence interval: 1.000, 1.000–1.000, P< 0.0001) and NT-proBNP ratio (the unadjusted hazard ratio and 95% confidence interval: 1.074, 1.059–1.088, P< 0.0001) had a significantly increased risk of in-hospital death in the COVID-19 patients. After multivariate Cox proportional hazards analyses for overall, the mortality of NT-proBNP ratio (the adjusted hazard ratio and 95% confidence interval: 1.141, 1.048–1.242, P= 0.003) persisted while that of NT-proBNP (the adjusted hazard ratio and 95% confidence interval: 0.9999, 0.9999-1.0000, P= 0.129) did not. As compared with the first (lowest) quartile, only the quartile 3 and 4 of NT-proBNP had a significantly

increased risk of death, but quartile 2, 3 and 4 of NT-proBNP ratio all had a significantly increased risk of death, in the unadjusted and adjusted analyses of COVID-19 patients (Supplyment 2).

Risk of death according to NT-proBNP and NT-proBNP ratio among the COVID-19 Participants

According to the cutoff point of NT-proBNP and NT-proBNP ratio for prediction in-hospital death, we combined the subgroups into categories designated low-risk (quartile 1 and quartile 2), intermediate-risk (quartile 3), and high-risk (quartile 4), corresponding to NT-proBNP and NT-proBNP ratio levels of the univariate and multivariate Cox proportional hazards analyses (Fig. 3C and Fig. 3D, Supplyment 3). The hazard ratios of NT-proBNP and NT-proBNP ratio in the intermediate-risk and high-risk subgroups were significantly higher than that of low-risk subgroup (Fig. 3C and Fig. 3D, Supplyment 3).

Discussion

In this study, we found NT-proBNP ratio as measured NT-proBNP relative to the maximal normal values specific to age to be a strong and independent predictor of in-hospital death in the patients of COVID-19. According to cutoff points of NT-proBNP and NT-proBNP ratio for prediction in-hospital death and the results of the univariate and multivariate Cox proportional hazards analyses, we defined the low-risk, intermediate-risk and high-risk subgroups with respect to in-hospital death of COVID-19 patients (NT-proBNP: 2.5 ~ 118, 119 ~ 363 and 364 ~ 70000, NT-proBNP ratio: 0.003 ~ 0.131, 0.132 ~ 0.371 and 0.376 ~ 77.778, respectively). And NT-proBNP ratio appears to provide a stronger estimate of the risk of in-hospital death among the patients of COVID-19 than NT-proBNP.

One study has demonstrated that NT-proBNP was presented as an independent risk factor after accounting the factors of cardiac injury, renal injury and systematic inflammation in the multivariate Cox[16]. They found that severe COVID-19 patients with high NT-proBNP levels tended to be older with increased cardiac injury markers and high levels of systematic inflammation markers. Our study showed that patients with elevated level of NT-proBNP ratio had the same age trends, but the levels of systematic inflammation markers had no significant difference among the quartiles in our study. The hazard ratio (HR) of female in the above-mentioned study was 0.348 (0.130–0.930, $P = 0.035$) and 1.077 (0.330–3.518, $P = 0.902$) in the univariate and multivariate Cox. But our Cox results indicated that no significant difference of the HR of female between them, 0.535 (0.364–0.785, $P = 0.001$) and 0.5032 (0.3338–0.7584, $P = 0.0010$). ROC in the above-mentioned study manifested the cutoff value of NT-proBNP for prediction in-hospital death was 88.64 pg/mL with sensitivity of 100% and specificity of 66.67% (AUC 0.909, 95% CI 0.799–0.970, $P < 0.001$). The cutoff value of NT-proBNP of our study (202.500 pg/mL) was higher than that with sensitivity of 89.47% and specificity of 69.64% (AUC 0.868, 95% CI 0.838–0.898, $P < 0.001$). Both cut-offs of NT-proBNP were much lower than the currently accepted laboratory cut-off thresholds for heart failure. These findings are consistent with an earlier report that the cutoffs of cardiac biomarkers (hs-TnI, NT-proBNP, CK-MB,CK) for effective prognosis of 28-day mortality of COVID-19 were found to be much lower than for regular heart disease at about 49% of the currently recommended thresholds[18]. The currently used laboratory upper limits of normal was based on the 99 percentiles of

distribution in a normal population. The researchers speculated that the much lower levels of cutoff values of the cardiac biomarkers might significantly underestimate the extent of cardiac injury associated with COVID-19[18].

The cutoff value of NT-proBNP ratio for prediction in-hospital death was 0.316 with sensitivity of 76.52% and specificity of 77.93% and the AUC was 0.850 (95% CI 0.815–0.884, $P < 0.0001$). Our ROC revealed that the specificity of NT-proBNP ratio was higher than that of NT-proBNP. And our results of univariate and multivariate Cox proportional hazards analyses of in-hospital death displayed that NT-proBNP had no significantly increased risk of death after the adjusted analyses of COVID-19 patients.

The causal effect of the elevation of NT-proBNP with COVID-19 death was unclear. Pneumonia is postulated to cause hypoxia-induced pulmonary hypertension, which may increase ventricular wall stress and leads to the release of NT-proBNP[19]. The SARS-CoV-2 infection and invasion cardiomyocytes via the binding site of angiotensin-converting enzyme-related carboxypeptidase (ACE2) appears to downregulate ACE2, which may contribute to myocardium dysfunction[20–25]. The ACE2 system is a critical protective pathway against heart failure. Genetic ACE2 deletion resulted in exacerbation of angiotensin 2 (Ang II)-mediated cardiorenal fibrosis and oxidative stress in the heart and kidney of hypertensive mice while administration of recombinant human ACE2 (rhACE2) remarkably rescued the Ang II-induced hypertension, pathological hypertrophy, oxidant injury and cardiac dysfunction[26,27]. So SARS-CoV-2 binds with ACE2, resulting the uncontrolled releasing of Ang II, and Ang II may facilitate the secretion of NT-proBNP.

Our study also had limitations. First, although a total of 3275 patients were enrolled in this study (in-hospital death 306), 1089 patients with available NT-proBNP (in-hospital death 115) were evaluated. The clinical implication due to the missing data are unknown. Second, the cutoffs of NT-proBNP or NT-proBNP ratio in predicting COVID-19 in-hospital death were established based on a single center population. Further external validations from other independent cohorts will be required. Third, there might be selection bias of the subjects, NT-proBNP was detected in the patients with suspected heart failure or cardiac injury. And not all examinations related to heart injury (eg. hs-TnI, CK-MB) were fully performed in every patient with available NT-proBNP. The imbalance data collected might introduce confounding factor in our conclusion. Fourth, because the double-blind principle, we can hardly evaluate the cardiac injury effect of the drug trial. Finally, the inherent limitations of retrospective studies make it impossible to determine the association between NT-proBNP ratio and COVID-19 in-hospital death. The exact cutoffs of NT-proBNP ratio for COVID-19 prognosis with adequate sensitivity and specificity need to be further investigated in large-scale rigorously prospective studies. Even if the study had the above slimitations, we believe NT-proBNP specific to age is a strong predictor of in-hospital death in patients with COVID-19 and NT-proBNP ratio would play important roles in the prognosis of patients with heart failure.

Methods

Study Design and Participants

The study was a retrospective, observational registry with identifier ChiCTR2000031587 on Chinese medical research registration information system. According to *Ethical Principles for Biomedical Research involving Humans (2016)* of the Ministry of Health's of the People's Republic of China, *Quality Management Practice for Clinical Drug Trials (2003)* and *Good Practice for Medical Device Clinical Trial (2016)* of China Food and Drug Adminstration, *Helsinki Manifesto* of World Medical Association, *International Ethical Guidelines for Human Biomedical Research* of the Council for International Organizations of Medical Sciences, the study protocol and exemption of informed consent applicaiton were approved by Ethics Commission of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China (approval NO. TJ-IRB20200387). All patients with fever (body temperature>37.2℃) admitted from January 11,2020 and April 26,2020 at the Affiliated Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology in Wuhan were studied. Eligible patients were men or non-pregnant women of 18 years of age or older with the diagnosis of confirmed cases or clinically diagnosed cases of COVID-19 in accordance with the following (at least two of them): two or more postive results of oropharyngeal or nasopharyngeal SARS-CoV-2 nucleic acid testing with the interval of more than 24 hours, plasma antibody IgM and/or IgG of SARS-CoV-2 positive, chest computed tomography suggested viral pneumonia. All the data were collected from reviewing medical history and examinatioins by well-trained researchers with a double-blind method. To observe the risk of in-hospital death, patients were followed up from admission to observation data (00:00 May 31,2020). The primary outcome was in-hospital death. A total of 3275 patients with in-hospital death 306 were enrolled in this study. 1089 patients (including in-hospital death 115) with available NT-proBNP were divided into four groups according to the NT-proBNP ratio, as measured NT-proBNP relative to the maximal normal values specific to age and follow up (Figure 1). The primary outcome was in-hospital death (n=115).

Data Collection

We collected data on demographic information, comorbidities (hypertension, coronary heart disease, diabetes, chronic obstructive pulmonary disease, chronic kidney disease), physical examinations (body temperature, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, body mass index), laboratory examinations (NT-proBNP, White-cell count, Lymphocyte%, Lymphocyte count, Monocyte%, Monocyte count, Neutrophil%, Neutrophil count, Urea, Creatinine, eGFR, High-sensitive C-Reactive Protein, Procalcitonin) from electronic medical records. Data collection of laboratory results were defined using the first-time examination at admission (within 24 h after admission). All the laboratory data was tested in a same laboratory with the same standard.

Statistical Analysis

Data is presented as categorical variables and continuous variables. Categorical variables were presented as counts (percentages) and were compared using the chi-square test. Continuous variables were presented as median [IQR] and the Kolmogorov-Smirnov test was used to determine the distribution of continuous data. For continuous variables with normal distribution, the independent t-test or a one-way

analysis of variance (ANOVA) was used to test the differences among groups. Otherwise, the Wilcoxon rank-sum or the Kruskal-Wallis test was applied. The best NT-proBNP ratio cut-off was that of the highest product of sensitivity and specificity for in-hospital death prediction. The time to in-hospital death was estimated using the Kaplan-Meier method and compared with the log-rank test. Cox proportional-hazards model was used to calculated hazard ratios with 95% confidence intervals. Statistical analyses were conducted with SPSS (version 22.0, Armonk, USA), R (version 3.6.0, Vienna, Austria).

Declarations

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Author contributions statement

Study design: Dan Li, Li Ni; Data collection: Dan Li; Data analysis: Dan Li, Li Ni; Data interpretation: Dan Li, Li Ni, Dao-Wen Wang, Xiaomei Guo; Writing: Dan Li; Revision: Li Ni. All authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of all part of the work are appropriately investigated and resolved.

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Figures

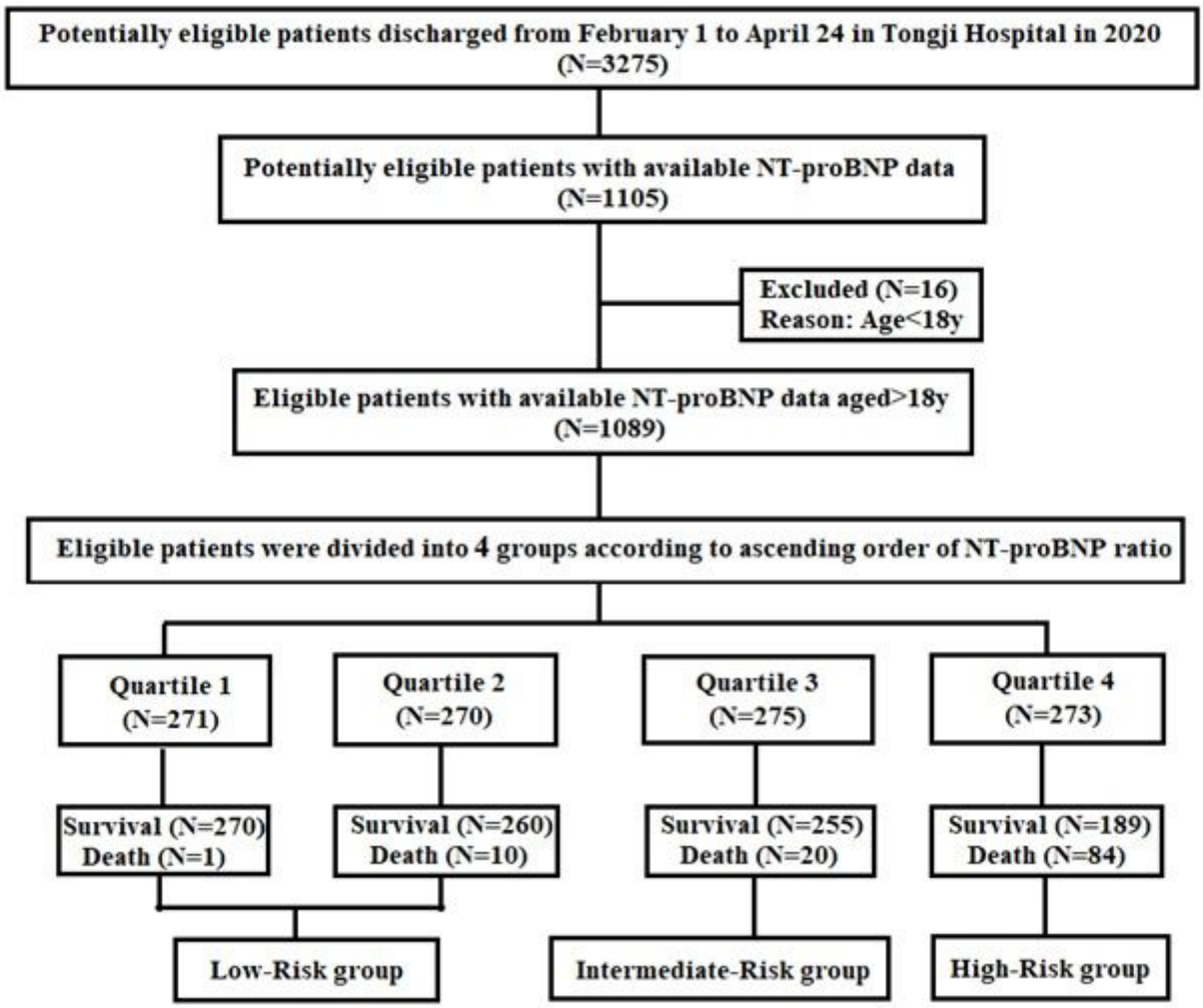

Figure 1

Study flow diagram.

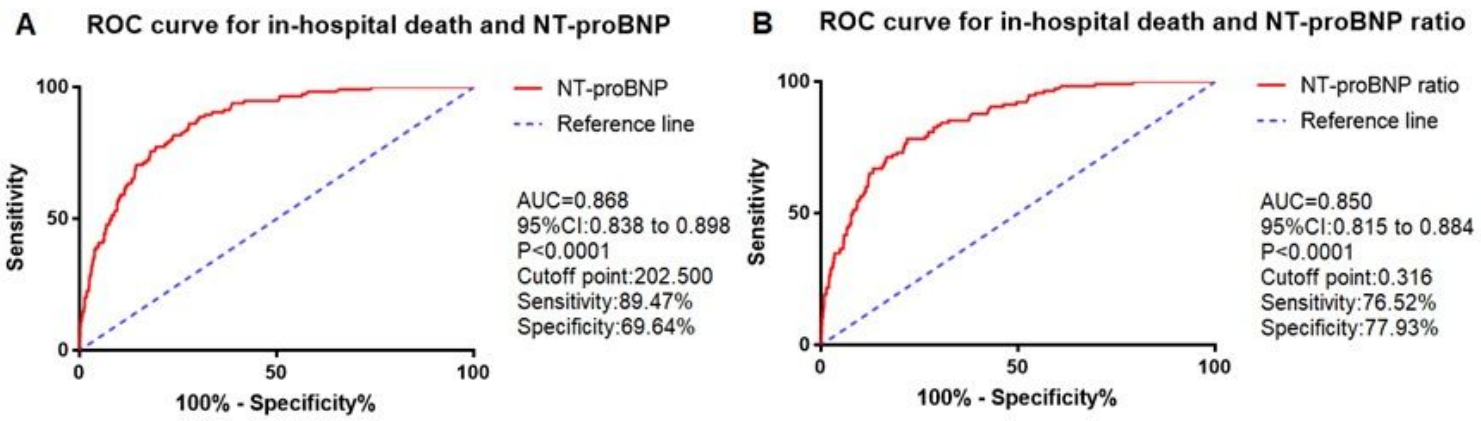

Figure 2

The NT-proBNP and NT-proBNP ratio for in-hospital death of COVID-19 by receiver operating characteristic (ROC) curves. A. The area under the curve (AUC) of NT-proBNP was 0.868 with the sensitivity of 89.47% and the specificity of 69.64% (P<0.0001). The cutoff point of the NT-proBNP for prediction in-hospital death was 202.500 (95%CI: 95% confidence interval). B. The area under the curve (AUC) of NT-proBNP ratio was 0.850 with the sensitivity of 76.52% and the specificity of 77.93% (P<0.0001). The cutoff point of the NT-proBNP ratio for prediction in-hospital death was 0.316 (95%CI: 95% confidence interval).

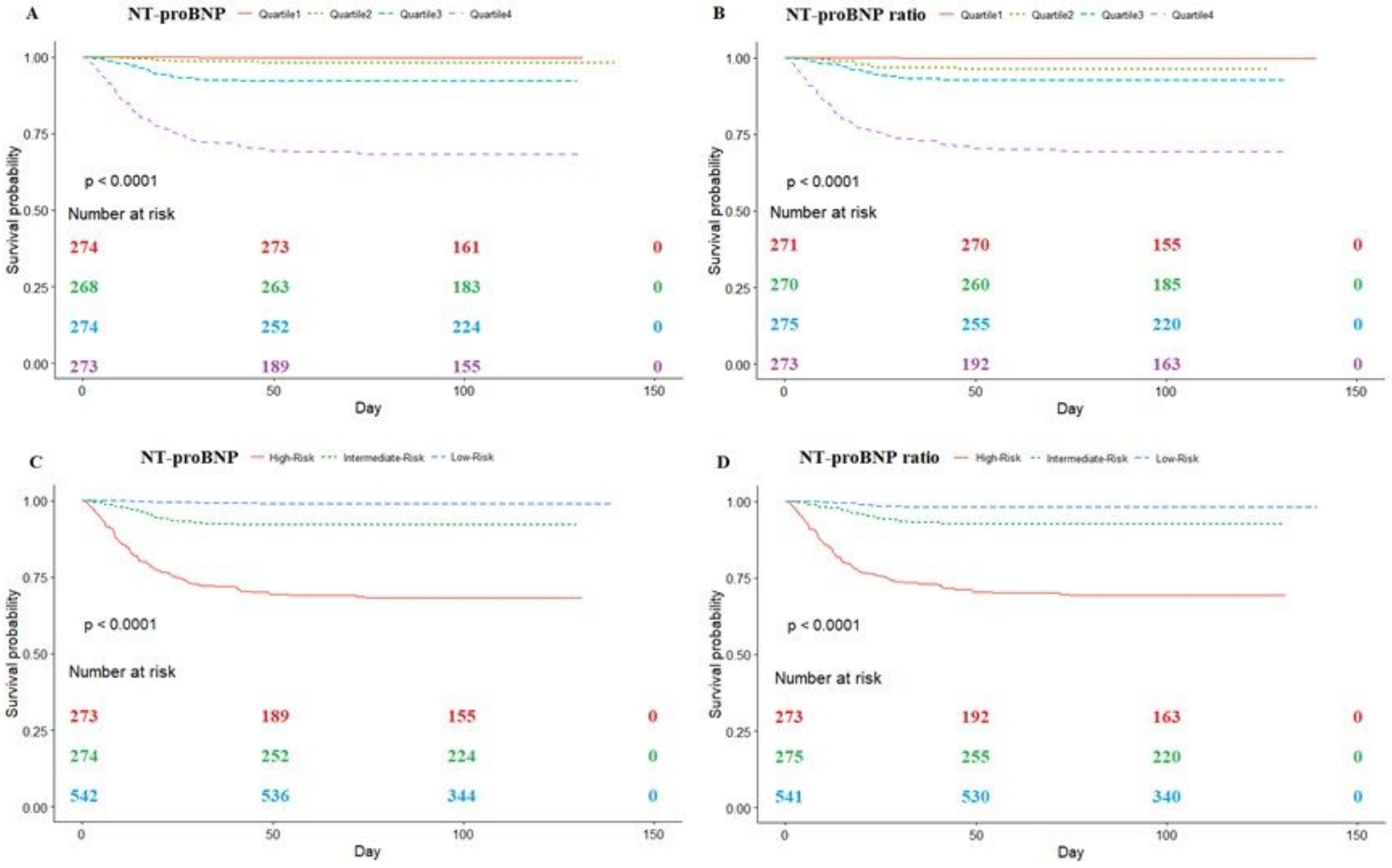

Figure 3

Kaplan-Meier plots showing the cumulative survival rate of adult inpatients of COVID-19. The inpatients were stratified into four groups according to NT-proBNP (A) and NT-proBNP ratio (B) (Log-Rank<0.0001). Red solid line, Quartile 1; Green dotted line, Quartile 2; Blue dotted line, Quartile 3; Pink dotted line, Quartile 4. The stratification of the inpatients of COVID-19 as low-risk, intermediate-risk and high risk was corresponding to NT-proBNP (C) and NT-proBNP ratio (D)(Log-Rank<0.0001). Red solid line, high-risk subgroup; Green dotted line, intermediate-risk subgroup; Blue dotted line, low-risk subgroup.

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