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Clinical Implication of NT-proBNP to Predict Mortality in Patients With Acute Type A Aortic Dissection: a Prospective Cohort Study

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Clinical Implication of NT-proBNP to Predict Mortality in Patients With Acute Type A Aortic Dissection: a Prospective Cohort Study

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Abstract

Objectives: Acute type A aortic dissection is a life-threatening cardiovascular disease commonly seen in Emergency Department, resulting in substantial mortality and morbidity. We aimed to investigate the prognostic value of N-terminal pro-B type natriuretic peptide (NT-proBNP) among this critically ill population.

Design: Prospective Cohort Study.

Setting: Emergency Department of a Fuwai hospital in China from 2018 to 2020.

Participants: We consecutive enrolled 829 patients with acute type A aortic dissection and measurable baseline NT-proBNP at the Emergency Department of Fuwai hospital in China from 2018 to 2020.

Interventions: The NT-proBNP levels.

Primary outcome: The primary endpoint was 1-year all-cause death.

Results: Based on tertiles of NT-proBNP (pg/ml), patients were stratified into low-risk (≤150.3, N=276), intermediate-risk (150.3-667.6, N=277), and high-risk (>667.6, N=276) groups. Compared with low-risk patients, the risk of primary endpoint 1-year all-cause death was higher in intermedi-ate-risk (32.5% vs. 18.1%; adjusted HR 1.52, 95% CI: 1.02 to 2.27), and high-risk groups (42.0% vs. 18.1%; adjusted HR 2.17, 95% CI: 1.41 to 3.32), respectively. Notably, the predictive performance of NT-proBNP for 1-year mortality was greater in patients receiving surgery than conservative treatment (between-cohorts difference in area under the curve 0.13, P=0.04). Moreover, a substantial prognostic value for NT-proBNP tertiles was observed in surgery cohort than conservative cohort with a significant interaction between NT-proBNP tertiles and treatment strategies for 1-year death (Interaction P=0.04).

Conclusion: NT-proBNP provides incremental prognostic information for mortality in patients with acute type A aortic dissection underwent surgical repairment which could aid in risk stratification as a pragmatic and versatile biomarker in this critically ill population, while has limited prognostic value for those receiving conservative treatment.

Keywords: acute aortic dissection; NT-proBNP; mortality.

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Introduction

Despite the improvement of diagnostic and therapeutic techniques in recent decades, acute aortic dissection is still a life-threatening cardiovascular disease commonly seen in emergency department, resulting in over half of mortality in patients without proper treatment.[1-3] In addition, acute aortic dissection is also a rapid-progressive disorder with the risk of death increased by 1% per hour in the early stage.[2] Compared to those with acute type B aortic dissection, patients with acute type A aortic dissection acquire substantially worse in-hospital and long-term prognosis as the ascending aorta is involved.[4, 5] Therefore, it is of great clinical implication to timely and effectively identify type A aortic dissection patients at higher risk, which would assist clinicians to develop the proper treatment and management strategy to improve the prognosis at the earliest possible stage.

Natriuretic peptides, including B-type natriuretic peptides (BNP) and the N-terminal fragment of its prohormone (NT-proBNP) are endogenous cardiac hormones mainly secreted by cardiomyocytes in response to increased stress of cardiac chamber wall.[6] As an established biomarker for heart failure,[6, 7] natriuretic peptides have been proved useful for the diagnosis and risk stratification in several other cardiovascular diseases, including coronary artery disease, valvular heart disease.[8-11] Previous studies have demonstrated the prognostic value of NT-proBNP in patients with acute aortic dissection.[12-16] However, these small-scale studies were generally conducted in earlier years and mainly focused on acute-phase prognosis with type B aortic dissection. In patients with acute type A aortic dissection, the association between NT-proBNP and long-term prognosis has not been fully clarified, and its clinical implication needs further validation. The present study was designed to investigate the value of NT-

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proBNP in prognostic assessment and stratification for acute phase and long-term follow-up in patients with acute type A aortic dissection in a relatively large cohort.

Methods

Study Population

The study was designed as a prospective, observational, single-center cohort study, including consecutive patients with acute type A aortic dissection at the Emergency Department of a hospital in China between January 2018 to December 2020. Acute aortic dissection was diagnosed by computed tomography and classified according to the Stanford system: 1) type A, involves the ascending aorta, regardless of the site of the primary intimal tear; and 2) type B, involves only the descending aorta. Adult patients were eligible for inclusion if they were diagnosed acute type A aortic dissection with onset time ≤14 days from symptom to diagnosis. Recurrent aortic dissection was excluded in the present study. The present study was approved by the Institutional Review Committee and followed the principles of the Declaration of Helsinki. All subjects provided written informed consent.

Data collection and follow-up

All data were obtained from the electronic health records. Demographic characteristics, cardiovascular risk factors, comorbidities, in-hospital assessment, laboratory biomarkers, and treatment strategy were recorded in real time by medical personnel. For NT-proBNP, blood samples were collected into EDTA-anticoagulant tubes by venipuncture and centrifuged for plasma. Plasma NT-proBNP concentration was measured using an Elecsys proBNP, Cobas E analyser (Roche Diagnostics GmbH, Mannheim, Germany) within measurable range between

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5 and 35 000 pg ml/1. Risk classification of patients was performed according to tertiles of NT-proBNP: 1) low-risk, ≤150.3 pg/ml; 2) intermediate-risk, 150.3-667.6 pg/ml; and 3) high-risk, >667.6 pg/ml.

The primary endpoint for the present study was the all-cause death within 1 year from emergency contact. The secondary endpoint was the 30-day rate of all-cause death.

Statistical analysis

Continuous variables are expressed as mean ± SD or median (interquartile range [IQR]) and were compared using Student t-test or Mann-Whitney U test as appropriate. Categorical variables are presented as counts (%) and were compared using chi-square test or Fisher's exact test as appropriate. Restricted cubic splines were applied to delineate the curve of associations between baseline NT-proBNP level and the risk of all-cause death. The receiver-operating characteristic (ROC) curve analysis was introduced to quantify the prediction capability of NT-proBNP for all-cause death during 1-year follow-up, with area under the curve (AUC). The ROC curve analysis with AUC, was also used to compare the prediction capability for 1-year mortality between cohorts with conservative or surgery treatments using the method of DeLong et al. For 1-year outcome Cox proportional hazards model was used to estimate hazard ratios (HR) and 95% confidence intervals (CI), while Logistic regression model was used to estimate odds ratios (OR) and 95% confidence interval (CI) for 30-day outcome. Multivariable adjusted analysis was used to identify independent predictors. The candidate variables for multivariable analysis were identified using historical confounder definition, based on clinical knowledge and previous literature reports.[17] The included covariates were age, admission SBP, smoking, syncope, coma, time from onset to admission, left ventricular diameter, left ventricular ejection

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fraction, pericardial effusion, troponin I, creatinine, C-reactive protein, artery affected – coronary artery, treatment strategies. The incremental prognostic value of NT-proBNP assessment, in addition to clinical risk factors (i.e., age, sex, previous stroke, previous aortic disease, syncope, coma, aortic valve regurgitation, time from onset to admission), was evaluated using the AUC, category-free net reclassification index (NRI), and the integrated discrimination improvement (IDI). Subgroup analysis was performed according to the treatment strategy (i.e., conservative treatment, and surgery) and the P value for interaction was calculated. Unless otherwise specified, a 2-sided p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using R software, version 4.2.0 (R Foundation for Statistical Computing,Vienna, Austria).

Results

A total of 847 consecutive patients with acute type A aortic dissection were enrolled between January 2018 to December 2020, among which 18 patients without available baseline NT-proBNP data (N=7) or completed 1-year follow-up (N=11) were excluded (**Figure S1**). Therefore, 829 patients were included in the present study. The median baseline NT-preBNP was 308.0 pg/ml (interquartile range [IQR] 104.8 to 974.5).

Risk classification of patients was performed according to tertiles of baseline NT-proBNP level (pg/mL): 1) ≤150.3 (low-risk group, N=276); 2) 150.3-667.6 (intermediate-risk group, N=277); 3) >667.6 (high-risk group, N=276).

Baseline characteristics

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Baseline characteristics of the NT-proBNP tertiles are summarized and stratified in **Table 1**. The median NT-preBNP levels were 74.0 (IQR 40.7 to 105.4), 308.0 (IQR 219.0-444.9), and 1490.5 (IQR 974.3-3108.5) in low-risk, intermediate-risk, and high-risk groups, respectively. Compared with lowest tertiles group, patients with higher NT-proBNP tertiles tended to have higher level of advanced age, heart rate, previous coronary artery disease, previous aortic disease, time from onset to admission, left ventricular diameter, creatinine, C-reactive protein, and troponin I, with lower levels of male proportion, admission blood pressure, smoking status, left ventricular ejection fraction, and haemoglobin. In addition, the percentage of surgery treatment was decreased along with the increasing NT-proBNP levels (77.5%, 61.7%, and 50.4%, respectively, P<0.001).

Prognostic value of NT-proBNP among the whole cohort

A total of 256 (30.9%) deaths occurred during 1-year follow-up, and the 30-day death was documented in 233 (28.1%) patients. Comparisons of demographic data and clinical characteristics of patients stratified by 1-year or 30-day outcomes are presented in **Table S1 and S2**. Median NT-proBNP level (pg/ml) in 1-year survivors versus non-survivors was 236.3 (IQR 90.9 to 794.0) vs. 517.2 (IQR 200.2 to 1,449.9; P<0.001) (**Figure S2**), and in patients without versus with 30-day death was 248.0 (IQR 91.5 to 846.5) and 482.0 (IQR 195.7 to 1,489.0), respectively (**Figure S3**).

The AUC of NT-proBNP for predicting 1-year all-cause death was 0.64 (95% CI: 0.60 to 0.68, p<0.001) (**Figure S4**). Restricted spline curve analysis showed there was a monotonic increase in the risk of 1-year death with increasing NT-proBNP concentrations (P for linearity =0.57) (**Figure 1B**). As a continuous variable, ln NT-proBNP was significantly associated with

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1-year mortality (HR 1.24, 95% CI: 1.15 to 1.34, P<0.001) (**Table 2**). As a categorical variable, Kaplan-Meier curves showed a graded risk for 1-year mortality with higher NT-proBNP levels (log-rank P<0.001) (**Figure 1A**). Compared with low-risk patients, the risk of 1-year death was higher in intermediate-risk (32.5% vs. 18.1%; HR 1.91, 95% CI: 1.35 to 2.69, P<0.001), and high-risk groups (42.0% vs. 18.1%; HR 2.56, 95% CI: 1.84 to 3.57, P<0.001), respectively (**Table 2**). In addition, NT-proBNP tertiles were independent predictors for 1-year mortality after multivariable adjustment (adjusted HR for intermediate-risk group 1.52, 95% CI: 1.02-2.27, p=0.04; adjusted HR for high-risk group 2.17, 95% CI: 1.41-3.32, p<0.001) (**Table 3**). Similar results were observed for the secondary endpoint (**Table 3** and **Figure S5**).

Moreover, when the ln NT-proBNP was added to clinical risk factors for predicting 1-year mortality, the model with ln NT-proBNP showed the significantly higher discrimination and reclassification ability (difference in AUC 0.05, P<0.001; NRI 0.49, P<0.001; IDI 5.90%, P<0.001) (**Figure 2**).

Performance of NT-proBNP tertiles in patients with conservative or surgery treatment

The comparison of baseline characteristics and clinical outcomes grouped by the treatment strategy were shown in **Table S3**. ROC analysis was performed in surgery and conservative treatment cohort separately to compare the predictive performance of NT-proBNP. As depicted in **Figure 3**, NT-proBNP showed greater predictive power in surgery treatment subgroup (AUC 0.64, 95% CI: 0.54 to 0.74), when compared to conservative treatment subgroup (AUC 0.51, 95% CI: 0.44 to 0.59), with significantly between-cohorts AUC difference (ΔAUC 0.13, 95% CI: 0.01 to 0.25, P =0.04).

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Subgroup analysis was conducted to investigate the impact of treatment strategy (surgery or conservative treatment) on the association between NT-proBNP tertiles and all-cause mortality. In surgery treatment cohort, the rate of 1-year mortality was significantly increased in intermediate-risk group (7.6% vs. 2.8%; HR 2.79, 95% CI: 1.06 to 7.33, P=0.04) and high-risk group (7.9% vs. 7.6%; HR 2.89, 95% CI: 1.07 to 7.81, P=0.04) when compared to low-risk (≤155.0 pg/ml) group (**Figure 4** and **Table 4**). In conservative treatment group, compared with low-risk group, the rate of 1-year mortality was comparable in intermediate-risk group (72.6% vs. 71.0%; HR 1.00, 95% CI: 0.69 to 1.45, P=0.99) and high-risk group (76.6% vs. 71.0%; HR 1.05, 95% CI: 0.74 to 1.49, P=0.79). Notably, there was a significant interaction between NT-proBNP tertiles and treatment strategy for 1-year death (P for interaction=0.04) (**Figure 4** and **Table 4**). Similar results were observed for 30-day mortality, although surgery treatment cohort did not reach statistical significance. However, no significant interaction between NT-proBNP levels and treatment strategy was observed for 30-day death (P for interaction=0.18).

Discussion

The present study was focused on association of baseline NT-proBNP levels and mortality (i.e., acute-phase and long-term mortality) in patients with acute type A aortic dissection, and the main findings are: 1) a graded risk for 1-year or acute-phase-mortality was present with higher NT-proBNP levels (P for trend <0.05); 2) baseline NT-proBNP tertiles were independent predictor of acute-phase or 1-year survival after multivariate adjustment; 3) the NT-proBNP levels significantly enhanced discrimination and reclassification ability of prediction model for

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1-year mortality based on clinical risk factors; and 4) NT-proBNP was more predictive of long-term outcomes in patients with acute type A aortic dissection undergoing surgery treatment. Therefore, baseline NT-proBNP, as a user-friendly and incremental prognostic factor, could assist in profiling risk among patients with acute type A aortic dissection.

NT-proBNP has been routinely used as a diagnostic tool for heart failure, besides, it has also been proven to be a novel and useful biomarker for the risk stratification of several other cardiac diseases and even non-cardiac conditions.[9, 18-20] A previous study has reported that the level of NT-proBNP was significantly higher in those with acute aortic dissection.[21] In addition, several studies have demonstrated the prognostic value of NT-proBNP in patients with acute aortic dissection.[14-16] For the first time, a prospective study of 104 type A aortic dissection patients revealed that higher levels of NT-proBNP predicted the occurrence of 30-day mortality and short-term major adverse events (i.e., postoperative heart failure, neurologic deficit, lung failure, renal failure, or sepsis).[14] Another study of 67 patients verified that NT-proBNP was an independent risk factor of in-hospital death in patients with type A aortic dissection.[16] However, these studies on type A aortic dissection were limited by the relatively small sample size and the lacking of long-term follow-up results. The present study further validated the prognosis value of NT-proBNP in the acute phase or 1 year later with the largest sample size so far (N=829).

Although the development of surgical repairment and intensive care has greatly improved the prognosis of type A aortic dissection, several studies still reported relatively high mortality rates.[22, 23] Many factors have been identified as predictors for short-term mortality, however, there is currently no established blood biomarker for risk stratification.[16] As a non-specific

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preoperative biomarker, it is not comprehensive to use NT-proBNP alone as a risk predictor, despite it was confirmed as an independent predictor in the present study. However, combined with the existing clinical risk factors, NT-proBNP could substantially improve prognosis prediction, which could assist physicians to identify high-risk patients and enhance perioperative and follow-up management.

In the present study, a total of 305 (36.8%) received conservative treatment, and the reasons are as following: 1) 133 (16.0%) patients suffered aortic rupture prior to emergency surgery, resulting in death and no opportunity for surgery; 2) some patients with multiple comorbidities are not suitable for surgery due to the contraindications after evaluation, which received conservative management; and 3) a small number of patients refused surgery due to the treatment costs.[24] Early surgical repair has been recommended as the gold standard treatment for most acute type A aortic dissection patients, which can significantly reduce mortality. This is also reflected in the present study, in which the 1-year mortality was 5.7% and 74.1% in the surgical and conservative treatment group, separately. Compared with the surgical group, patients in the conservative group had worse basic conditions and were more likely to have severe complications such as hypotension, shock, pericardial effusion and heart failure, which may be the cause of the elevated NT-proBNP and worse prognosis. Thus, we suggest that it should be cautiously interpreted the prognostic value of NT-proBNP in conservative cohorts. Besides, in the subgroup analysis, mortality risks were significantly higher in patients with higher NT-proBNP tertiles among surgical cohort while were comparable in conservative cohort, and significant interaction was observed between NT-proBNP tertiles and treatment strategy for 1-year death, indicating that only a particular

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population with surgery requirement might benefit of using NT-proBNP in their risk stratification.

There are several possible interpretations for the increased mortality in patients with elevated NT-proBNP levels. First, the increased plasma NT-proBNP levels were proven to be associated with cardiovascular dysfunction in critical ill patients regardless of surgery or not.[25-28] And Cardiac dysfunction is a common and significant predictor of poor prognosis among critically ill patients.[29, 30] Second, the occurrence and development of acute aortic syndrome involved activation of inflammatory pathway,[2, 22] and studies have demonstrated that systemic inflammation state contributed to morbidity and mortality in acute aortic syndrome.[31, 32] Moreover, severe systemic inflammation could further induce or exacerbate cardiac dysfunction which contribute to the increased plasma levels of NT-proBNP.[33] Third, the troponin I levels were gradually increased along with the elevation of NT-proBNP levels, indicating a relatively poor coronary perfusion in patients with high NT-proBNP level, which is also an important predictor of mortality.[34] Fourth, NT-proBNP levels is associated with abnormal kidney function,[35] which could independently predict acute-phase and long-term prognosis. Finally, increased plasma levels of NT-proBNP may reflect the overall disease severity and the proportion of patients received surgery was significantly reduced along with elevated NT-proBNP levels.

In addition, it was of great interest to observe that NT-proBNP levels significantly elevated along with the increase of time from onset of symptoms to admission, further indicating the importance of early diagnosis and treatment of acute type A aortic dissection in improving survival.[2, 3, 14]

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Limitations of the study

The strength of the present study is this large-scale prospective cohort of type A aortic dissection incorporated acute-phase and long-term prognosis, which reflect the current status of diagnosis and treatment of aortic dissection in China to a certain extent. However, this study has several limitations. First, this study was conducted in single center although the enrolled patients came from multiple provinces in China, the external validity of the present study need to be further confirmed in future multicenter studies. Second, longer follow-up results are warrant (e.g., 3-year, or 5-year) to further investigated the prognostic value of NT-proBNP especially for patients underwent index surgery. Third, the impact of NT-proBNP levels on outcomes other than mortality, such as life quality and ischemic events, is also worth investigating in future studies. Forth, although the possible confounders were adjusted by multivariate analysis, we cannot exclude an effect from unmeasured confounders due to the observational design (e.g., patient-management at the emergency department, operating theater, and intensive care unit). Finally, serial measurements of NT-proBNP levels are not available in this study, and the impact of the dynamic change of NT-proBNP on outcomes cannot be evaluated. Therefore, the findings of the present study are hypothesis generating, and the clinical implications of NT-proBNP levels among patients with type A aortic dissection should be evaluated in future massive prospective multicenter studies.

CONCLUSIONS

NT-proBNP provides incremental prognostic information for mortality in patients with acute type A aortic dissection underwent surgical repairment which could aid in risk stratification as a pragmatic and versatile biomarker in this critically ill population, while has limited prognostic

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value for those receiving conservative treatment. Further large-scale prospective studies are needed to confirm these findings.

Supplemental Information

Tables S1-S3 of the supplementary information

Figures S1-S5 of the supplementary information

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Figure legends

Figure 1. Death within 1-year from emergency contact according to NT-proBNP levels

Incidence of 1-year all-cause death is presented according to (A) NT-proBNP tertiles and (B) continuous value of ln NT-proBNP among patients with acute type A aortic dissection.

CI, confidence interval; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Figure 2. Comparison of discrimination and reclassification ability of models with ln NT-proBNP in addition to clinical risk factors for 1-year death

AUC, NRI, and IDI values of models with ln NT-proBNP in addition to clinical risk factors were compared. *The reference model (model 1) included clinical risk factors only, including age, sex, previous stroke, previous aortic disease, syncope, coma, aortic valve regurgitation, time from onset to admission. Model 2 included clinical risk factors plus ln NT-proBNP.

AUC, area under the curve; NRI, net reclassification improvement; IDI, integrated discrimination index; other abbreviations as in Figure 1.

Figure 3. The Receiver-Operating Characteristic Curve of NT-proBNP for Predicting 1-year Death in Conservative and Surgery Treatment Cohorts.

AUC, area under curve; CI, confidence interval.

Figure 4. Outcomes in patients Stratified by NT-proBNP Tertiles in Conservative and Surgery Cohorts.

Abbreviations as in Figure 1 and Figure 2.

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Table1. Patient Characteristics According to the tertiles of NT-pro BNP levels

	Total (N=829)	NT-pro BNP tertiles, pg/ml			*P* value
		T1 (≤150.3) (N=276)	T2 (150.3-667.6) (N=277)	T3 (>667.6) (N=276)	
Baseline Characteristics					
Age, yrs	55.1 ± 13.1	50.1 ± 11.5	58.7 ± 13.0	56.5 ± 13.2	<0.001
Male	587 (70.8)	224 (81.2)	176 (63.5)	187 (67.8)	<0.001
Heart rate	79.4 ± 18.1	75.8 ± 14.6	80.3 ± 18.2	82.2 ± 20.6	<0.001
Admission SBP (mmHg)	144.5 ± 31.9	149.5 ± 30.6	143.8 ± 31.3	140.1 ± 32.5	0.002
Admission DBP (mmHg)	77.3 ± 19.8	80.3 ± 19.9	77.0 ± 18.1	74.5 ± 21.1	0.002
Diabetes mellitus	40 (4.8)	16 (5.8)	17 (6.1)	7 (2.5)	0.09
Hypertension	690 (83.2)	232 (84.1)	236 (85.2)	222 (80.4)	0.29
Hyperlipidemia	180 (21.7)	64 (23.2)	58 (20.9)	58 (21.0)	0.77
Smoking	264 (31.8)	111 (40.2)	85 (30.7)	68 (24.6)	<0.001
Coronary artery disease	123 (14.8)	26 (9.4)	43 (15.5)	54 (19.6)	0.003
Previous stroke	63 (7.6)	18 (6.5)	27 (9.7)	18 (6.5)	0.26
Previous aortic disease	22 (2.7)	3 (1.1)	13 (4.7)	6 (2.2)	0.03
Previous replacement of aorta valve	12 (1.4)	0 (0)	3 (1.1)	9 (3.3)	0.005
Syncope	61 (7.4)	9 (3.3)	23 (8.3)	29 (10.5)	0.004
Coma	14 (1.7)	6 (2.2)	6 (2.2)	2 (0.7)	0.31
Shock	35 (4.2)	6 (2.2)	9 (3.2)	20 (7.2)	0.008
Time from onset to admission, hrs	12.0 (7.0-24.0)	7.0 (5.0-13.0)	12.0 (7.0-24.0)	22.0 (10.0-48.0)	<0.001
In-hospital assessment					

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Left ventricular diameter, mm	49.9 ± 7.4	49.3 ± 6.7	48.7 ± 6.8	51.7 ± 8.3	<0.001
Left ventricular ejection fraction, %	58.8 ± 7.7	60.6 ± 4.9	59.1 ± 6.7	56.5 ± 10.0	<0.001
Aortic valve regurgitation	210 (25.4)	47 (17.0)	61 (22.2)	102 (37.1)	<0.001
Pericardial effusion	61 (7.4)	12 (4.3)	20 (7.3)	29 (10.5)	0.02
Artery affected					
Coronary artery	213 (27.0)	61 (22.8)	70 (26.7)	82 (31.7)	0.07
Brachiocephalic trunk	522 (66.2)	165 (61.6)	177 (67.6)	180 (69.5)	0.13
Coeliac axis	227 (28.8)	80 (29.9)	64 (24.4)	83 (32.0)	0.14
Superior mesenteric artery	198 (25.1)	69 (25.7)	62 (23.7)	67 (25.9)	0.81
Renal artery	211 (26.7)	66 (24.6)	71 (27.1)	74 (28.6)	0.59
Iliac artery	298 (37.8)	100 (37.3)	92 (35.1)	100 (37.3)	0.39
Baseline biomarkers					
NT-proBNP, pg/ml	308.0 (104.8-974.5)	74.0 (40.7-105.4)	308.0 (219.0-444.9)	1490.5 (974.3-3108.5)	<0.001
ln NT-proBNP	5.8 ± 1.6	4.1 ± 0.7	5.7 ± 0.4	7.6 ± 0.9	<0.001
Haemoglobin, g/dl	134.8 ± 19.2	140.3 ± 18.8	133.8 ± 16.1	130.3 ± 20.5	<0.001
D-dimerse, mg/l	10.9 (3.8-20.0)	11.3 (3.4-20.0)	12.5 (4.1-20.0)	9.9 (3.7-20.0)	0.36
Creatinine, umol/L	110.9 ± 58.2	94.8 ± 32.1	100.4 ± 38.1	137.5 ± 81.1	<0.001
C-reactive protein, mg/l	11.4 (4.6-53.2)	6.4 (3.3-14.8)	12.8 (5.1-53.2)	26.4 (9.0-80.3)	<0.001
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0)	0 (0-0.05)	0.03 (0-0.21)	<0.001
Treatment					<0.001
Conservative treatment	305 (36.8)	62 (22.5)	106 (38.3)	137 (49.6)	
Surgery treatment	524 (63.2)	214 (77.5)	171 (61.7)	139 (50.4)	

1 Values are median (IQR) or n (%).

2 SB, stress blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-B type natriuretic peptide.

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Table 2. Association Between NT-proBNP and Clinical Outcome.

	1-Year death			30-Day death		
	No. of events/total patients (%)*	Hazard ratio (95% CI)	*P* value	No. of events/total patients (%)	Odds ratio (95% CI)	*P* value
ln NT-proBNP	–	1.24 (1.15-1.34)	<0.001	–	1.32 (1.19-1.46)	<0.001
NT-proBNP tertiles						
T1 (≤155.0)	50/276 (18.1)	Reference	–	47/276 (17.0)	Reference	–
T2 (155.0-671.4)	90/277 (32.5)	1.91 (1.35-2.69)	<0.001	83/277 (30.0)	2.08 (1.39-3.13)	<0.001
T3 (>671.4)	116/276 (42.0)	2.56 (1.84-3.57)	<0.001	103/276 (37.3)	2.90 (1.95-4.32)	<0.001
p value for trend			<0.001			<0.001

*Values are Kaplan-Meier estimated rates.

CI, confidence interval.

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Table 3. Independent Predictors of Clinical Outcomes

	1-Year death			30-Day death		
	Adjusted HR	**95% CI**	***P* Value**	**Adjusted OR**	**95% CI**	***P* Value**
Age	1.01	1.00-1.03	0.03	1.01	1.00-1.03	0.13
Admission SBP	0.99	0.97-1.00	<0.001	0.99	0.98-0.99	0.001
Smoking	0.54	0.38-0.77	<0.001	0.43	0.27-0.69	<0.001
Syncope	0.99	0.62-1.59	0.97	1.41	0.69-2.89	0.35
Coma	2.55	1.26-5.13	0.009	12.1	2.37-107.3	0.02
Time from onset to admission	0.98	0.97-0.99	<0.001	0.98	0.96-0.99	<0.001
Left ventricular diameter	0.99	0.97-1.01	0.35	0.99	0.96-1.02	0.34
Left ventricular ejection fraction	0.98	0.96-1.00	0.02	0.96	0.93-0.99	0.007
Pericardial effusion	1.00	0.62-1.60	0.99	1.56	0.70-3.43	0.27
Troponin I	1.02	1.00-1.04	0.052	1.15	1.01-1.30	0.04
Creatinine	1.01	1.00-1.01	<0.001	1.01	1.01-1.01	<0.001
C-reactive protein	1.00	0.99-1.00	0.25	0.99	0.99-1.00	0.06
Artery affected – coronary artery	1.08	0.80-1.47	0.61	0.98	0.63-1.53	0.92
NT-proBNP tertile						
T1 (≤155.0)	Reference	Reference	Reference	Reference	Reference	Reference
T2 (155.0-671.4)	1.52	1.02-2.27	0.04	1.62	0.97-2.71	0.07
T3 (>671.4)	2.17	1.41-3.32	<0.001	2.18	1.24-3.84	0.007

Abbreviations as in Table 1.

OR, odds ratio; HR, hazard ratio; CI, confidence interval.

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Table 4. Clinical Outcomes in Cohorts with Conservative or Surgery Treatment, according to NT-proBNP Tertiles

	1-Year death			30-Day death		
	No. of events/total patients (%)*	Hazard ratio (95% CI)	*P* value	No. of events/total patients (%)	Odds ratio (95% CI)	*P* value
Conservative†						
T1 (≤155.0)	44/62 (71.0)	Reference	-	43/62 (69.4)	Reference	-
T2 (155.0-671.4)	77/106 (72.6)	1.00 (0.69-1.45)	0.99	75/106 (70.8)	1.07 (0.54-2.12)	0.85
T3 (>671.4)	105/137 (76.6)	1.05 (0.74-1.49)	0.79	98/137 (71.5)	1.10 (0.58-2.14)	0.75
Surgery†						
T1 (≤155.0)	6/214 (2.8)	Reference	-	4/214 (1.9)	Reference	-
T2 (155.0-671.4)	13/171 (7.6)	2.79 (1.06-7.33)	0.04	8/171 (4.7)	2.58 (0.76-8.70)	0.13
T3 (>671.4)	11/139 (7.9)	2.89 (1.07-7.81)	0.04	5/139 (3.6)	1.96 (0.52-7.43)	0.32

*Values are Kaplan-Meier estimated rates. † *P* for interaction for the risk of 1-year death: NT-proBNP tertiles and treatment strategy (conservative or surgery) = 0.04; *P* for interaction for the risk of 30-day death: NT-proBNP levels (low or high) and treatment strategy (conservative or surgery) = 0.18.

OR, odds ratio; HR, hazard ratio; CI, confidence interval.

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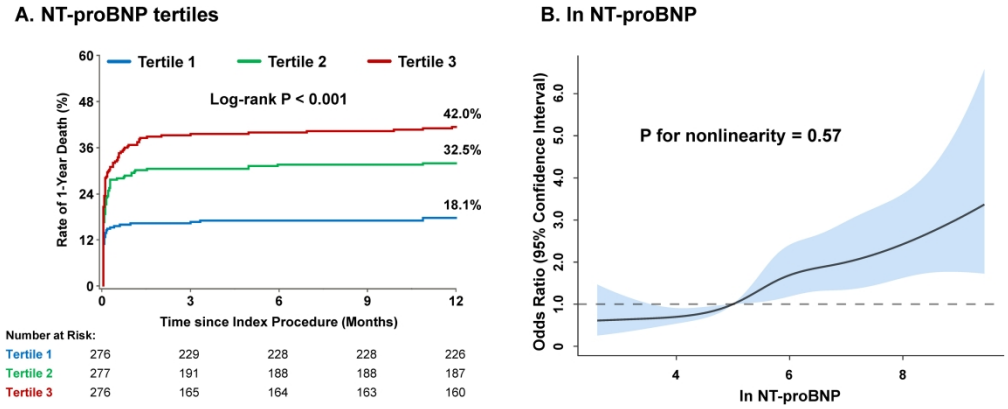

Figure 1

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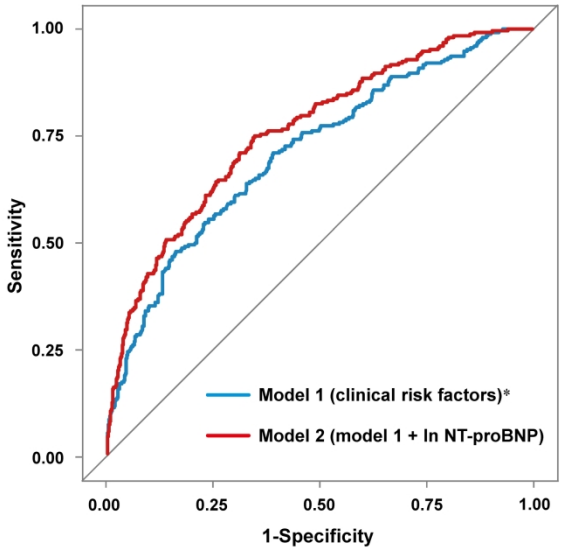

Model	AUC (95% CI)	Difference in AUC	*P* value	NRI	*P* value	IDI	*P* value
Model 1	0.71 (0.67-0.75)	Reference		Reference		Reference	
Model 2	0.76 (0.72-0.80)	0.05	<0.001	0.49	<0.001	5.90%	<0.001

Figure 2

258x179mm (300 x 300 DPI)

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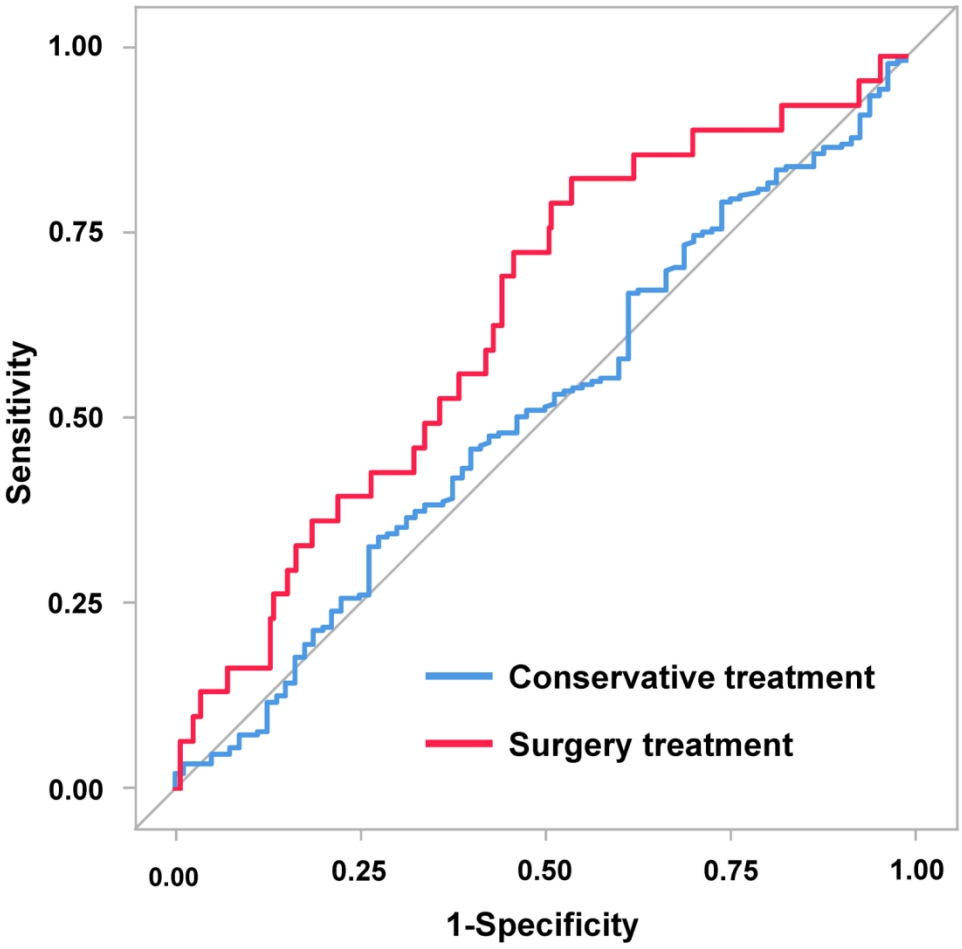

	AUC (95% CI)	Difference in AUC (95% CI)	P value
Conservative	0.51 (0.44-0.59)	Reference	-
Surgery	0.64 (0.54-0.74)	0.13 (0.01-0.25)	0.04

Figure 3

143x179mm (300 x 300 DPI)

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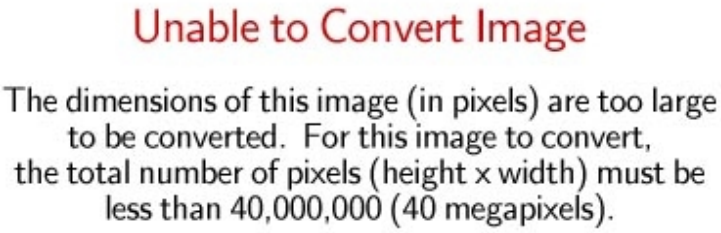

Figure 4

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Supplementary Information

Clinical implication of N-terminal pro-B type natriuretic peptide to predict mortality in patients with acute type A aortic dissection: a prospective cohort study

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Table S1. Patient Characteristics According to the 1-year Survival

	Total (N=829)	1-year Survival (N=573)	1-year Death (N=256)	*P* value
Baseline Characteristics				
Age, yrs	55.1 ± 13.1	53.4 ± 12.3	59.0 ± 14.0	<0.001
Male	587 (70.8)	416 (72.6)	171 (66.8)	0.10
Heart rate	79.4 ± 18.1	79.0 ± 17.3	80.4 ± 20.0	0.28
Admission SBP (mmHg)	144.5 ± 31.9	150.0 ± 29.4	132.9 ± 34.0	<0.001
Admission DBP (mmHg)	77.3 ± 19.8	79.2 ± 19.9	73.1 ± 19.2	0.001
Diabetes mellitus	40 (4.8)	24 (4.2)	16 (6.3)	0.22
Hypertension	690 (83.2)	490 (85.5)	200 (78.1)	0.01
Hyperlipidemia	180 (21.7)	134 (23.4)	46 (18.0)	0.08
Smoking	264 (31.8)	217 (37.9)	47 (18.4)	<0.001
Coronary artery disease	123 (14.8)	81 (14.1)	42 (16.4)	0.40
Previous stroke	63 (7.6)	45 (7.9)	18 (7.0)	0.68
Previous aortic disease	22 (2.7)	14 (2.4)	8 (3.1)	0.57
Previous replacement of aorta valve	12 (1.4)	7 (1.2)	5 (2.0)	0.42
Syncope	61 (7.4)	31 (5.4)	30 (11.7)	0.002
Coma	14 (1.7)	1 (0.2)	13 (5.1)	<0.001
Shock	35 (4.2)	0 (0)	35 (13.7)	<0.001
Time from onset to admission, hrs	12.0 (7.0-24.0)	13.0 (7.0-30.0)	9.0 (6.0-19.0)	<0.001
In-hospital assessment				
Left ventricular diameter, mm	49.9 ± 7.4	50.6 ± 6.6	48.4 ± 8.8	<0.001
Left ventricular ejection fraction, %	58.8 ± 7.7	59.7 ± 6.0	56.4 ± 10.3	<0.001
Aortic valve regurgitation	210 (25.4)	138 (24.1)	72 (28.5)	0.19
Pericardial effusion	61 (7.4)	21 (3.7)	40 (15.8)	<0.001

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Artery affected				
Coronary artery	213 (27.0)	136 (23.8)	77 (35.5)	0.001
Brachiocephalic trunk	522 (66.2)	358 (62.6)	164 (75.6)	0.001
Coeliac axis	227 (28.8)	155 (27.1)	72 (33.2)	0.10
Superior mesenteric artery	198 (25.1)	138 (24.1)	60 (27.6)	0.31
Renal artery	211 (26.7)	139 (24.3)	72 (33.2)	0.01
Iliac artery	298 (37.8)	209 (36.5)	89 (41.0)	0.25
Baseline biomarkers				
NT-proBNP, pg/ml	308.0 (104.8-974.5)	236.3 (90.9-796.0)	7.2 (199.2-1453.9)	<0.001
ln NT-proBNP	5.8 ± 1.6	5.6 ± 1.6	6.3 ± 1.5	<0.001
Haemoglobin, g/dl	134.8 ± 19.2	135.6 ± 18.2	133.0 ± 21.2	0.07
D-dimers, mg/l	10.9 (3.8-20.0)	7.8 (2.8-20.0)	20.0 (8.8-20.0)	<0.001
Creatinine, umol/L	110.9 ± 58.2	99.0 ± 41.4	137.6 ± 78.1	<0.001
C-reactive protein, mg/l	11.4 (4.6-53.2)	12.8 (5.0-66.2)	8.9 (4.2-31.3)	0.006
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0.02)	0.03 (0-0.19)	<0.001
Treatment				<0.001
Conservative treatment	305 (36.8)	79 (13.8)	226 (88.3)	
Surgery treatment	524 (63.2)	494 (86.2)	30 (11.7)	

Values are median (IQR) or n (%).
Abbreviations as in Table 1.

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Table S2. Patient Characteristics According to the 30-day Survival

	Total (N=829)	30-day Survival (N=596)	30-day Death (N=233)	*P* value
Baseline Characteristics				
Age, yrs	55.1 ± 13.1	53.7 ± 12.5	58.6 ± 13.9	<0.001
Male	587 (70.8)	430 (72.1)	157 (67.4)	0.18
Heart rate	79.4 ± 18.1	78.9 ± 17.1	80.5 ± 20.5	0.16
Admission SBP (mmHg)	144.5 ± 31.9	149.2 ± 29.6	132.5 ± 34.4	<0.001
Admission DBP (mmHg)	77.3 ± 19.8	78.9 ± 19.8	73.2 ± 19.4	<0.001
Diabetes mellitus	40 (4.8)	26 (4.4)	14 (6.0)	0.37
Hypertension	690 (83.2)	508 (85.2)	182 (78.1)	0.02
Hyperlipidemia	180 (21.7)	139 (23.3)	41 (17.6)	0.08
Smoking	264 (31.8)	221 (37.1)	43 (18.5)	<0.001
Coronary artery disease	123 (14.8)	83 (13.9)	40 (17.2)	0.23
Previous stroke	63 (7.6)	47 (7.9)	16 (6.9)	0.66
Previous aortic disease	22 (2.7)	14 (2.3)	8 (3.4)	0.47
Previous replacement of aorta valve	12 (1.4)	8 (1.3)	4 (1.7)	0.75
Syncope	61 (7.4)	31 (5.2)	30 (12.9)	<0.001
Coma	14 (1.7)	1 (0.2)	13 (5.6)	<0.001
Shock	35 (4.2)	0 (0)	35 (15.0)	<0.001
Time from onset to admission, hrs	12.0 (7.0-24.0)	13.0 (7.0-30.0)	9.0 (6.0-18.0)	<0.001
In-hospital assessment				
Left ventricular diameter, mm	49.9 ± 7.4	50.5 ± 6.6	48.4 ± 9.0	<0.001
Left ventricular ejection fraction, %	58.8 ± 7.7	59.7 ± 5.9	56.0 ± 10.7	<0.001
Aortic valve regurgitation	210 (25.4)	145 (24.3)	65 (28.3)	0.25
Pericardial effusion	61 (7.4)	21 (3.5)	40 (17.4)	<0.001

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Artery affected				
Coronary artery	213 (27.0)	144 (24.2)	69 (35.6)	0.003
Brachiocephalic trunk	522 (66.2)	375 (63.0)	147 (75.8)	0.001
Coeliac axis	227 (28.8)	164 (27.6)	63 (32.5)	0.20
Superior mesenteric artery	198 (25.1)	143 (24.0)	55 (28.4)	0.25
Renal artery	211 (26.7)	148 (24.9)	63 (32.5)	0.04
Iliac artery	298 (37.8)	218 (36.6)	80 (41.2)	0.27
Baseline biomarkers				
NT-proBNP, pg/ml	308.0 (104.8-974.5)	245.7 (91.3-841.3)	2.0 (193.4-1489.0)	<0.001
ln NT-proBNP	5.8 ± 1.6	5.6 ± 1.6	6.3 ± 1.5	<0.001
Haemoglobin, g/dl	134.8 ± 19.2	135.2 ± 18.9	133.8 ± 19.7	0.36
D-dimers, mg/l	10.9 (3.8-20.0)	8.0 (2.9-20.0)	20.0 (8.2-20.0)	<0.001
Creatinine, umol/L	110.9 ± 58.2	99.3 ± 41.6	140.5 ± 80.1	<0.001
C-reactive protein, mg/l	11.4 (4.6-53.2)	12.9 (5.0-68.6)	8.9 (4.2-29.5)	0.001
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0.02)	0.03 (0-0.17)	<0.001
Treatment				<0.001
Conservative treatment	305 (36.8)	89 (14.9)	216 (92.7)	
Surgery treatment	524 (63.2)	507 (85.1)	17 (7.3)	

Values are median (IQR) or n (%).

SBP, stress blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-B type natriuretic peptide.

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Table S3. Patient Characteristics and Outcomes According to the Treatment Strategy

	Total (N=829)	Conservative (N=305)	Surgery (N=524)	*P* value
Baseline Characteristics				
Age, yrs	55.1 ± 13.1	53.7 ± 12.5	58.6 ± 13.9	<0.001
Male	587 (70.8)	202 (66.2)	385 (73.5)	0.03
Heart rate	79.4 ± 18.1	81.1 ± 20.4	78.5 ± 16.6	0.05
Admission SBP (mmHg)	144.5 ± 31.9	137.9 ± 33.8	148.3 ± 30.0	<0.001
Admission DBP (mmHg)	77.3 ± 19.8	75.3 ± 19.4	78.4 ± 20.0	0.03
Diabetes mellitus	40 (4.8)	14 (4.6)	26 (5.0)	0.81
Hypertension	690 (83.2)	249 (81.6)	441 (84.2)	0.39
Hyperlipidemia	180 (21.7)	57 (18.7)	123 (23.5)	0.12
Smoking	264 (31.8)	55 (18.0)	209 (39.9)	<0.001
Coronary artery disease	123 (14.8)	52 (17.0)	71 (13.5)	0.19
Previous stroke	63 (7.6)	28 (9.2)	35 (6.7)	0.22
Previous aortic disease	22 (2.7)	11 (3.6)	22 (2.7)	0.26
Previous replacement of aorta valve	12 (1.4)	7 (2.3)	5 (1.0)	0.14
Syncope	61 (7.4)	34 (11.1)	27 (5.2)	0.002
Coma	14 (1.7)	13 (4.3)	1 (0.2)	<0.001
Shock	35 (4.2)	35 (15.0)	0 (0)	<0.001
Time from onset to admission, hrs	12.0 (7.0-24.0)	10.0 (6.0-24.0)	13.0 (7.0-24.5)	<0.001
In-hospital assessment				
Left ventricular diameter, mm	49.9 ± 7.4	48.7 ± 8.5	50.6 ± 6.7	<0.001
Left ventricular ejection fraction, %	58.8 ± 7.7	56.4 ± 10.4	60.1 ± 5.2	<0.001
Aortic valve regurgitation	210 (25.4)	77 (25.5)	133 (25.4)	0.97
Pericardial effusion	61 (7.4)	42 (13.9)	19 (3.6)	<0.001

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Artery affected				
Coronary artery	213 (27.0)	82 (30.9)	131 (25.0)	0.09
Brachiocephalic trunk	522 (66.2)	183 (69.1)	339 (64.7)	0.23
Coeliac axis	227 (28.8)	85 (32.1)	142 (27.1)	0.16
Superior mesenteric artery	198 (25.1)	67 (25.3)	131 (25.0)	0.93
Renal artery	211 (26.7)	75 (28.3)	36 (26.0)	0.50
Iliac artery	298 (37.8)	95 (35.8)	203 (38.7)	0.44
Baseline biomarkers				
NT-proBNP, pg/ml	308.0 (104.8-974.5)	524.9 (192.6-1490.5)	227.9 (82.9-722.3)	<0.001
ln NT-proBNP	5.8 ± 1.6	6.3 ± 1.5	5.5 ± 1.5	<0.001
Haemoglobin, g/dl	134.8 ± 19.2	131.8 ± 21.1	136.6 ± 17.8	0.001
D-dimers, mg/l	10.9 (3.8-20.0)	16.6 (6.3-20.0)	8.2 (2.9-20.0)	<0.001
Creatinine, umol/L	110.9 ± 58.2	131.3 ± 75.4	99.0 ± 40.9	<0.001
C-reactive protein, mg/l	11.4 (4.6-53.2)	10.0 (4.7-50.0)	11.9 (4.5-54.2)	0.001
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0.13)	0 (0-0.02)	<0.001
Clinical Outcomes				
1-year death	256 (30.9)	226 (74.1)	30 (5.7)	<0.001
30-day death	233 (28.1)	216 (70.8)	17 (3.2)	<0.001

Values are median (IQR) or n (%).

Abbreviations as in Table 1.

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Figure S1. Flowchart

NT-proBNP = N-terminal pro-brain natriuretic peptide.

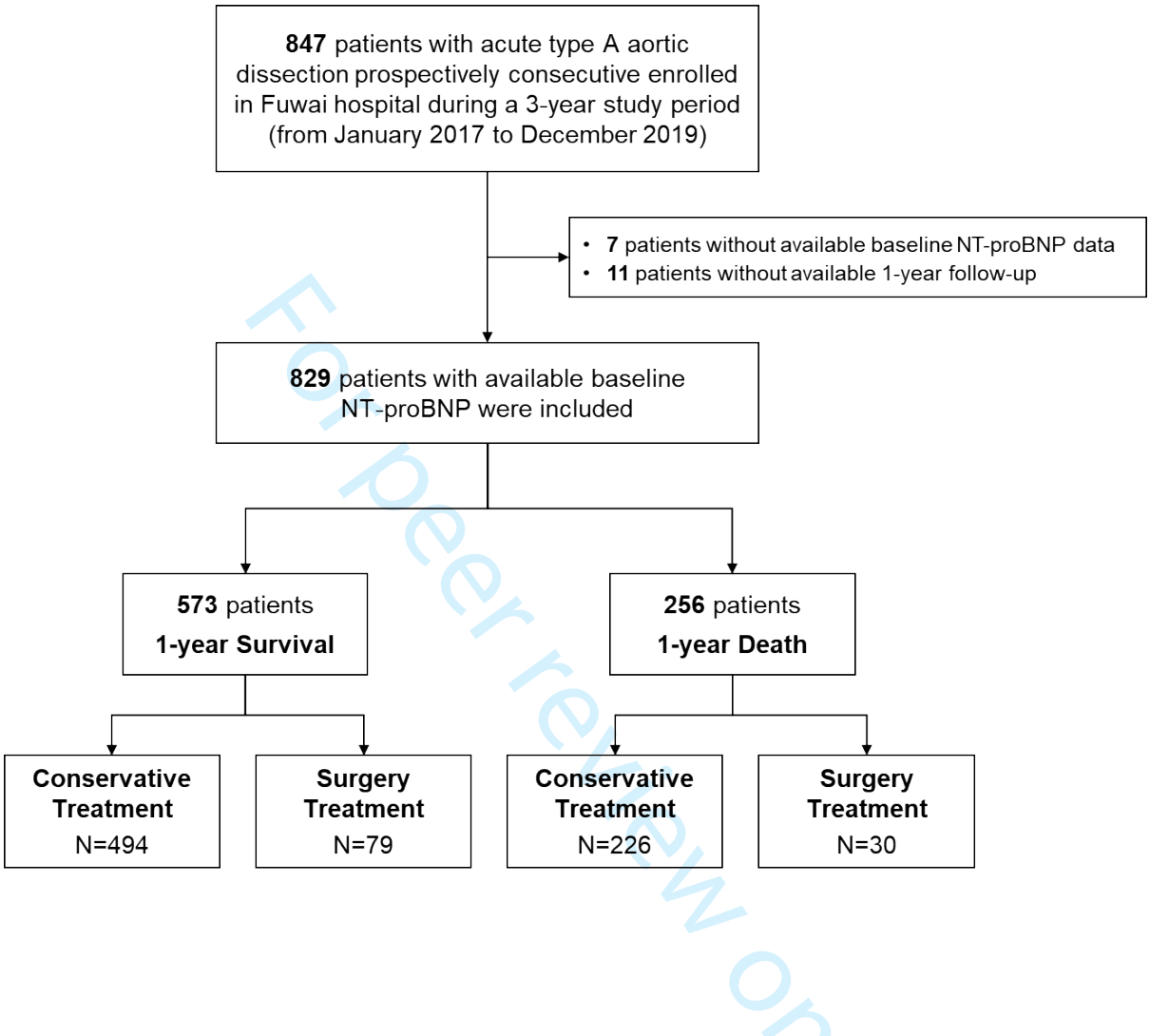

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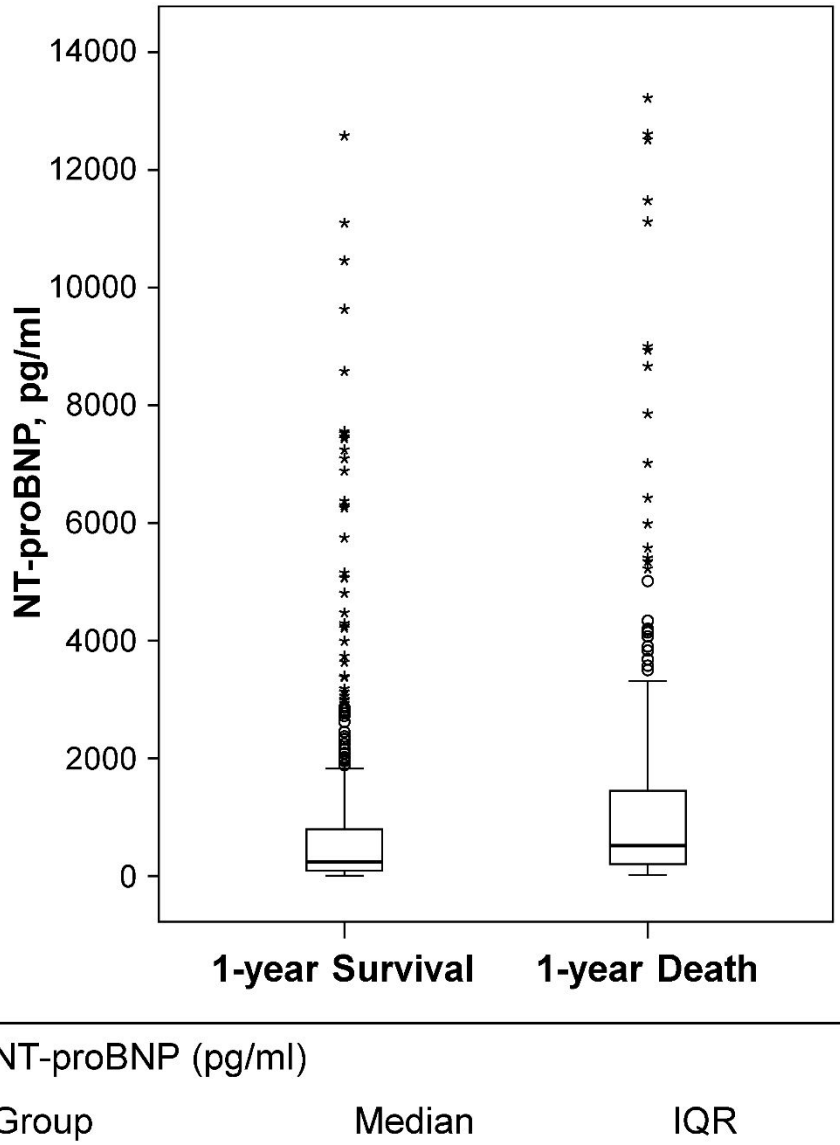
Figure S2. Baseline NT-proBNP as a predictor of 1-year outcome

Abbreviations as in Figure 1.



NT-proBNP (pg/ml)		
Group	Median	IQR
1-year Survival	236.3	90.9 to 794.0
1-year Death	517.2	200.2 to 1448.9

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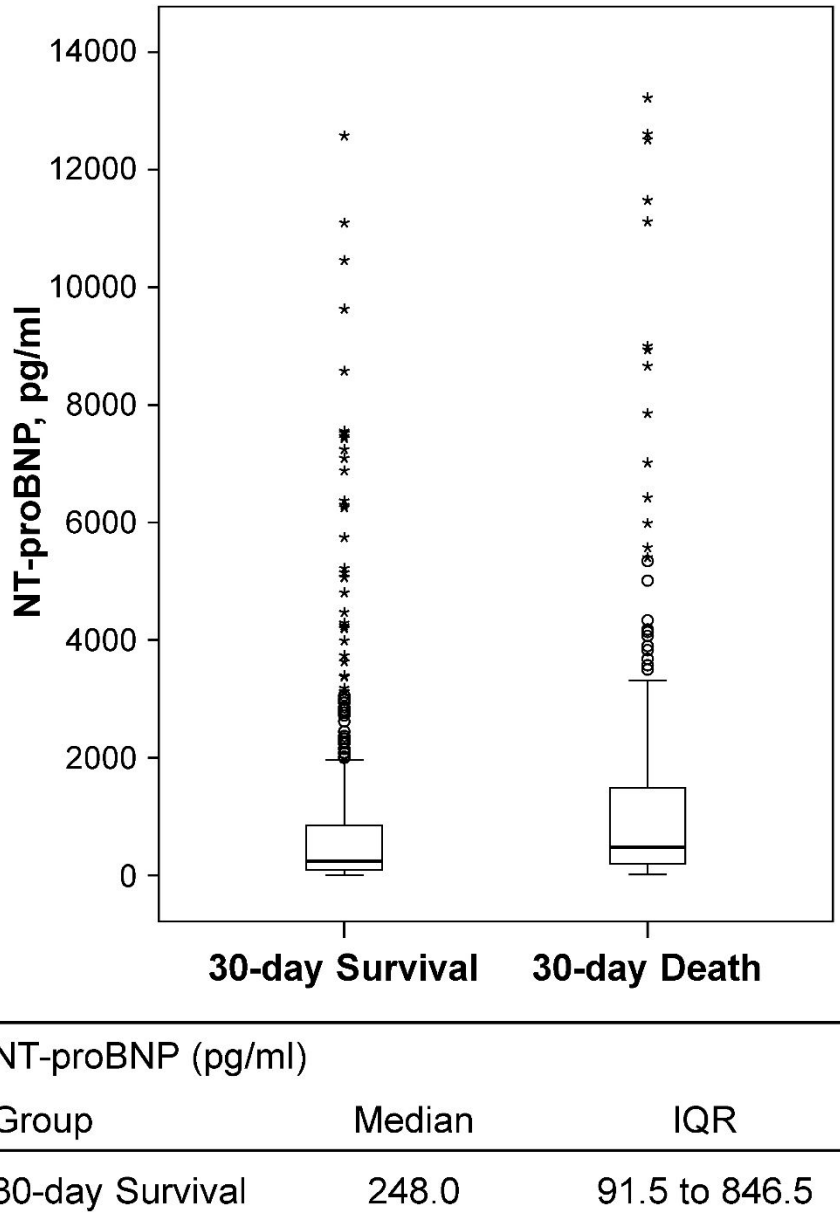
Figure S3. Baseline NT-proBNP as a predictor of 30-day outcome

Abbreviations as in Figure 1.



NT-proBNP (pg/ml)		
Group	Median	IQR
30-day Survival	248.0	91.5 to 846.5
30-day Death	482.0	195.7 to 1489.0

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Figure S4. Receiver-Operating Characteristic Curve of NT-proBNP value for Predicting 1-year death

AUC = area under curve; CI = confidence interval.

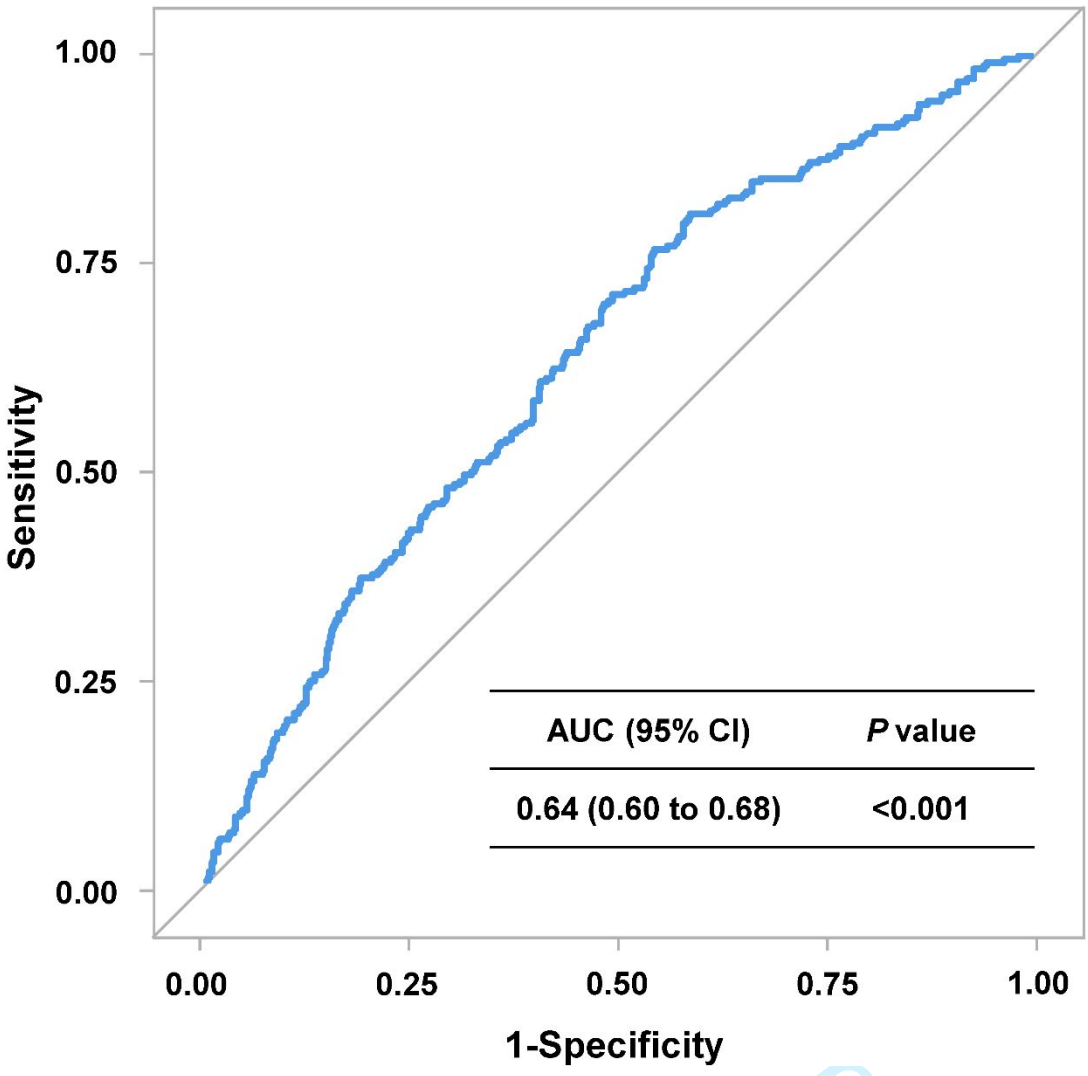

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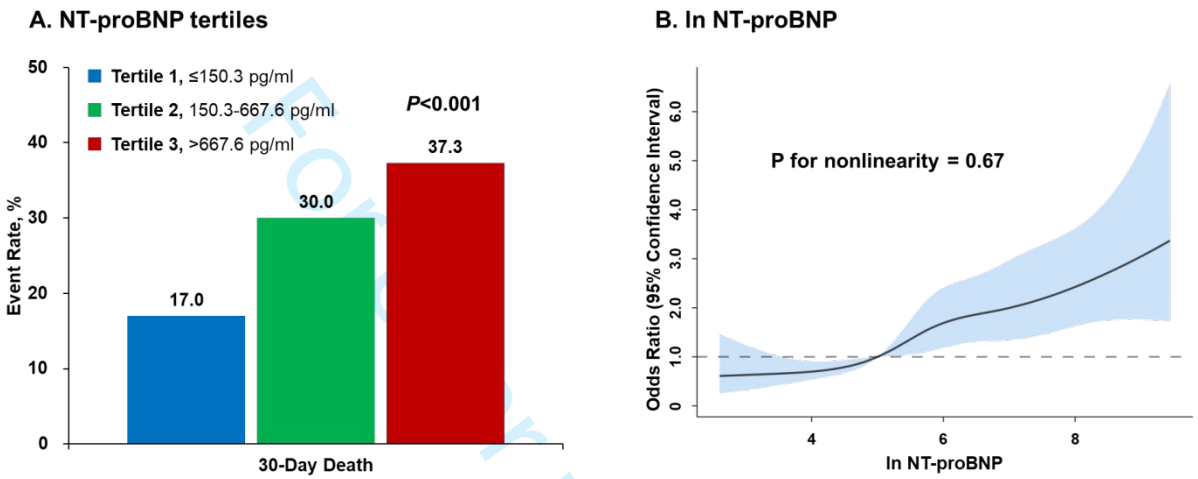
Figure S5. Death within 30 days from admission according to NT-proBNP levels

Incidence of 30-day all-cause death is presented according to (A) NT-proBNP tertiles and (B) continuous value of ln NT-proBNP among patients with acute type A aortic dissection.

CI, confidence interval; OR, odds ratio; other abbreviations as in Figure 1.



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Clinical Implication of NT-proBNP to Predict Mortality in Patients With Acute Type A Aortic Dissection: a Retrospective Cohort Study

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Primary Subject Heading:	Emergency medicine
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Keywords:	Mortality, Emergency Departments < Emergency Service, Hospital, Cardiovascular Disease

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Clinical Implication of NT-proBNP to Predict Mortality in Patients With Acute Type A Aortic Dissection: a Retrospective Cohort Study

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Abstract

Objectives: Acute type A aortic dissection is a life-threatening cardiovascular disease commonly seen in Emergency Department, resulting in substantial mortality and morbidity. We aimed to investigate the prognostic value of N-terminal pro-B type natriuretic peptide (NT-proBNP) among this critically ill population.

Design: Retrospective Cohort Study.

Setting: Emergency Department of a Fuwai hospital in China from 2018 to 2020.

Participants: We consecutive enrolled 829 patients with acute type A aortic dissection and measurable baseline NT-proBNP at the Emergency Department of Fuwai hospital in China from 2018 to 2020.

Primary outcome: The primary endpoint was 1-year all-cause death.

Results: Based on tertiles of NT-proBNP (pg/ml), patients were stratified into low (≤150.3, N=276), intermediate (150.3-667.6, N=277), and high (>667.6, N=276) NT-proBNP groups. Compared with patients with low NT-proBNP, the Kaplan–Meier estimates for primary 1-year mortality were higher in intermediate (32.5% vs. 18.1%; HR 1.91, 95% CI: 1.35 to 2.69) and high (42.0% vs. 18.1%; HR 2.56, 95% CI: 1.84 to 3.57) NT-proBNP groups, respectively. After multivariable adjustment, NT-proBNP tertiles were independent predictors for 1-year mortality (adjusted HR for intermediate group 1.52, 95% CI: 1.02-2.27; adjusted HR for high group 2.17, 95% CI: 1.41-3.32). Notably, the predictive performance of NT-proBNP for 1-year mortality was greater in patients receiving surgery than conservative treatment (between-cohorts difference in area under the curve 0.13, Delong's test P=0.04).

Conclusion: NT-proBNP provides incremental prognostic information for mortality in patients with acute type A aortic dissection underwent surgical repairment, which could aid in risk stratification as a pragmatic and versatile biomarker in this critically ill population while has limited prognostic value for those receiving conservative treatment.

Keywords: acute aortic dissection; NT-proBNP; mortality.

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Strengths and limitations of this study

- ✓ Among patients with Acute type A aortic dissection, a graded risk for acute-phase or 1-year mortality was present with higher NT-proBNP levels.
- ✓ The NT-proBNP levels significantly enhanced discrimination and reclassification ability of prediction model for 30-day mortality based on clinical risk factors.
- ✓ The external validity of this single-center study needs to be further confirmed in future multicenter studies.

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Introduction

Despite the improvement of diagnostic and therapeutic techniques in recent decades, acute aortic dissection is still a life-threatening cardiovascular disease commonly seen in emergency department, resulting in over half of mortality in patients without proper treatment.[1-4] In addition, acute aortic dissection is also a rapid-progressive disorder with the risk of death increased by 1% per hour in the early stage.[3] Compared to those with acute type B aortic dissection, patients with acute type A aortic dissection acquire substantially worse in-hospital and long-term prognosis as the ascending aorta is involved.[5 6] Therefore, it is of great clinical implication to timely and effectively identify type A aortic dissection patients at higher risk, which would assist clinicians in developing the proper treatment and management strategy to improve the prognosis at the earliest possible stage. However, although there is increasing interest in the use of circulating biomarkers for risk stratification of patients with aortopathy, biomarker expression has not been clearly associated with relevant aortic clinical events.[1]

Natriuretic peptides, including B-type natriuretic peptides (BNP) and the N-terminal fragment of its prohormone (NT-proBNP), are endogenous cardiac hormones mainly secreted by cardiomyocytes in response to increased stress of cardiac chamber wall.[7] As an established biomarker for heart failure,[7 8] natriuretic peptides have been proven useful for the diagnosis and risk stratification in several other cardiovascular diseases, including coronary artery disease and valvular heart disease.[9-12] Previous studies have demonstrated the prognostic value of NT-proBNP in patients with acute aortic dissection.[13-17] However, these small-scale studies were generally conducted in earlier years and mainly focused on acute-phase prognosis with type B aortic dissection. In patients with acute type A aortic dissection, the association between

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NT-proBNP and long-term prognosis has not been fully clarified, and its clinical implication needs further validation. The present study was designed to investigate the prognostic value of NT-proBNP tertiles for 1-year mortality, and whether the prognostic value differed between patients with conservative and surgery treatment in patients with acute type A aortic dissection in a relatively large cohort.

Methods

Study Population

A total of 847 consecutive patients were recruited with acute type A aortic dissection diagnosed by aortic computed tomography (CT) angioplasty in the emergency department of Fuwai hospital from January 2018 to December 2020. Acute aortic dissection was diagnosed by computed tomography and classified according to the Stanford system: 1) type A, involves the ascending aorta, regardless of the site of the primary intimal tear; and 2) type B, involves only the descending aorta. Adult patients were eligible for inclusion if they were diagnosed with acute type A aortic dissection with onset time ≤14 days from symptom to diagnosis. Recurrent aortic dissection was excluded in the present study. The present study was approved by the Ethics Committee of Fuwai Hospital and followed the principles of the Declaration of Helsinki. All participants provided written informed consent.

Data collection and follow-up

All data were obtained from the electronic health records. Demographic characteristics, cardiovascular risk factors, comorbidities, in-hospital assessment, laboratory biomarkers, and treatment strategy were recorded in real-time by medical personnel. For NT-proBNP, blood

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samples were collected into EDTA-anticoagulant tubes by venipuncture in emergency department, and the sample would be sent to the laboratory immediately for analysis. Plasma NT-proBNP concentration was measured using an Elecsys proBNP, Cobas E analyser (Roche Diagnostics GmbH, Mannheim, Germany) within a measurable range between 5 and 35 000 pg ml/L. Risk classification of patients was performed according to tertiles of NT-proBNP: 1) low NT-proBNP, ≤150.3 pg/ml; 2) intermediate NT-proBNP, 150.3-667.6 pg/ml; and 3) high NT-proBNP, >667.6 pg/ml. In subgroup analysis, patients were further stratified according to the treatment strategy into conservative group or surgery (open repair) group.

The primary endpoint for the present study was the all-cause death within 1 year from emergency contact (i.e., date of emergency admittance). The secondary endpoint was the 30-day rate of all-cause death.

Statistical analysis

Continuous variables are expressed as mean ± SD or median (interquartile range [IQR]) and categorical variables are presented as counts (%). Restricted cubic splines were applied to delineate the curve of associations between baseline NT-proBNP level and the risk of all-cause death. The receiver-operating characteristic (ROC) curve analysis was introduced to quantify the prediction capability of NT-proBNP for all-cause death during 1-year follow-up, with area under the curve (AUC). The ROC curve analysis with AUC was also used to compare the prediction capability for 1-year mortality between cohorts with conservative or surgery treatments using the DeLong's test.[18] For 1-year outcome, Cox proportional hazards model was used to estimate hazard ratios (HR) and 95% confidence intervals (CI), while Logistic regression model was used to estimate odds ratios (OR) and 95% confidence interval (CI) for

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30-day outcome. Multivariable adjusted analysis was used to identify independent predictors. The candidate variables for multivariable analysis were identified using historical confounder definition based on clinical knowledge and previous literature reports.[19] The included covariates were age, admission SBP, smoking, syncope, coma, time from onset to admission, left ventricular diameter, left ventricular ejection fraction, pericardial effusion, troponin I, creatinine, C-reactive protein, and artery affected – coronary artery. Subgroup analysis was performed according to the treatment strategy (i.e., conservative treatment and surgery), and the P value for interaction was calculated from a multivariable Cox proportional hazards model. Unless otherwise specified, a 2-sided p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using R software, version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

None.

Results

A total of 847 consecutive patients with acute type A aortic dissection were enrolled between January 2018 and December 2020, among which 18 patients without available baseline NT-proBNP data (N=7) or completed 1-year follow-up (N=11) were excluded (**Figure 1**). Therefore, 829 patients were included in the present study. The median baseline NT-preBNP was 308.0 pg/ml (interquartile range [IQR] 104.8 to 974.5).

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Risk classification of patients was performed according to tertiles of baseline NT-proBNP level (pg/mL): 1) ≤150.3 (low NT-proBNP group, N=276); 2) 150.3-667.6 (intermediate NT-proBNP group, N=277); 3) >667.6 (high NT-proBNP group, N=276).

Baseline characteristics

Baseline characteristics of the NT-proBNP tertiles are summarized and stratified in **Table 1**. Among 829 patients, 587 were male (70.8%), with an average age of 55.1 years. The median NT-preBNP levels were 74.0 (IQR 40.7 to 105.4), 308.0 (IQR 219.0-444.9), and 1490.5 (IQR 974.3-3108.5) in low, intermediate, and high NT-proBNP groups, respectively. Compared with the lowest tertiles group, patients with higher NT-proBNP tertiles tended to have higher level of advanced age, heart rate, previous coronary artery disease, previous aortic disease, time from onset to admission, left ventricular diameter, creatinine, C-reactive protein, and troponin I, with lower levels of male proportion, admission blood pressure, smoking status, left ventricular ejection fraction, and haemoglobin. In addition, the percentage of surgery treatment was decreased along with the increasing NT-proBNP levels (77.5%, 61.7%, and 50.4%, respectively, P<0.001).

Prognostic value of NT-proBNP among the whole cohort

A total of 256 (30.9%) deaths occurred during 1-year follow-up, and the 30-day death was documented in 233 (28.1%) patients. Comparisons of demographic data and clinical characteristics of patients stratified by 1-year or 30-day outcomes are presented in **Table S1 and S2**. Median NT-proBNP level (pg/ml) in 1-year survivors versus non-survivors was 236.3 (IQR 90.9 to 794.0) vs. 517.2 (IQR 200.2 to 1,449.9; P<0.001) (**Figure 2**), and in patients

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without versus with 30-day death was 248.0 (IQR 91.5 to 846.5) and 482.0 (IQR 195.7 to 1,489.0), respectively (**Figure S1**).

As a categorical variable, Kaplan-Meier curves showed a graded risk for 1-year mortality with higher NT-proBNP levels (log-rank P<0.001) (**Figure 3A**). Compared with patients with low NT-proBNP, the risk of 1-year death was higher in intermediate (32.5% vs. 18.1%; HR 1.91, 95% CI: 1.35 to 2.69, P<0.001), and high groups (42.0% vs. 18.1%; HR 2.56, 95% CI: 1.84 to 3.57, P<0.001), respectively (**Table S3**).

As a continuous variable, restricted spline curve analysis showed there was a monotonic increase in the risk of 1-year death with increasing NT-proBNP concentrations (P for linearity =0.57) (**Figure 3B**). The ln NT-proBNP was significantly associated with 1-year mortality (HR 1.24, 95% CI: 1.15 to 1.34, P<0.001) (**Table S3**).

Multivariable Adjustment Analysis

In addition, by multivariable analysis, age, admission SBP, smoking, coma, time from onset to admission, left ventricular ejection fraction, creatinine, and NT-proBNP tertiles (adjusted HR for intermediate group 1.52, 95% CI: 1.02-2.27, p=0.04; adjusted HR for high group 2.17, 95% CI: 1.41-3.32, p<0.001) were independent predictors for 1-year mortality (**Table 2**). Similar results were observed for the secondary endpoint (**Table 2** and **Figure S2**).

Performance of NT-proBNP tertiles in patients with conservative or surgery treatment

The comparison of baseline characteristics and clinical outcomes grouped by the treatment strategy was shown in **Table S4**. ROC analysis was performed in surgery and conservative treatment cohort separately to compare the predictive performance of NT-proBNP. As depicted in **Figure 4**, NT-proBNP showed greater predictive power in surgery treatment subgroup (AUC

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0.64, 95% CI: 0.54 to 0.74) when compared to conservative treatment subgroup (AUC 0.51, 95% CI: 0.44 to 0.59), with significantly between-cohorts AUC difference (ΔAUC 0.13, 95% CI: 0.01 to 0.25, P =0.04).

Subgroup analysis was conducted to investigate the impact of treatment strategy (surgery or conservative treatment) on the association between NT-proBNP tertiles and all-cause mortality. In surgery treatment cohort, the rate of 1-year mortality was significantly increased in intermediate group (7.6% vs. 2.8%; HR 2.79, 95% CI: 1.06 to 7.33, P=0.04) and high group (7.9% vs. 7.6%; HR 2.89, 95% CI: 1.07 to 7.81, P=0.04) when compared to low NT-proBNP (≤155.0 pg/ml) group (**Figure 5** and **Table 3**). In conservative treatment group, compared with low NT-proBNP group, the rate of 1-year mortality was comparable in intermediate group (72.6% vs. 71.0%; HR 1.00, 95% CI: 0.69 to 1.45, P=0.99) and high group (76.6% vs. 71.0%; HR 1.05, 95% CI: 0.74 to 1.49, P=0.79). Notably, there was a significant interaction between NT-proBNP tertiles and treatment strategy for 1-year death (P for interaction=0.04) (**Figure 5** and **Table 3**). Similar results were observed for 30-day mortality, although surgery treatment cohort did not reach statistical significance. However, no significant interaction between NT-proBNP levels and treatment strategy was observed for 30-day death (P for interaction=0.18).

Discussion

The present study was focused on association of baseline NT-proBNP levels and mortality (i.e., acute-phase and long-term mortality) in patients with acute type A aortic dissection, and the main findings are: 1) baseline NT-proBNP tertiles were independent predictor of acute-phase or 1-year survival after multivariate adjustment; and 2) NT-proBNP was more predictive of

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long-term outcomes in patients with acute type A aortic dissection undergoing surgery treatment. Therefore, baseline NT-proBNP, as a user-friendly and incremental prognostic factor, could assist in profiling risk among patients with acute type A aortic dissection.

NT-proBNP has been routinely used as a diagnostic tool for heart failure; besides, it has also been proven to be a novel and useful biomarker for the risk stratification of several other cardiac diseases and even non-cardiac conditions.[10 20-22] A previous study has reported that the level of NT-proBNP was significantly higher in those with acute aortic dissection.[23] In addition, several studies have demonstrated the prognostic value of NT-proBNP in patients with acute aortic dissection.[15-17] For the first time, a prospective study of 104 type A aortic dissection patients revealed that higher levels of NT-proBNP predicted the occurrence of 30-day mortality and short-term major adverse events (i.e., postoperative heart failure, neurologic deficit, lung failure, renal failure, or sepsis).[15] Another study of 67 patients verified that NT-proBNP was an independent risk factor of in-hospital death in patients with type A aortic dissection.[17] However, these studies on type A aortic dissection were limited by the relatively small sample size and the lack of long-term follow-up results. The present study further validated the prognosis value of NT-proBNP in the acute phase or 1 year later with the largest sample size so far (N=829).

Although the development of surgical repairment and intensive care has greatly improved the prognosis of type A aortic dissection, several studies still reported relatively high mortality rates.[24 25] Many factors have been identified as predictors for short-term mortality, however, there is currently no established blood biomarker for risk stratification.[17] As a non-specific preoperative biomarker, it is not comprehensive to use NT-proBNP alone as a risk predictor

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despite it being confirmed as an independent predictor in the present study. However, combined with the existing clinical risk factors, NT-proBNP could substantially improve prognosis prediction, which could assist physicians in identifying high-risk patients and enhance perioperative and follow-up management.

In the present study, a total of 305 (36.8%) received conservative treatment, and the reasons are as follows: 1) 133 (16.0%) patients suffered aortic rupture prior to emergency surgery, resulting in death and no opportunity for surgery; 2) some patients with multiple comorbidities are not suitable for surgery due to the contraindications after evaluation, which received conservative management; and 3) a small number of patients refused surgery due to the treatment costs.[26] Early surgical repair has been recommended as the gold standard treatment for most acute type A aortic dissection patients, which can significantly reduce mortality. This is also reflected in the present study, in which the 1-year mortality was 5.7% and 74.1% in the surgical and conservative treatment group, separately. Compared with the surgical group, patients in the conservative group had worse basic conditions and were more likely to have severe complications such as hypotension, shock, pericardial effusion and heart failure, which may be the cause of the elevated NT-proBNP and worse prognosis. Thus, we suggest that it should be cautiously interpreted the prognostic value of NT-proBNP in conservative cohorts. Besides, in the subgroup analysis, mortality risks were significantly higher in patients with higher NT-proBNP tertiles among surgical cohort while were comparable in conservative cohort, and a significant interaction was observed between NT-proBNP tertiles and treatment strategy for 1-year death, indicating that only a particular population with surgery requirement might benefit of using NT-proBNP in their risk

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stratification.

There are several possible interpretations for the increased mortality in patients with elevated NT-proBNP levels. First, the increased plasma NT-proBNP levels were proven to be associated with cardiovascular dysfunction in critically ill patients regardless of surgery or not.[27-30] And Cardiac dysfunction is a common and significant predictor of poor prognosis among critically ill patients.[31 32] Second, the occurrence and development of acute aortic syndrome involved activation of inflammatory pathway,[3 24] and studies have demonstrated that systemic inflammation state contributed to morbidity and mortality in acute aortic syndrome.[33 34] Moreover, severe systemic inflammation could further induce or exacerbate cardiac dysfunction which contributes to the increased plasma levels of NT-proBNP.[35] Third, the troponin I levels were gradually increased along with the elevation of NT-proBNP levels, indicating a relatively poor coronary perfusion in patients with high NT-proBNP level, which is also an important predictor of mortality.[36] Fourth, NT-proBNP levels are associated with abnormal kidney function,[37] which could independently predict acute-phase and long-term prognosis. Finally, increased plasma levels of NT-proBNP may reflect the overall disease severity and the proportion of patients received surgery was significantly reduced along with elevated NT-proBNP levels.

In addition, it was of great interest to observe that NT-proBNP levels significantly elevated along with the increase of time from onset of symptoms to admission, further indicating the importance of early diagnosis and treatment of acute type A aortic dissection in improving survival.[3 4 15]

Limitations of the study

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The strength of the present study is this large-scale retrospective cohort of type A aortic dissection incorporated acute-phase and long-term prognosis, which reflect the current status of diagnosis and treatment of aortic dissection in China to a certain extent. However, this study has several limitations. First, this study was conducted in a single center, although the enrolled patients came from multiple provinces in China; the external validity of the present study needs to be further confirmed in future multicenter studies. Second, longer follow-up results are warranted (e.g., 3-year or 5-year) to further investigate the prognostic value of NT-proBNP especially for patients underwent index surgery. Third, the impact of NT-proBNP levels on outcomes other than mortality, such as life quality and ischemic events, is also worth investigating in future studies. Fourth, although the possible confounders were adjusted by multivariate analysis, we cannot exclude an effect from residual confounding (from measured covariates) and unmeasured confounders due to the observational design (e.g., patient-management at the emergency department, operating theater, and intensive care unit). Finally, serial measurements of NT-proBNP levels are not available in this study, and the impact of the dynamic change of NT-proBNP on outcomes cannot be evaluated. Therefore, the findings of the present study are hypothesis generating, and the clinical implications of NT-proBNP levels among patients with type A aortic dissection should be evaluated in future massive prospective multicenter studies.

CONCLUSIONS

NT-proBNP provides incremental prognostic information for mortality in patients with acute type A aortic dissection underwent surgical repairment, which could aid in risk stratification as a pragmatic and versatile biomarker in this critically ill population while having limited

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prognostic value for those receiving conservative treatment. Further large-scale prospective studies are needed to confirm these findings.

Supplemental Information

Tables S1-S4 of the supplementary information

Figures S1-S2 of the supplementary information

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Figure legends

Figure 1. Flowchart

NT-proBNP = N-terminal pro-brain natriuretic peptide.

Figure 2. Baseline NT-proBNP as a predictor of 1-year outcome

Abbreviations as in Figure 1.

Figure 3. Death within 1-year from emergency contact according to NT-proBNP levels

Incidence of 1-year all-cause death is presented according to (A) NT-proBNP tertiles and (B) continuous value of ln NT-proBNP among patients with acute type A aortic dissection.

CI, confidence interval; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Figure 4. The Receiver-Operating Characteristic Curve of NT-proBNP for Predicting 1-year Death in Conservative and Surgery Treatment Cohorts.

AUC, area under curve; CI, confidence interval.

Figure 5. Outcomes in patients Stratified by NT-proBNP Tertiles in Conservative and Surgery Cohorts.

Abbreviations as in Figure 1 and Figure 2.

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Table1. Patient Characteristics According to the tertiles of NT-pro BNP levels

	Total (N=829)	NT-pro BNP tertiles, pg/ml		
		T1 (≤150.3) (N=276)	T2 (150.3-667.6) (N=277)	T3 (>667.6) (N=276)
Baseline Characteristics				
Age, yrs	55.1 ± 13.1	50.1 ± 11.5	58.7 ± 12.7	56.5 ± 13.2
Male	587 (70.8)	224 (81.2)	176 (63.5)	187 (67.8)
Heart rate	79.4 ± 18.1	75.8 ± 14.6	80.3 ± 17.9	82.2 ± 20.6
Admission SBP (mmHg)	144.5 ± 31.9	149.5 ± 30.6	143.8 ± 33.9	140.1 ± 32.5
Admission DBP (mmHg)	77.3 ± 19.8	80.3 ± 19.9	77.0 ± 19.8	74.5 ± 21.1
Diabetes mellitus	40 (4.8)	16 (5.8)	17 (6.1)	7 (2.5)
Hypertension	690 (83.2)	232 (84.1)	236 (85.2)	222 (80.4)
Hyperlipidemia	180 (21.7)	64 (23.2)	58 (20.9)	58 (21.0)
Smoking	264 (31.8)	111 (40.2)	85 (30.7)	68 (24.6)
Coronary artery disease	123 (14.8)	26 (9.4)	43 (15.5)	54 (19.6)
Previous stroke	63 (7.6)	18 (6.5)	27 (9.7)	18 (6.5)
Previous aortic disease	22 (2.7)	3 (1.1)	13 (4.7)	6 (2.2)
Previous replacement of aorta valve	12 (1.4)	0 (0)	3 (1.1)	9 (3.3)
Syncope	61 (7.4)	9 (3.3)	23 (8.3)	29 (10.5)
Coma	14 (1.7)	6 (2.2)	6 (2.2)	2 (0.7)
Shock	35 (4.2)	6 (2.2)	9 (3.2)	20 (7.2)
Time from onset to admission, hrs	12.0 (7.0-24.0)	7.0 (5.0-13.0)	12.0 (7.0-24.0)	22.0 (10.0-48.0)
In-hospital assessment				

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Left ventricular diameter, mm	49.9 ± 7.4	49.3 ± 6.7	48.7 ± 6.8	51.7 ± 8.3
Left ventricular ejection fraction, %	58.8 ± 7.7	60.6 ± 4.9	59.1 ± 6.1	56.5 ± 10.0
Aortic valve regurgitation	210 (25.4)	47 (17.0)	61 (22.2)	102 (37.1)
Pericardial effusion	61 (7.4)	12 (4.3)	20 (7.3)	29 (10.5)
Artery affected				
Coronary artery	213 (27.0)	61 (22.8)	70 (25.6)	82 (31.7)
Brachiocephalic trunk	522 (66.2)	165 (61.6)	177 (67.0)	180 (69.5)
Coeliac axis	227 (28.8)	80 (29.9)	64 (24.2)	83 (32.0)
Superior mesenteric artery	198 (25.1)	69 (25.7)	62 (23.5)	67 (25.9)
Renal artery	211 (26.7)	66 (24.6)	71 (27.0)	74 (28.6)
Iliac artery	298 (37.8)	100 (37.3)	92 (34.1)	100 (37.3)
Baseline biomarkers				
NT-proBNP, pg/ml	308.0 (104.8-974.5)	74.0 (40.7-105.4)	308.0 (219.0-444.9)	1490.5 (974.3-3108.5)
ln NT-proBNP	5.8 ± 1.6	4.1 ± 0.7	5.7 ± 0.4	7.6 ± 0.9
Haemoglobin, g/dl	134.8 ± 19.2	140.3 ± 18.8	133.8 ± 16.8	130.3 ± 20.5
D-dimerse, mg/l	10.9 (3.8-20.0)	11.3 (3.4-20.0)	12.5 (4.1-20.0)	9.9 (3.7-20.0)
Creatinine, umol/L	110.9 ± 58.2	94.8 ± 32.1	100.4 ± 38.6	137.5 ± 81.1
C-reactive protein, mg/l	11.4 (4.6-53.2)	6.4 (3.3-14.8)	12.8 (5.1-53.3)	26.4 (9.0-80.3)
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0)	0 (0-0.05)	0.03 (0-0.21)
Treatment				
Conservative treatment	305 (36.8)	62 (22.5)	106 (38.3)	137 (49.6)
Surgery treatment	524 (63.2)	214 (77.5)	171 (61.7)	139 (50.4)

Values are median (IQR) or n (%).

SB, stress blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-B type natriuretic peptide.

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Table 2. Independent Predictors of Clinical Outcomes

	1-Year death			30-Day death		
	Adjusted HR	**95% CI**	***P* Value**	**Adjusted OR**	**95% CI**	***P* Value**
Age	1.01	1.00-1.03	0.03	1.01	1.00-1.03	0.13
Admission SBP	0.99	0.97-1.00	<0.001	0.99	0.98-0.99	0.001
Smoking	0.54	0.38-0.77	<0.001	0.43	0.27-0.69	<0.001
Syncope	0.99	0.62-1.59	0.97	1.41	0.69-2.89	0.35
Coma	2.55	1.26-5.13	0.009	12.1	2.37-107.3	0.02
Time from onset to admission	0.98	0.97-0.99	<0.001	0.98	0.96-0.99	<0.001
Left ventricular diameter	0.99	0.97-1.01	0.35	0.99	0.96-1.02	0.34
Left ventricular ejection fraction	0.98	0.96-1.00	0.02	0.96	0.93-0.99	0.007
Pericardial effusion	1.00	0.62-1.60	0.99	1.56	0.70-3.43	0.27
Troponin I	1.02	1.00-1.04	0.052	1.15	1.01-1.30	0.04
Creatinine	1.01	1.00-1.01	<0.001	1.01	1.01-1.01	<0.001
C-reactive protein	1.00	0.99-1.00	0.25	0.99	0.99-1.00	0.06
Artery affected – coronary artery	1.08	0.80-1.47	0.61	0.98	0.63-1.53	0.92
NT-proBNP tertile						
T1 (≤155.0)	Reference	Reference	Reference	Reference	Reference	Reference
T2 (155.0-671.4)	1.52	1.02-2.27	0.04	1.62	0.97-2.71	0.07
T3 (>671.4)	2.17	1.41-3.32	<0.001	2.18	1.24-3.84	0.007

Abbreviations as in Table 1.

OR, odds ratio; HR, hazard ratio; CI, confidence interval.

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Table 3. Clinical Outcomes in Cohorts with Conservative or Surgery Treatment, according to NT-proBNP Tertiles

	1-Year death			30-Day death		
	No. of events/total patients (%)*	Hazard ratio (95% CI)	*P* value	No. of events/total patients (%)	Odds ratio (95% CI)	*P* value
Conservative†						
T1 (≤155.0)	44/62 (71.0)	Reference	-	43/62 (69.4)	Reference	-
T2 (155.0-671.4)	77/106 (72.6)	1.00 (0.69-1.45)	0.99	75/106 (70.8)	1.07 (0.54-2.12)	0.85
T3 (>671.4)	105/137 (76.6)	1.05 (0.74-1.49)	0.79	98/137 (71.5)	1.10 (0.58-2.14)	0.75
Surgery†						
T1 (≤155.0)	6/214 (2.8)	Reference	-	4/214 (1.9)	Reference	-
T2 (155.0-671.4)	13/171 (7.6)	2.79 (1.06-7.33)	0.04	8/171 (4.7)	2.58 (0.76-8.70)	0.13
T3 (>671.4)	11/139 (7.9)	2.89 (1.07-7.81)	0.04	5/139 (3.6)	1.96 (0.52-7.43)	0.32

*Values are Kaplan-Meier estimated rates. † *P* for interaction for the risk of 1-year death: NT-proBNP tertiles and treatment strategy (conservative or surgery) = 0.04; *P* for interaction for the risk of 30-day death: NT-proBNP levels (low or high) and treatment strategy (conservative or surgery) = 0.18.

OR, odds ratio; HR, hazard ratio; CI, confidence interval.

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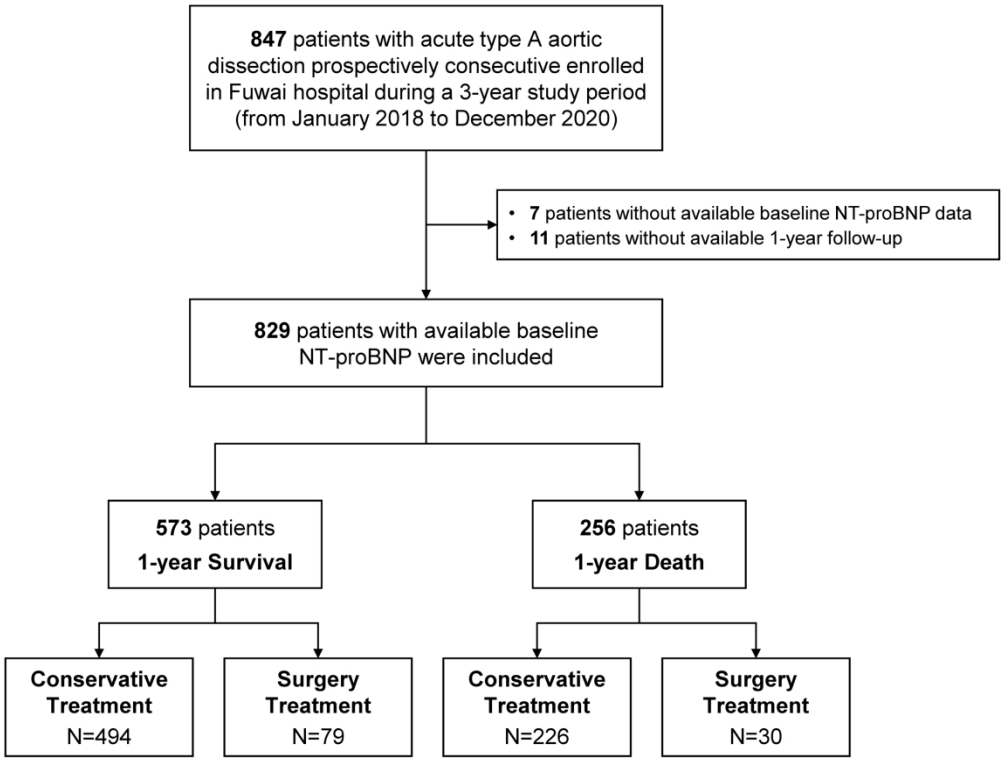

Fugure 1

224x169mm (300 x 300 DPI)

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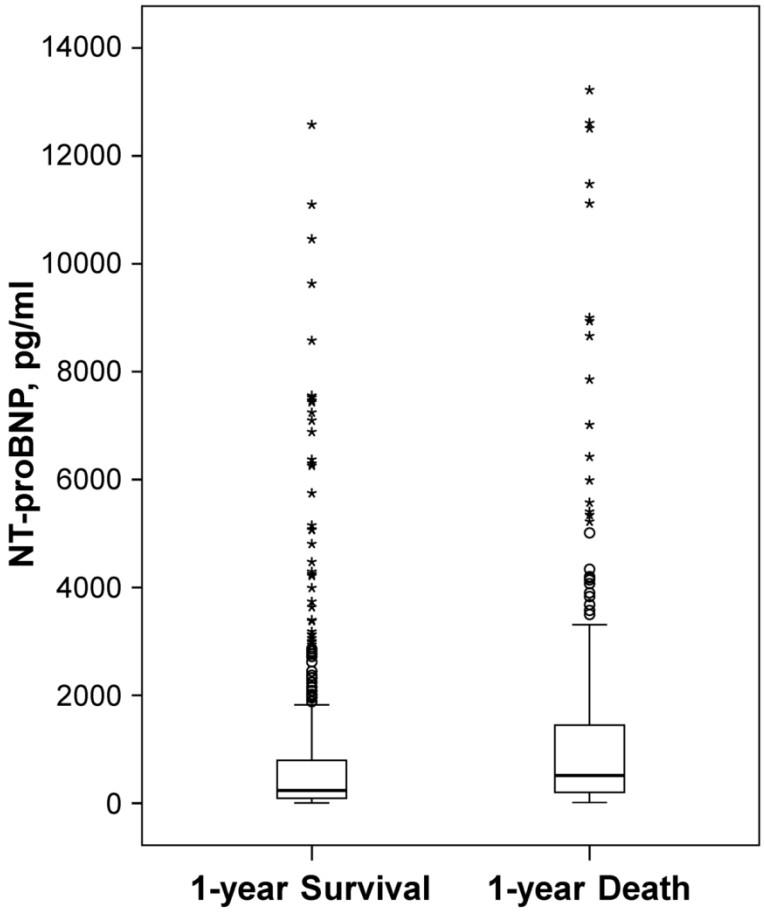

NT-proBNP (pg/ml)		
Group	Median	IQR
1-year Survival	236.3	90.9 to 794.0
1-year Death	517.2	200.2 to 1448.9

Fugure 2

117x173mm (300 x 300 DPI)

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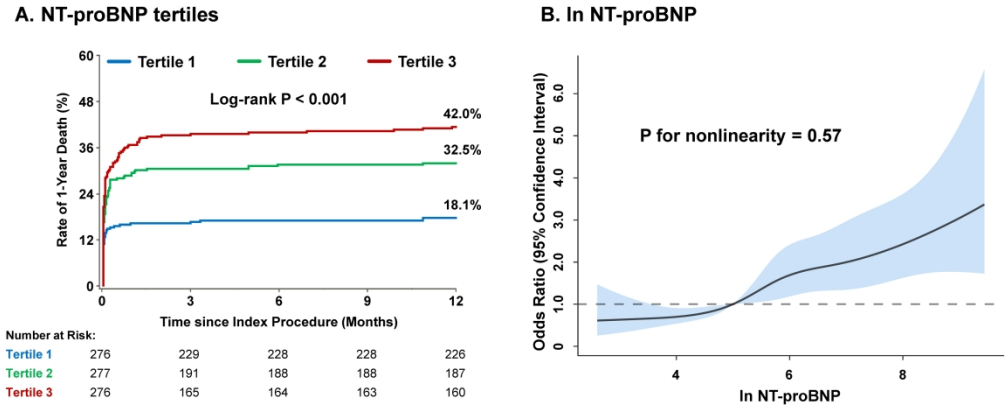

Fugure 3

315x125mm (300 x 300 DPI)

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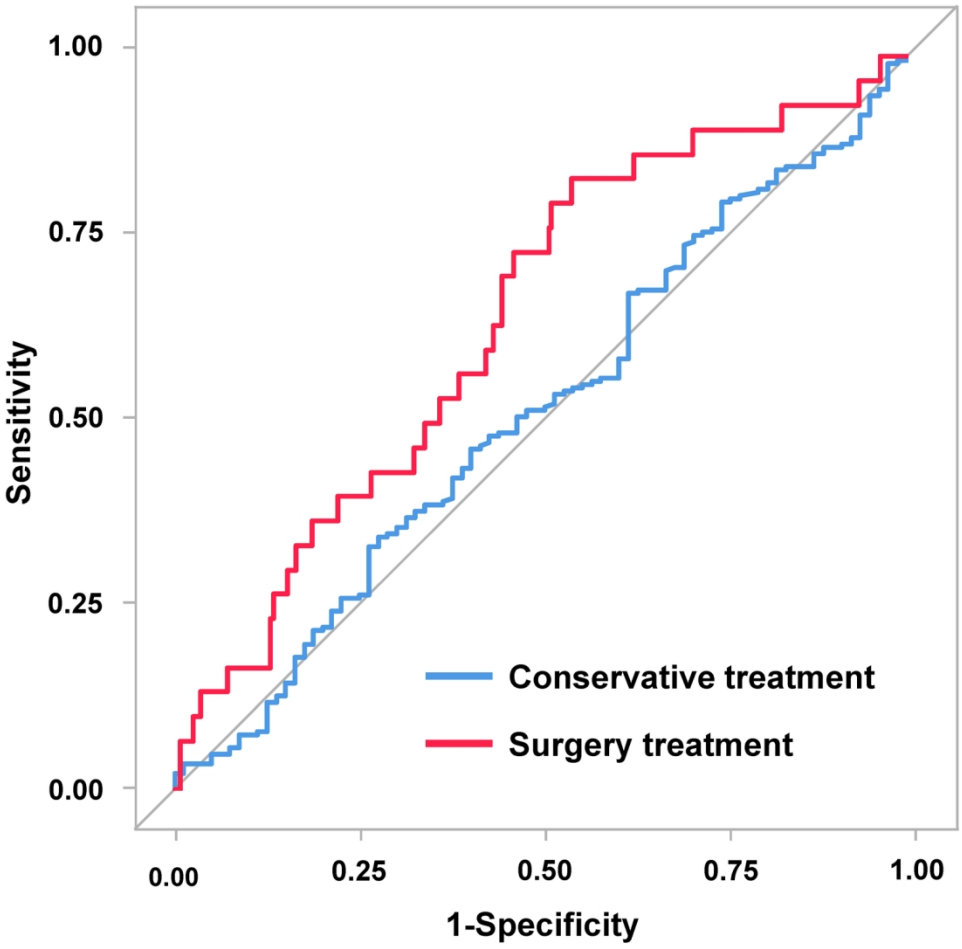

	AUC (95% CI)	Difference in AUC (95% CI)	P value
Conservative	0.51 (0.44-0.59)	Reference	-
Surgery	0.64 (0.54-0.74)	0.13 (0.01-0.25)	0.04

Fugure 4

143x179mm (300 x 300 DPI)

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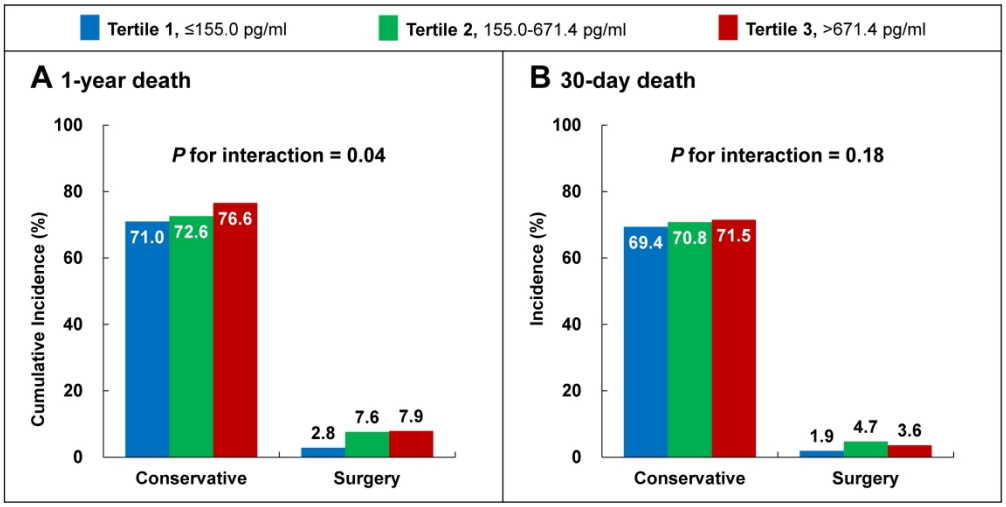

Figure 5

317x158mm (300 x 300 DPI)

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Supplementary Information

Clinical implication of N-terminal pro-B type natriuretic peptide to predict mortality in patients with acute type A aortic dissection: a retrospective cohort study

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Table S1. Patient Characteristics According to the 1-year Survival

	Total (N=829)	1-year Survival (N=573)	1-year Death (N=256)
Baseline Characteristics			
Age, yrs	55.1 ± 13.1	53.4 ± 12.3	59.0 ± 14.0
Male	587 (70.8)	416 (72.6)	171 (66.8)
Heart rate	79.4 ± 18.1	79.0 ± 17.3	80.4 ± 20.0
Admission SBP (mmHg)	144.5 ± 31.9	150.0 ± 29.4	132.9 ± 34.0
Admission DBP (mmHg)	77.3 ± 19.8	79.2 ± 19.9	73.1 ± 19.2
Diabetes mellitus	40 (4.8)	24 (4.2)	16 (6.3)
Hypertension	690 (83.2)	490 (85.5)	200 (78.1)
Hyperlipidemia	180 (21.7)	134 (23.4)	46 (18.0)
Smoking	264 (31.8)	217 (37.9)	47 (18.4)
Coronary artery disease	123 (14.8)	81 (14.1)	42 (16.4)
Previous stroke	63 (7.6)	45 (7.9)	18 (7.0)
Previous aortic disease	22 (2.7)	14 (2.4)	8 (3.1)
Previous replacement of aorta valve	12 (1.4)	7 (1.2)	5 (2.0)
Syncope	61 (7.4)	31 (5.4)	30 (11.7)
Coma	14 (1.7)	1 (0.2)	13 (5.1)
Shock	35 (4.2)	0 (0)	35 (13.7)
Time from onset to admission, hrs	12.0 (7.0-24.0)	13.0 (7.0-30.0)	9.0 (6.0-19.0)
In-hospital assessment			
Left ventricular diameter, mm	49.9 ± 7.4	50.6 ± 6.6	48.4 ± 8.8
Left ventricular ejection fraction, %	58.8 ± 7.7	59.7 ± 6.0	56.4 ± 10.3
Aortic valve regurgitation	210 (25.4)	138 (24.1)	72 (28.5)
Pericardial effusion	61 (7.4)	21 (3.7)	40 (15.8)

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Artery affected			
Coronary artery	213 (27.0)	136 (23.8)	77 (35.5)
Brachiocephalic trunk	522 (66.2)	358 (62.6)	164 (75.6)
Coeliac axis	227 (28.8)	155 (27.1)	72 (33.2)
Superior mesenteric artery	198 (25.1)	138 (24.1)	60 (27.6)
Renal artery	211 (26.7)	139 (24.3)	72 (33.2)
Iliac artery	298 (37.8)	209 (36.5)	89 (41.0)
Baseline biomarkers			
NT-proBNP, pg/ml	308.0 (104.8-974.5)	236.3 (90.9-796.0)	7.2 (199.2-1453.9)
ln NT-proBNP	5.8 ± 1.6	5.6 ± 1.6	6.3 ± 1.5
Haemoglobin, g/dl	134.8 ± 19.2	135.6 ± 18.2	133.0 ± 21.2
D-dimers, mg/l	10.9 (3.8-20.0)	7.8 (2.8-20.0)	20.0 (8.8-20.0)
Creatinine, umol/L	110.9 ± 58.2	99.0 ± 41.4	137.6 ± 78.1
C-reactive protein, mg/l	11.4 (4.6-53.2)	12.8 (5.0-66.2)	8.9 (4.2-31.3)
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0.02)	0.03 (0-0.19)
Treatment			
Conservative treatment	305 (36.8)	79 (13.8)	226 (88.3)
Surgery treatment	524 (63.2)	494 (86.2)	30 (11.7)

Values are median (IQR) or n (%).
Abbreviations as in Table 1.

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Table S2. Patient Characteristics According to the 30-day Survival

	Total (N=829)	30-day Survival (N=596)	30-day Death (N=233)
Baseline Characteristics			
Age, yrs	55.1 ± 13.1	53.7 ± 12.5	58.6 ± 13.9
Male	587 (70.8)	430 (72.1)	157 (67.4)
Heart rate	79.4 ± 18.1	78.9 ± 17.1	80.5 ± 20.5
Admission SBP (mmHg)	144.5 ± 31.9	149.2 ± 29.6	132.5 ± 34.4
Admission DBP (mmHg)	77.3 ± 19.8	78.9 ± 19.8	73.2 ± 19.4
Diabetes mellitus	40 (4.8)	26 (4.4)	14 (6.0)
Hypertension	690 (83.2)	508 (85.2)	182 (78.1)
Hyperlipidemia	180 (21.7)	139 (23.3)	41 (17.6)
Smoking	264 (31.8)	221 (37.1)	43 (18.5)
Coronary artery disease	123 (14.8)	83 (13.9)	40 (17.2)
Previous stroke	63 (7.6)	47 (7.9)	16 (6.9)
Previous aortic disease	22 (2.7)	14 (2.3)	8 (3.4)
Previous replacement of aorta valve	12 (1.4)	8 (1.3)	4 (1.7)
Syncope	61 (7.4)	31 (5.2)	30 (12.9)
Coma	14 (1.7)	1 (0.2)	13 (5.6)
Shock	35 (4.2)	0 (0)	35 (15.0)
Time from onset to admission, hrs	12.0 (7.0-24.0)	13.0 (7.0-30.0)	9.0 (6.0-18.0)
In-hospital assessment			
Left ventricular diameter, mm	49.9 ± 7.4	50.5 ± 6.6	48.4 ± 9.0
Left ventricular ejection fraction, %	58.8 ± 7.7	59.7 ± 5.9	56.0 ± 10.7
Aortic valve regurgitation	210 (25.4)	145 (24.3)	65 (28.3)
Pericardial effusion	61 (7.4)	21 (3.5)	40 (17.4)

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Artery affected			
Coronary artery	213 (27.0)	144 (24.2)	69 (35.6)
Brachiocephalic trunk	522 (66.2)	375 (63.0)	147 (75.8)
Coeliac axis	227 (28.8)	164 (27.6)	63 (32.5)
Superior mesenteric artery	198 (25.1)	143 (24.0)	55 (28.4)
Renal artery	211 (26.7)	148 (24.9)	63 (32.5)
Iliac artery	298 (37.8)	218 (36.6)	80 (41.2)
Baseline biomarkers			
NT-proBNP, pg/ml	308.0 (104.8-974.5)	245.7 (91.3-841.3)	792.0 (193.4-1489.0)
ln NT-proBNP	5.8 ± 1.6	5.6 ± 1.6	6.3 ± 1.5
Haemoglobin, g/dl	134.8 ± 19.2	135.2 ± 18.9	133.8 ± 19.7
D-dimers, mg/l	10.9 (3.8-20.0)	8.0 (2.9-20.0)	20.0 (8.2-20.0)
Creatinine, umol/L	110.9 ± 58.2	99.3 ± 41.6	140.5 ± 80.1
C-reactive protein, mg/l	11.4 (4.6-53.2)	12.9 (5.0-68.6)	8.9 (4.2-29.5)
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0.02)	0.03 (0-0.17)
Treatment			
Conservative treatment	305 (36.8)	89 (14.9)	216 (92.7)
Surgery treatment	524 (63.2)	507 (85.1)	17 (7.3)

Values are median (IQR) or n (%).

SBP, stress blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-B type natriuretic peptide.

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Table S3. Association Between NT-proBNP and Clinical Outcome.

	1-Year death			30-Day death		
	No. of events/total patients (%)*	Hazard ratio (95% CI)	*P* value	No. of events/total patients (%)*	Odds ratio (95% CI)	*P* value
ln NT-proBNP	–	1.24 (1.15-1.34)	<0.001	–	1.32 (1.19-1.46)	<0.001
NT-proBNP tertiles						
T1 (≤155.0)	50/276 (18.1)	Reference	–	47/276 (17.0)	Reference	–
T2 (155.0-671.4)	90/277 (32.5)	1.91 (1.35-2.69)	<0.001	83/277 (30.0)	2.08 (1.39-3.13)	<0.001
T3 (>671.4)	116/276 (42.0)	2.56 (1.84-3.57)	<0.001	103/276 (37.3)	2.90 (1.95-4.32)	<0.001

*Values are Kaplan-Meier estimated rates.

CI, confidence interval.

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Table S4. Patient Characteristics and Outcomes According to the Treatment Strategy

	Total (N=829)	Conservative (N=305)	Surgery (N=524)
Baseline Characteristics			
Age, yrs	55.1 ± 13.1	53.7 ± 12.5	58.6 ± 13.9
Male	587 (70.8)	202 (66.2)	385 (73.5)
Heart rate	79.4 ± 18.1	81.1 ± 20.4	78.5 ± 16.6
Admission SBP (mmHg)	144.5 ± 31.9	137.9 ± 33.8	148.3 ± 30.0
Admission DBP (mmHg)	77.3 ± 19.8	75.3 ± 19.4	78.4 ± 20.0
Diabetes mellitus	40 (4.8)	14 (4.6)	26 (5.0)
Hypertension	690 (83.2)	249 (81.6)	441 (84.2)
Hyperlipidemia	180 (21.7)	57 (18.7)	123 (23.5)
Smoking	264 (31.8)	55 (18.0)	209 (39.9)
Coronary artery disease	123 (14.8)	52 (17.0)	71 (13.5)
Previous stroke	63 (7.6)	28 (9.2)	35 (6.7)
Previous aortic disease	22 (2.7)	11 (3.6)	22 (2.7)
Previous replacement of aorta valve	12 (1.4)	7 (2.3)	5 (1.0)
Syncope	61 (7.4)	34 (11.1)	27 (5.2)
Coma	14 (1.7)	13 (4.3)	1 (0.2)
Shock	35 (4.2)	35 (15.0)	0 (0)
Time from onset to admission, hrs	12.0 (7.0-24.0)	10.0 (6.0-24.0)	13.0 (7.0-24.5)
In-hospital assessment			
Left ventricular diameter, mm	49.9 ± 7.4	48.7 ± 8.5	50.6 ± 6.7
Left ventricular ejection fraction, %	58.8 ± 7.7	56.4 ± 10.4	60.1 ± 5.2
Aortic valve regurgitation	210 (25.4)	77 (25.5)	133 (25.4)
Pericardial effusion	61 (7.4)	42 (13.9)	19 (3.6)

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Artery affected			
Coronary artery	213 (27.0)	82 (30.9)	131 (25.0)
Brachiocephalic trunk	522 (66.2)	183 (69.1)	339 (64.7)
Coeliac axis	227 (28.8)	85 (32.1)	142 (27.1)
Superior mesenteric artery	198 (25.1)	67 (25.3)	131 (25.0)
Renal artery	211 (26.7)	75 (28.3)	36 (26.0)
Iliac artery	298 (37.8)	95 (35.8)	203 (38.7)
Baseline biomarkers			
NT-proBNP, pg/ml	308.0 (104.8-974.5)	524.9 (192.6-1490.5)	227.9 (82.9-722.3)
ln NT-proBNP	5.8 ± 1.6	6.3 ± 1.5	5.5 ± 1.5
Haemoglobin, g/dl	134.8 ± 19.2	131.8 ± 21.1	136.6 ± 17.8
D-dimers, mg/l	10.9 (3.8-20.0)	16.6 (6.3-20.0)	8.2 (2.9-20.0)
Creatinine, umol/L	110.9 ± 58.2	131.3 ± 75.4	99.0 ± 40.9
C-reactive protein, mg/l	11.4 (4.6-53.2)	10.0 (4.7-50.0)	11.9 (4.5-54.2)
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0.13)	0 (0-0.02)
Clinical Outcomes			
1-year death	256 (30.9)	226 (74.1)	30 (5.7)
30-day death	233 (28.1)	216 (70.8)	17 (3.2)

Values are median (IQR) or n (%).

Abbreviations as in Table 1.

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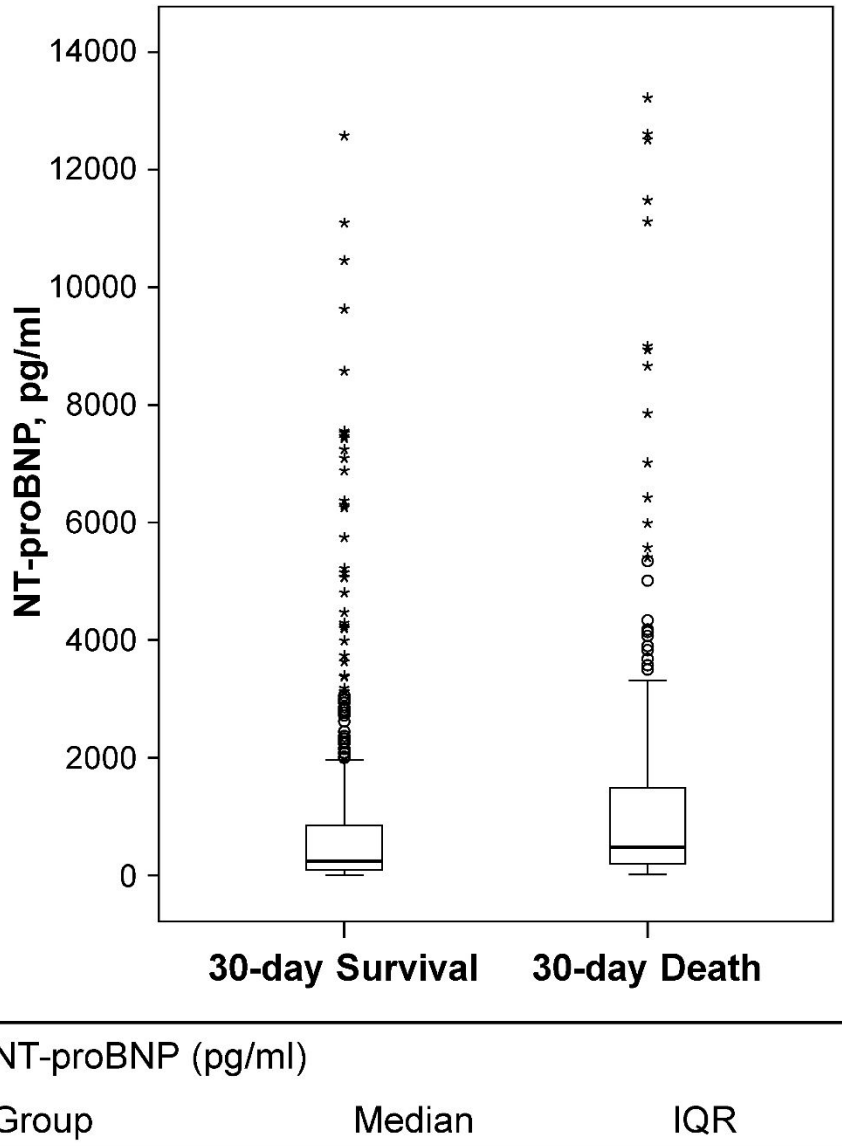
Figure S1. Baseline NT-proBNP as a predictor of 30-day outcome

Abbreviations as in Figure 1.



NT-proBNP (pg/ml)		
Group	Median	IQR
30-day Survival	248.0	91.5 to 846.5
30-day Death	482.0	195.7 to 1489.0

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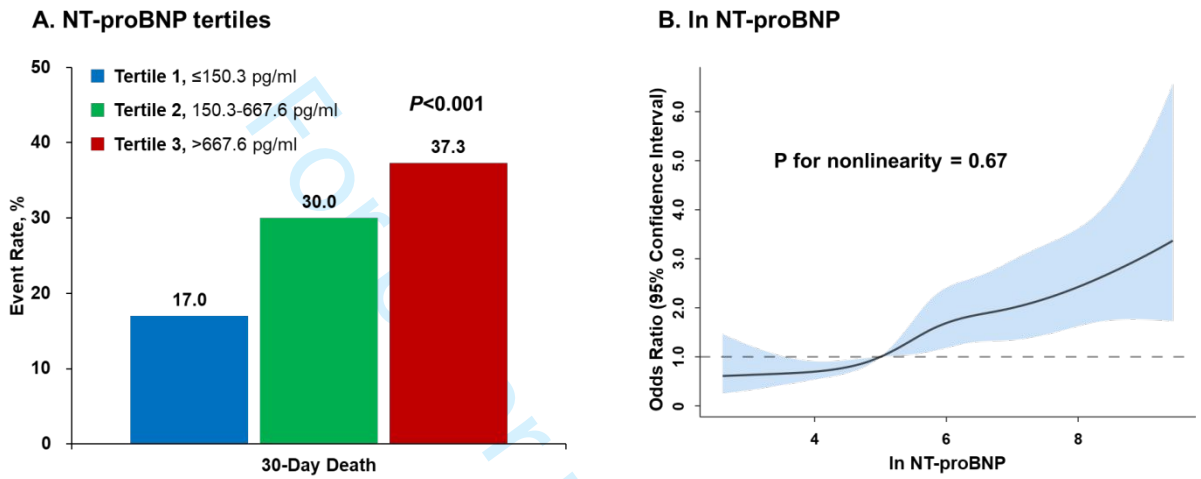
Figure S2. Death within 30 days from admission according to NT-proBNP levels

Incidence of 30-day all-cause death is presented according to (A) NT-proBNP tertiles and (B) continuous value of ln NT-proBNP among patients with acute type A aortic dissection.

CI, confidence interval; OR, odds ratio; other abbreviations as in Figure 1.



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Clinical Implication of NT-proBNP to Predict Mortality in Patients With Acute Type A Aortic Dissection: a Retrospective Cohort Study

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Clinical Implication of NT-proBNP to Predict Mortality in Patients With Acute Type A Aortic Dissection: a Retrospective Cohort Study

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Abstract

Objectives: Acute type A aortic dissection is a life-threatening cardiovascular disease commonly seen in Emergency Department, resulting in substantial mortality and morbidity. We aimed to investigate the prognostic value of N-terminal pro-B type natriuretic peptide (NT-proBNP) among this critically ill population.

Design: Retrospective Cohort Study.

Setting: Emergency Department of a Fuwai hospital in China from 2018 to 2020.

Participants: We consecutive enrolled 829 patients with acute type A aortic dissection and measurable baseline NT-proBNP at the Emergency Department of Fuwai hospital in China from 2018 to 2020.

Primary outcome: The primary endpoint was 1-year all-cause death.

Results: Based on tertiles of NT-proBNP (pg/ml), patients were stratified into low (≤150.3, N=276), intermediate (150.3-667.6, N=277), and high (>667.6, N=276) NT-proBNP groups. Compared with patients with low NT-proBNP, the Kaplan–Meier estimates for primary 1-year mortality were higher in intermediate (32.5% vs. 18.1%; HR 1.91, 95% CI: 1.35 to 2.69) and high (42.0% vs. 18.1%; HR 2.56, 95% CI: 1.84 to 3.57) NT-proBNP groups, respectively. After multivariable regression adjusted for confounders, NT-proBNP tertiles were independent predictors for 1-year mortality (adjusted HR for intermediate group 1.52, 95% CI: 1.02-2.27; adjusted HR for high group 2.17, 95% CI: 1.41-3.32). Notably, the predictive performance of NT-proBNP for 1-year mortality was greater in patients receiving surgery than conservative treatment (between-cohorts difference in area under the curve 0.13, Delong's test P=0.04).

Conclusion: NT-proBNP provides incremental prognostic information for mortality in patients with acute type A aortic dissection underwent surgical repairment, which could aid in risk stratification as a pragmatic and versatile biomarker in this critically ill population while has limited prognostic value for those receiving conservative treatment.

Keywords: acute aortic dissection; NT-proBNP; mortality.

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Strengths and limitations of this study

- ✓ This study consecutively enrolled patients with type A aortic dissection incorporated acute-phase and long-term prognosis representing a well-phenotyped group in China
- ✓ Not all participants had an N-terminal pro-B-type natriuretic peptide measurement.
- ✓ This study was conducted in a single center which may affect the external validity of the present results.

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Introduction

Despite the improvement of diagnostic and therapeutic techniques in recent decades, acute aortic dissection is still a life-threatening cardiovascular disease commonly seen in emergency department, resulting in over half of mortality in patients without proper treatment.[1-4] In addition, acute aortic dissection is also a rapid-progressive disorder with the risk of death increased by 1% per hour in the early stage.[3] Compared to those with acute type B aortic dissection, patients with acute type A aortic dissection acquire substantially worse in-hospital and long-term prognosis as the ascending aorta is involved.[5 6] Therefore, it is of great clinical implication to timely and effectively identify type A aortic dissection patients at higher risk, which would assist clinicians in developing the proper treatment and management strategy to improve the prognosis at the earliest possible stage. However, although there is increasing interest in the use of circulating biomarkers for risk stratification of patients with aortopathy, biomarker expression has not been clearly associated with relevant aortic clinical events.[1]

Natriuretic peptides, including B-type natriuretic peptides (BNP) and the N-terminal fragment of its prohormone (NT-proBNP), are endogenous cardiac hormones mainly secreted by cardiomyocytes in response to increased stress of cardiac chamber wall.[7] As an established biomarker for heart failure,[7 8] natriuretic peptides have been proven useful for the diagnosis and risk stratification in several other cardiovascular diseases, including coronary artery disease and valvular heart disease.[9-12] Previous studies have demonstrated the prognostic value of NT-proBNP in patients with acute aortic dissection.[13-17] However, these small-scale studies were generally conducted in earlier years and mainly focused on acute-phase prognosis with type B aortic dissection. In patients with acute type A aortic dissection, the association between

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NT-proBNP and long-term prognosis has not been fully clarified, and its clinical implication needs further validation. The present study was designed to investigate the prognostic value of NT-proBNP tertiles for 1-year mortality, and whether the prognostic value differed between patients with conservative and surgery treatment in patients with acute type A aortic dissection in a relatively large cohort.

Methods

Study Population

A total of 847 consecutive patients were recruited with acute type A aortic dissection diagnosed by aortic computed tomography (CT) angioplasty in the emergency department of Fuwai hospital from January 2018 to December 2020. Acute aortic dissection was diagnosed by computed tomography and classified according to the Stanford system: 1) type A, involves the ascending aorta, regardless of the site of the primary intimal tear; and 2) type B, involves only the descending aorta. Adult patients were eligible for inclusion if they were diagnosed with acute type A aortic dissection with onset time ≤14 days from symptom to diagnosis. Recurrent aortic dissection was excluded in the present study. The present study was approved by the Ethics Committee of Fuwai Hospital and followed the principles of the Declaration of Helsinki. All participants provided written informed consent.

Data collection and follow-up

All data were obtained from the electronic health records. Demographic characteristics, cardiovascular risk factors, comorbidities, in-hospital assessment, laboratory biomarkers, and treatment strategy were recorded in real-time by medical personnel. For NT-proBNP, blood

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samples were collected into EDTA-anticoagulant tubes by venipuncture in emergency department, and the sample would be sent to the laboratory immediately for analysis. Plasma NT-proBNP concentration was measured using an Elecsys proBNP, Cobas E analyser (Roche Diagnostics GmbH, Mannheim, Germany) within a measurable range between 5 and 35 000 pg ml/L. Risk classification of patients was performed according to tertiles of NT-proBNP: 1) low NT-proBNP, ≤150.3 pg/ml; 2) intermediate NT-proBNP, 150.3-667.6 pg/ml; and 3) high NT-proBNP, >667.6 pg/ml. In subgroup analysis, patients were further stratified according to the treatment strategy into conservative group or surgery (open repair) group.

The primary endpoint for the present study was the all-cause death within 1 year from emergency contact (i.e., date of emergency admittance). The secondary endpoint was the 30-day rate of all-cause death. Considering that the visualization of the relationship between NT-proBNP and prognosis is more intuitive when it is used as a categorical variable (e.g., KM curve, mortality increase with increasing tertiles), the results with NT-proBNP tertiles were used as the primary outcome.

Statistical analysis

Continuous variables are expressed as mean ± SD or median (interquartile range [IQR]) and categorical variables are presented as counts (%). Restricted cubic splines were applied to delineate the curve of associations between baseline NT-proBNP level and the risk of all-cause death. The receiver-operating characteristic (ROC) curve analysis with AUC was used to compare the prediction capability for 1-year mortality between cohorts with conservative or surgery treatments using the DeLong's test.[18] For 1-year outcome, considering ROC curve analysis could not adjust impact of potential confounders, cox proportional hazards model was

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used to estimate hazard ratios (HR) and 95% confidence intervals (CI), while Logistic regression model was used to estimate odds ratios (OR) and 95% confidence interval (CI) for 30-day outcome. Multivariable adjusted analysis was used to identify independent predictors. The candidate variables for multivariable analysis were identified using historical confounder definition based on clinical knowledge and previous literature reports.[19] The included covariates were age, admission SBP, smoking, syncope, coma, time from onset to admission, left ventricular diameter, left ventricular ejection fraction, pericardial effusion, troponin I, creatinine, C-reactive protein, and artery affected – coronary artery. Subgroup analysis was performed according to the treatment strategy (i.e., conservative treatment and surgery), and the P value for interaction was calculated from a multivariable Cox proportional hazards model. Unless otherwise specified, a 2-sided p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using R software, version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

None.

Results

A total of 847 consecutive patients with acute type A aortic dissection were enrolled between January 2018 and December 2020, among which 18 patients without available baseline NT-proBNP data (N=7) or completed 1-year follow-up (N=11) were excluded (**Figure 1**). Therefore, 829 patients were included in the present study. The median baseline NT-preBNP was 308.0 pg/ml (interquartile range [IQR] 104.8 to 974.5).

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Risk classification of patients was performed according to tertiles of baseline NT-proBNP level (pg/mL): 1) ≤150.3 (low NT-proBNP group, N=276); 2) 150.3-667.6 (intermediate NT-proBNP group, N=277); 3) >667.6 (high NT-proBNP group, N=276).

Baseline characteristics

Baseline characteristics of the NT-proBNP tertiles are summarized and stratified in **Table 1**. Among 829 patients, 587 were male (70.8%), with an average age of 55.1 years. The median NT-preBNP levels were 74.0 (IQR 40.7 to 105.4), 308.0 (IQR 219.0-444.9), and 1490.5 (IQR 974.3-3108.5) in low, intermediate, and high NT-proBNP groups, respectively. Compared with the lowest tertiles group, patients with higher NT-proBNP tertiles tended to have higher level of advanced age, heart rate, previous coronary artery disease, previous aortic disease, time from onset to admission, left ventricular diameter, creatinine, C-reactive protein, and troponin I, with lower levels of male proportion, admission blood pressure, smoking status, left ventricular ejection fraction, and haemoglobin. In addition, the percentage of surgery treatment was decreased along with the increasing NT-proBNP levels (77.5%, 61.7%, and 50.4%, respectively, P<0.001).

Prognostic value of NT-proBNP among the whole cohort

A total of 256 (30.9%) deaths occurred during 1-year follow-up, and the 30-day death was documented in 233 (28.1%) patients. Comparisons of demographic data and clinical characteristics of patients stratified by 1-year or 30-day outcomes are presented in **Table S1 and S2**. Median NT-proBNP level (pg/ml) in 1-year survivors versus non-survivors was 236.3 (IQR 90.9 to 794.0) vs. 517.2 (IQR 200.2 to 1,449.9; P<0.001) (**Figure 2**), and in patients

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without versus with 30-day death was 248.0 (IQR 91.5 to 846.5) and 482.0 (IQR 195.7 to 1,489.0), respectively (**Figure S1**).

As a categorical variable, Kaplan-Meier curves showed a graded risk for 1-year mortality with higher NT-proBNP levels (log-rank P<0.001) (**Figure 3A**). Compared with patients with low NT-proBNP, the risk of 1-year death was higher in intermediate (32.5% vs. 18.1%; HR 1.91, 95% CI: 1.35 to 2.69, P<0.001), and high groups (42.0% vs. 18.1%; HR 2.56, 95% CI: 1.84 to 3.57, P<0.001), respectively (**Table S3**).

As a continuous variable, restricted spline curve analysis showed there was a monotonic increase in the risk of 1-year death with increasing NT-proBNP concentrations (P for linearity =0.57) (**Figure 3B**). The ln NT-proBNP was significantly associated with 1-year mortality (HR 1.24, 95% CI: 1.15 to 1.34, P<0.001) (**Table S3**).

Multivariable Adjustment Analysis

In addition, by multivariable analysis, age, admission SBP, smoking, coma, time from onset to admission, left ventricular ejection fraction, creatinine, and NT-proBNP tertiles (adjusted HR for intermediate group 1.52, 95% CI: 1.02-2.27, p=0.04; adjusted HR for high group 2.17, 95% CI: 1.41-3.32, p<0.001) were independent predictors for 1-year mortality (**Table 2**). Similar results were observed for the secondary endpoint (**Table 2** and **Figure S2**).

Performance of NT-proBNP tertiles in patients with conservative or surgery treatment

The comparison of baseline characteristics and clinical outcomes grouped by the treatment strategy was shown in **Table S4**. ROC analysis was performed in surgery and conservative treatment cohort separately to compare the predictive performance of NT-proBNP. As depicted in **Figure 4**, NT-proBNP showed greater predictive power in surgery treatment subgroup (AUC

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0.64, 95% CI: 0.54 to 0.74) when compared to conservative treatment subgroup (AUC 0.51, 95% CI: 0.44 to 0.59), with significantly between-cohorts AUC difference (ΔAUC 0.13, 95% CI: 0.01 to 0.25, P =0.04).

Subgroup analysis was conducted to investigate the impact of treatment strategy (surgery or conservative treatment) on the association between NT-proBNP tertiles and all-cause mortality. In surgery treatment cohort, the rate of 1-year mortality was significantly increased in intermediate group (7.6% vs. 2.8%; HR 2.79, 95% CI: 1.06 to 7.33, P=0.04) and high group (7.9% vs. 7.6%; HR 2.89, 95% CI: 1.07 to 7.81, P=0.04) when compared to low NT-proBNP (≤155.0 pg/ml) group (**Figure 5** and **Table 3**). In conservative treatment group, compared with low NT-proBNP group, the rate of 1-year mortality was comparable in intermediate group (72.6% vs. 71.0%; HR 1.00, 95% CI: 0.69 to 1.45, P=0.99) and high group (76.6% vs. 71.0%; HR 1.05, 95% CI: 0.74 to 1.49, P=0.79). Notably, there was a significant interaction between NT-proBNP tertiles and treatment strategy for 1-year death (P for interaction=0.04) (**Figure 5** and **Table 3**). Similar results were observed for 30-day mortality, although surgery treatment cohort did not reach statistical significance. However, no significant interaction between NT-proBNP levels and treatment strategy was observed for 30-day death (P for interaction=0.18).

Discussion

The present study was focused on association of baseline NT-proBNP levels and mortality (i.e., acute-phase and long-term mortality) in patients with acute type A aortic dissection, and the main findings are: 1) in our primary analysis, baseline NT-proBNP tertiles were independent predictor of acute-phase or 1-year survival after multivariate adjustment; and 2) in our

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secondary analysis, NT-proBNP was more predictive of long-term outcomes in patients with acute type A aortic dissection undergoing surgery treatment. Therefore, baseline NT-proBNP, as a user-friendly and incremental prognostic factor, could assist in profiling risk among patients with acute type A aortic dissection.

NT-proBNP has been routinely used as a diagnostic tool for heart failure; besides, it has also been proven to be a novel and useful biomarker for the risk stratification of several other cardiac diseases and even non-cardiac conditions.[10 20-22] A previous study has reported that the level of NT-proBNP was significantly higher in those with acute aortic dissection.[23] In addition, several studies have demonstrated the prognostic value of NT-proBNP in patients with acute aortic dissection.[15-17] For the first time, a prospective study of 104 type A aortic dissection patients revealed that higher levels of NT-proBNP predicted the occurrence of 30-day mortality and short-term major adverse events (i.e., postoperative heart failure, neurologic deficit, lung failure, renal failure, or sepsis).[15] Another study of 67 patients verified that NT-proBNP was an independent risk factor of in-hospital death in patients with type A aortic dissection.[17] However, these studies on type A aortic dissection were limited by the relatively small sample size and the lack of long-term follow-up results. The present study further validated the prognosis value of NT-proBNP in the acute phase or 1 year later with the largest sample size so far (N=829).

Although the development of surgical repairment and intensive care has greatly improved the prognosis of type A aortic dissection, several studies still reported relatively high mortality rates.[24 25] Many factors have been identified as predictors for short-term mortality, however, there is currently no established blood biomarker for risk stratification.[17] As a non-specific

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preoperative biomarker, it is not comprehensive to use NT-proBNP alone as a risk predictor despite it being confirmed as an independent predictor in the present study. However, combined with the existing clinical risk factors, NT-proBNP could substantially improve prognosis prediction, which could assist physicians in identifying high-risk patients and enhance perioperative and follow-up management.

In the present study, a total of 305 (36.8%) received conservative treatment, and the reasons are as follows: 1) 133 (16.0%) patients suffered aortic rupture prior to emergency surgery, resulting in death and no opportunity for surgery; 2) some patients with multiple comorbidities are not suitable for surgery due to the contraindications after evaluation, which received conservative management; and 3) a small number of patients refused surgery due to the treatment costs.[26] Early surgical repair has been recommended as the gold standard treatment for most acute type A aortic dissection patients, which can significantly reduce mortality. This is also reflected in the present study, in which the 1-year mortality was 5.7% and 74.1% in the surgical and conservative treatment group, separately. Compared with the surgical group, patients in the conservative group had worse basic conditions and were more likely to have severe complications such as hypotension, shock, pericardial effusion and heart failure, which may be the cause of the elevated NT-proBNP and worse prognosis. Thus, we suggest that it should be cautiously interpreted the prognostic value of NT-proBNP in conservative cohorts. Besides, in the subgroup analysis, mortality risks were significantly higher in patients with higher NT-proBNP tertiles among surgical cohort while were comparable in conservative cohort, and a significant interaction was observed between NT-proBNP tertiles and treatment strategy for 1-year death, indicating that only a particular

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population with surgery requirement might benefit of using NT-proBNP in their risk stratification.

There are several possible interpretations for the increased mortality in patients with elevated NT-proBNP levels. First, the increased plasma NT-proBNP levels were proven to be associated with cardiovascular dysfunction in critically ill patients regardless of surgery or not.[27-30] And Cardiac dysfunction is a common and significant predictor of poor prognosis among critically ill patients.[31 32] Second, the occurrence and development of acute aortic syndrome involved activation of inflammatory pathway,[3 24] and studies have demonstrated that systemic inflammation state contributed to morbidity and mortality in acute aortic syndrome.[33 34] Moreover, severe systemic inflammation could further induce or exacerbate cardiac dysfunction which contributes to the increased plasma levels of NT-proBNP.[35] Third, the troponin I levels were gradually increased along with the elevation of NT-proBNP levels, indicating a relatively poor coronary perfusion in patients with high NT-proBNP level, which is also an important predictor of mortality.[36] Fourth, NT-proBNP levels are associated with abnormal kidney function,[37] which could independently predict acute-phase and long-term prognosis. Finally, increased plasma levels of NT-proBNP may reflect the overall disease severity and the proportion of patients received surgery was significantly reduced along with elevated NT-proBNP levels.

In addition, it was of great interest to observe that NT-proBNP levels significantly elevated along with the increase of time from onset of symptoms to admission, further indicating the importance of early diagnosis and treatment of acute type A aortic dissection in improving survival.[3 4 15]

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Limitations of the study

The strength of the present study is this large-scale retrospective cohort of type A aortic dissection incorporated acute-phase and long-term prognosis, which reflect the current status of diagnosis and treatment of aortic dissection in China to a certain extent. However, this study has several limitations. First, this study was conducted in a single center, although the enrolled patients came from multiple provinces in China; the external validity of the present study needs to be further confirmed in future multicenter studies. Second, longer follow-up results are warranted (e.g., 3-year or 5-year) to further investigate the prognostic value of NT-proBNP especially for patients underwent index surgery. Third, the impact of NT-proBNP levels on outcomes other than mortality, such as life quality and ischemic events, is also worth investigating in future studies. Fourth, although the possible confounders were adjusted by multivariate analysis, we cannot exclude an effect from residual confounding (from measured covariates) and unmeasured confounders due to the observational design (e.g., patient-management at the emergency department, operating theater, and intensive care unit). Finally, serial measurements of NT-proBNP levels are not available in this study, and the impact of the dynamic change of NT-proBNP on outcomes cannot be evaluated. Therefore, the findings of the present study are hypothesis generating, and the clinical implications of NT-proBNP levels among patients with type A aortic dissection should be evaluated in future massive prospective multicenter studies.

CONCLUSIONS

NT-proBNP provides incremental prognostic information for mortality in patients with acute type A aortic dissection underwent surgical repairment, which could aid in risk stratification as

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a pragmatic and versatile biomarker in this critically ill population while having limited prognostic value for those receiving conservative treatment. Further large-scale prospective studies are needed to confirm these findings.

Supplemental Information

Tables S1-S4 of the supplementary information

Figures S1-S2 of the supplementary information

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Figure legends

Figure 1. Flowchart

NT-proBNP = N-terminal pro-brain natriuretic peptide.

Figure 2. Baseline NT-proBNP as a predictor of 1-year outcome

Abbreviations as in Figure 1.

Figure 3. Death within 1-year from emergency contact according to NT-proBNP levels

Incidence of 1-year all-cause death is presented according to (A) NT-proBNP tertiles and (B) continuous value of ln NT-proBNP among patients with acute type A aortic dissection.

CI, confidence interval; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Figure 4. The Receiver-Operating Characteristic Curve of NT-proBNP for Predicting 1-year Death in Conservative and Surgery Treatment Cohorts.

AUC, area under curve; CI, confidence interval.

Figure 5. Outcomes in patients Stratified by NT-proBNP Tertiles in Conservative and Surgery Cohorts.

Abbreviations as in Figure 1 and Figure 2.

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Table1. Patient Characteristics According to the tertiles of NT-pro BNP levels

	Total (N=829)	NT-pro BNP tertiles, pg/ml		
		T1 (≤150.3) (N=276)	T2 (150.3-667.6) (N=277)	T3 (>667.6) (N=276)
Baseline Characteristics				
Age, yrs	55.1 ± 13.1	50.1 ± 11.5	58.7 ± 12.7	56.5 ± 13.2
Male	587 (70.8)	224 (81.2)	176 (63.5)	187 (67.8)
Heart rate	79.4 ± 18.1	75.8 ± 14.6	80.3 ± 17.9	82.2 ± 20.6
Admission SBP (mmHg)	144.5 ± 31.9	149.5 ± 30.6	143.8 ± 33.9	140.1 ± 32.5
Admission DBP (mmHg)	77.3 ± 19.8	80.3 ± 19.9	77.0 ± 19.8	74.5 ± 21.1
Diabetes mellitus	40 (4.8)	16 (5.8)	17 (6.1)	7 (2.5)
Hypertension	690 (83.2)	232 (84.1)	236 (85.2)	222 (80.4)
Hyperlipidemia	180 (21.7)	64 (23.2)	58 (20.9)	58 (21.0)
Smoking	264 (31.8)	111 (40.2)	85 (30.7)	68 (24.6)
Coronary artery disease	123 (14.8)	26 (9.4)	43 (15.5)	54 (19.6)
Previous stroke	63 (7.6)	18 (6.5)	27 (9.7)	18 (6.5)
Previous aortic disease	22 (2.7)	3 (1.1)	13 (4.7)	6 (2.2)
Previous replacement of aorta valve	12 (1.4)	0 (0)	3 (1.1)	9 (3.3)
Syncope	61 (7.4)	9 (3.3)	23 (8.3)	29 (10.5)
Coma	14 (1.7)	6 (2.2)	6 (2.2)	2 (0.7)
Shock	35 (4.2)	6 (2.2)	9 (3.2)	20 (7.2)
Time from onset to admission, hrs	12.0 (7.0-24.0)	7.0 (5.0-13.0)	12.0 (7.0-24.0)	22.0 (10.0-48.0)
In-hospital assessment				

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Left ventricular diameter, mm	49.9 ± 7.4	49.3 ± 6.7	48.7 ± 6.8	51.7 ± 8.3
Left ventricular ejection fraction, %	58.8 ± 7.7	60.6 ± 4.9	59.1 ± 6.1	56.5 ± 10.0
Aortic valve regurgitation	210 (25.4)	47 (17.0)	61 (22.2)	102 (37.1)
Pericardial effusion	61 (7.4)	12 (4.3)	20 (7.3)	29 (10.5)
Artery affected				
Coronary artery	213 (27.0)	61 (22.8)	70 (25.6)	82 (31.7)
Brachiocephalic trunk	522 (66.2)	165 (61.6)	177 (67.0)	180 (69.5)
Coeliac axis	227 (28.8)	80 (29.9)	64 (24.2)	83 (32.0)
Superior mesenteric artery	198 (25.1)	69 (25.7)	62 (23.5)	67 (25.9)
Renal artery	211 (26.7)	66 (24.6)	71 (27.0)	74 (28.6)
Iliac artery	298 (37.8)	100 (37.3)	92 (34.1)	100 (37.3)
Baseline biomarkers				
NT-proBNP, pg/ml	308.0 (104.8-974.5)	74.0 (40.7-105.4)	308.0 (219.0-444.9)	1490.5 (974.3-3108.5)
ln NT-proBNP	5.8 ± 1.6	4.1 ± 0.7	5.7 ± 0.4	7.6 ± 0.9
Haemoglobin, g/dl	134.8 ± 19.2	140.3 ± 18.8	133.8 ± 16.8	130.3 ± 20.5
D-dimerse, mg/l	10.9 (3.8-20.0)	11.3 (3.4-20.0)	12.5 (4.1-20.0)	9.9 (3.7-20.0)
Creatinine, umol/L	110.9 ± 58.2	94.8 ± 32.1	100.4 ± 38.6	137.5 ± 81.1
C-reactive protein, mg/l	11.4 (4.6-53.2)	6.4 (3.3-14.8)	12.8 (5.1-53.3)	26.4 (9.0-80.3)
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0)	0 (0-0.05)	0.03 (0-0.21)
Treatment				
Conservative treatment	305 (36.8)	62 (22.5)	106 (38.3)	137 (49.6)
Surgery treatment	524 (63.2)	214 (77.5)	171 (61.7)	139 (50.4)

Values are median (IQR) or n (%).

SB, stress blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-B type natriuretic peptide.

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Table 2. Independent Predictors of Clinical Outcomes

	1-Year death			30-Day death		
	Adjusted HR	**95% CI**	***P* Value**	**Adjusted OR**	**95% CI**	***P* Value**
Age	1.01	1.00-1.03	0.03	1.01	1.00-1.03	0.13
Admission SBP	0.99	0.97-1.00	<0.001	0.99	0.98-0.99	0.001
Smoking	0.54	0.38-0.77	<0.001	0.43	0.27-0.69	<0.001
Syncope	0.99	0.62-1.59	0.97	1.41	0.69-2.89	0.35
Coma	2.55	1.26-5.13	0.009	12.1	2.37-107.3	0.02
Time from onset to admission	0.98	0.97-0.99	<0.001	0.98	0.96-0.99	<0.001
Left ventricular diameter	0.99	0.97-1.01	0.35	0.99	0.96-1.02	0.34
Left ventricular ejection fraction	0.98	0.96-1.00	0.02	0.96	0.93-0.99	0.007
Pericardial effusion	1.00	0.62-1.60	0.99	1.56	0.70-3.43	0.27
Troponin I	1.02	1.00-1.04	0.052	1.15	1.01-1.30	0.04
Creatinine	1.01	1.00-1.01	<0.001	1.01	1.01-1.01	<0.001
C-reactive protein	1.00	0.99-1.00	0.25	0.99	0.99-1.00	0.06
Artery affected – coronary artery	1.08	0.80-1.47	0.61	0.98	0.63-1.53	0.92
NT-proBNP tertile						
T1 (≤155.0)	Reference	Reference	Reference	Reference	Reference	Reference
T2 (155.0-671.4)	1.52	1.02-2.27	0.04	1.62	0.97-2.71	0.07
T3 (>671.4)	2.17	1.41-3.32	<0.001	2.18	1.24-3.84	0.007

Abbreviations as in Table 1.

OR, odds ratio; HR, hazard ratio; CI, confidence interval.

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Table 3. Clinical Outcomes in Cohorts with Conservative or Surgery Treatment, according to NT-proBNP Tertiles

	1-Year death			30-Day death		
	No. of events/total patients (%)*	Hazard ratio (95% CI)	*P* value	No. of events/total patients (%)	Odds ratio (95% CI)	*P* value
Conservative†						
T1 (≤155.0)	44/62 (71.0)	Reference	-	43/62 (69.4)	Reference	-
T2 (155.0-671.4)	77/106 (72.6)	1.00 (0.69-1.45)	0.99	75/106 (70.8)	1.07 (0.54-2.12)	0.85
T3 (>671.4)	105/137 (76.6)	1.05 (0.74-1.49)	0.79	98/137 (71.5)	1.10 (0.58-2.14)	0.75
Surgery†						
T1 (≤155.0)	6/214 (2.8)	Reference	-	4/214 (1.9)	Reference	-
T2 (155.0-671.4)	13/171 (7.6)	2.79 (1.06-7.33)	0.04	8/171 (4.7)	2.58 (0.76-8.70)	0.13
T3 (>671.4)	11/139 (7.9)	2.89 (1.07-7.81)	0.04	5/139 (3.6)	1.96 (0.52-7.43)	0.32

*Values are Kaplan-Meier estimated rates. † *P* for interaction for the risk of 1-year death: NT-proBNP tertiles and treatment strategy (conservative or surgery) = 0.04; *P* for interaction for the risk of 30-day death: NT-proBNP levels (low or high) and treatment strategy (conservative or surgery) = 0.18.

OR, odds ratio; HR, hazard ratio; CI, confidence interval.

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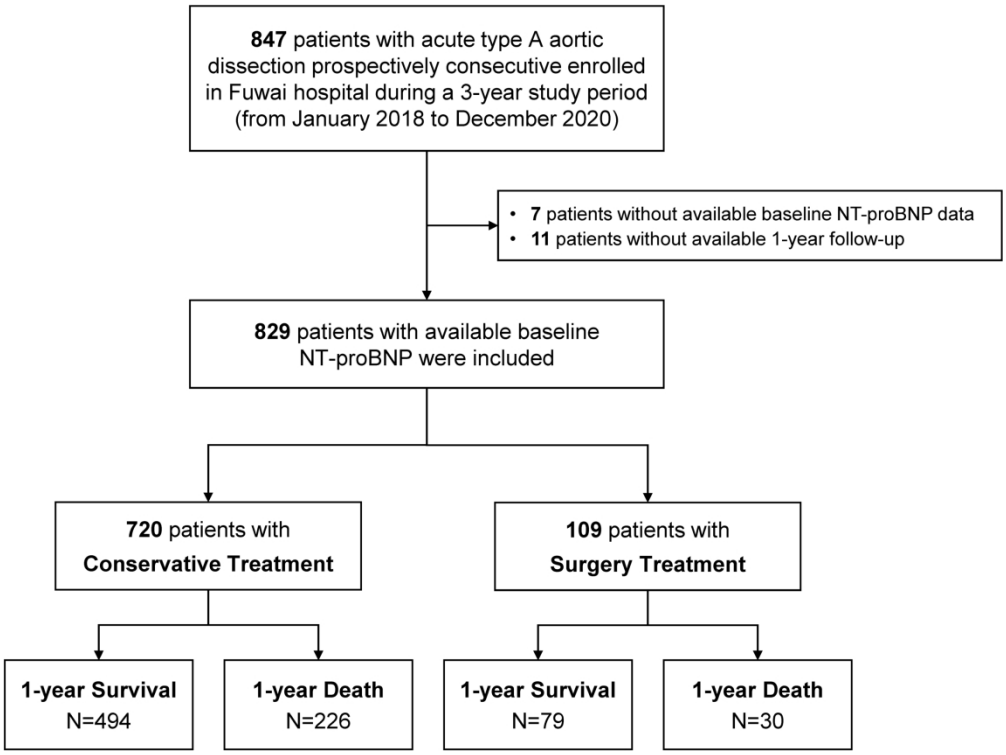

Figure 1

224x167mm (300 x 300 DPI)

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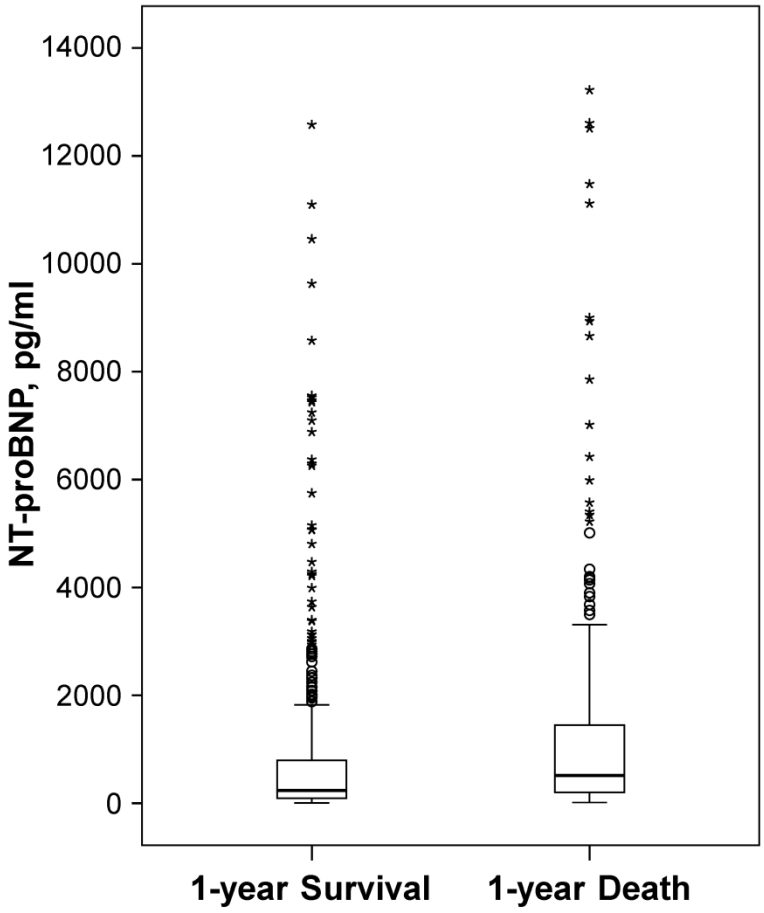

NT-proBNP (pg/ml)		
Group	Median	IQR
1-year Survival	236.3	90.9 to 794.0
1-year Death	517.2	200.2 to 1448.9

Fugure 2

117x173mm (600 x 600 DPI)

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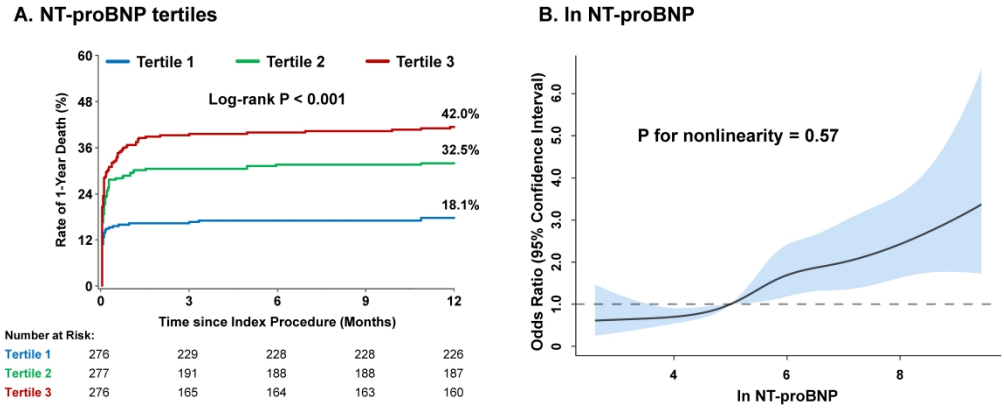

Fugure 3

315x125mm (600 x 600 DPI)

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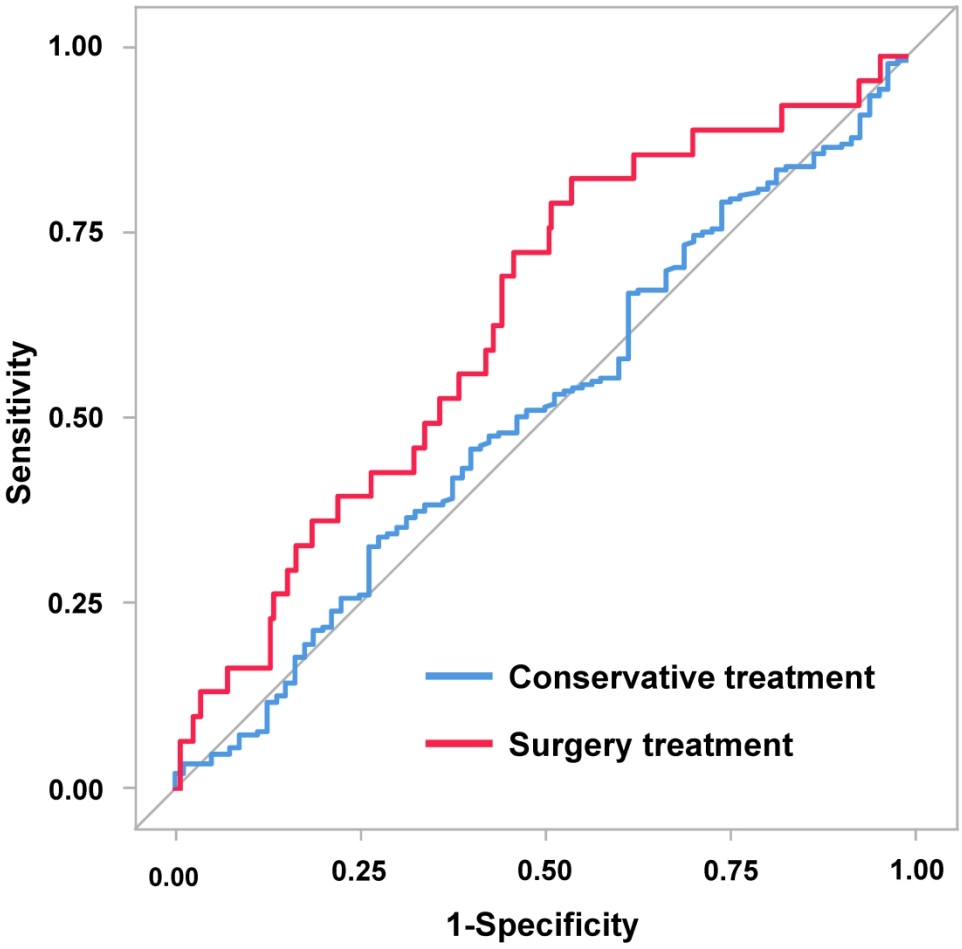

	AUC (95% CI)	Difference in AUC (95% CI)	P value
Conservative	0.51 (0.44-0.59)	Reference	-
Surgery	0.64 (0.54-0.74)	0.13 (0.01-0.25)	0.04

Fugure 4

143x179mm (600 x 600 DPI)

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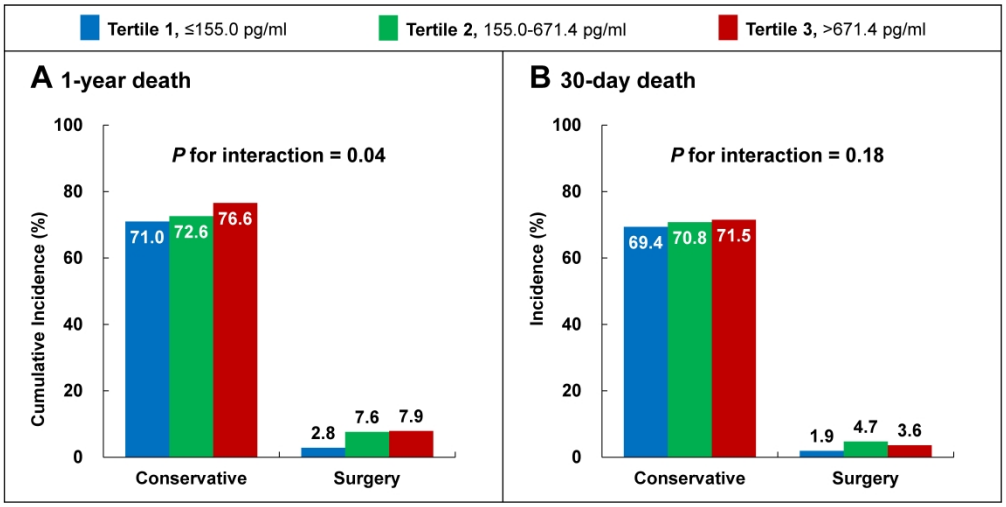

Figure 5

317x158mm (600 x 600 DPI)

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Supplementary Information

Clinical implication of N-terminal pro-B type natriuretic peptide to predict mortality in patients with acute type A aortic dissection: a retrospective cohort study

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Table S1. Patient Characteristics According to the 1-year Survival

	Total (N=829)	1-year Survival (N=573)	1-year Death (N=256)
Baseline Characteristics			
Age, yrs	55.1 ± 13.1	53.4 ± 12.3	59.0 ± 14.0
Male	587 (70.8)	416 (72.6)	171 (66.8)
Heart rate	79.4 ± 18.1	79.0 ± 17.3	80.4 ± 20.0
Admission SBP (mmHg)	144.5 ± 31.9	150.0 ± 29.4	132.9 ± 34.0
Admission DBP (mmHg)	77.3 ± 19.8	79.2 ± 19.9	73.1 ± 19.2
Diabetes mellitus	40 (4.8)	24 (4.2)	16 (6.3)
Hypertension	690 (83.2)	490 (85.5)	200 (78.1)
Hyperlipidemia	180 (21.7)	134 (23.4)	46 (18.0)
Smoking	264 (31.8)	217 (37.9)	47 (18.4)
Coronary artery disease	123 (14.8)	81 (14.1)	42 (16.4)
Previous stroke	63 (7.6)	45 (7.9)	18 (7.0)
Previous aortic disease	22 (2.7)	14 (2.4)	8 (3.1)
Previous replacement of aorta valve	12 (1.4)	7 (1.2)	5 (2.0)
Syncope	61 (7.4)	31 (5.4)	30 (11.7)
Coma	14 (1.7)	1 (0.2)	13 (5.1)
Shock	35 (4.2)	0 (0)	35 (13.7)
Time from onset to admission, hrs	12.0 (7.0-24.0)	13.0 (7.0-30.0)	9.0 (6.0-19.0)
In-hospital assessment			
Left ventricular diameter, mm	49.9 ± 7.4	50.6 ± 6.6	48.4 ± 8.8
Left ventricular ejection fraction, %	58.8 ± 7.7	59.7 ± 6.0	56.4 ± 10.3
Aortic valve regurgitation	210 (25.4)	138 (24.1)	72 (28.5)
Pericardial effusion	61 (7.4)	21 (3.7)	40 (15.8)

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Artery affected			
Coronary artery	213 (27.0)	136 (23.8)	77 (35.5)
Brachiocephalic trunk	522 (66.2)	358 (62.6)	164 (75.6)
Coeliac axis	227 (28.8)	155 (27.1)	72 (33.2)
Superior mesenteric artery	198 (25.1)	138 (24.1)	60 (27.6)
Renal artery	211 (26.7)	139 (24.3)	72 (33.2)
Iliac artery	298 (37.8)	209 (36.5)	89 (41.0)
Baseline biomarkers			
NT-proBNP, pg/ml	308.0 (104.8-974.5)	236.3 (90.9-796.0)	7.2 (199.2-1453.9)
ln NT-proBNP	5.8 ± 1.6	5.6 ± 1.6	6.3 ± 1.5
Haemoglobin, g/dl	134.8 ± 19.2	135.6 ± 18.2	133.0 ± 21.2
D-dimers, mg/l	10.9 (3.8-20.0)	7.8 (2.8-20.0)	20.0 (8.8-20.0)
Creatinine, umol/L	110.9 ± 58.2	99.0 ± 41.4	137.6 ± 78.1
C-reactive protein, mg/l	11.4 (4.6-53.2)	12.8 (5.0-66.2)	8.9 (4.2-31.3)
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0.02)	0.03 (0-0.19)
Treatment			
Conservative treatment	305 (36.8)	79 (13.8)	226 (88.3)
Surgery treatment	524 (63.2)	494 (86.2)	30 (11.7)

Values are median (IQR) or n (%).
Abbreviations as in Table 1.

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Table S2. Patient Characteristics According to the 30-day Survival

	Total (N=829)	30-day Survival (N=596)	30-day Death (N=233)
Baseline Characteristics			
Age, yrs	55.1 ± 13.1	53.7 ± 12.5	58.6 ± 13.9
Male	587 (70.8)	430 (72.1)	157 (67.4)
Heart rate	79.4 ± 18.1	78.9 ± 17.1	80.5 ± 20.5
Admission SBP (mmHg)	144.5 ± 31.9	149.2 ± 29.6	132.5 ± 34.4
Admission DBP (mmHg)	77.3 ± 19.8	78.9 ± 19.8	73.2 ± 19.4
Diabetes mellitus	40 (4.8)	26 (4.4)	14 (6.0)
Hypertension	690 (83.2)	508 (85.2)	182 (78.1)
Hyperlipidemia	180 (21.7)	139 (23.3)	41 (17.6)
Smoking	264 (31.8)	221 (37.1)	43 (18.5)
Coronary artery disease	123 (14.8)	83 (13.9)	40 (17.2)
Previous stroke	63 (7.6)	47 (7.9)	16 (6.9)
Previous aortic disease	22 (2.7)	14 (2.3)	8 (3.4)
Previous replacement of aorta valve	12 (1.4)	8 (1.3)	4 (1.7)
Syncope	61 (7.4)	31 (5.2)	30 (12.9)
Coma	14 (1.7)	1 (0.2)	13 (5.6)
Shock	35 (4.2)	0 (0)	35 (15.0)
Time from onset to admission, hrs	12.0 (7.0-24.0)	13.0 (7.0-30.0)	9.0 (6.0-18.0)
In-hospital assessment			
Left ventricular diameter, mm	49.9 ± 7.4	50.5 ± 6.6	48.4 ± 9.0
Left ventricular ejection fraction, %	58.8 ± 7.7	59.7 ± 5.9	56.0 ± 10.7
Aortic valve regurgitation	210 (25.4)	145 (24.3)	65 (28.3)
Pericardial effusion	61 (7.4)	21 (3.5)	40 (17.4)

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Artery affected			
Coronary artery	213 (27.0)	144 (24.2)	69 (35.6)
Brachiocephalic trunk	522 (66.2)	375 (63.0)	147 (75.8)
Coeliac axis	227 (28.8)	164 (27.6)	63 (32.5)
Superior mesenteric artery	198 (25.1)	143 (24.0)	55 (28.4)
Renal artery	211 (26.7)	148 (24.9)	63 (32.5)
Iliac artery	298 (37.8)	218 (36.6)	80 (41.2)
Baseline biomarkers			
NT-proBNP, pg/ml	308.0 (104.8-974.5)	245.7 (91.3-841.3)	792.0 (193.4-1489.0)
ln NT-proBNP	5.8 ± 1.6	5.6 ± 1.6	6.3 ± 1.5
Haemoglobin, g/dl	134.8 ± 19.2	135.2 ± 18.9	133.8 ± 19.7
D-dimers, mg/l	10.9 (3.8-20.0)	8.0 (2.9-20.0)	20.0 (8.2-20.0)
Creatinine, umol/L	110.9 ± 58.2	99.3 ± 41.6	140.5 ± 80.1
C-reactive protein, mg/l	11.4 (4.6-53.2)	12.9 (5.0-68.6)	8.9 (4.2-29.5)
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0.02)	0.03 (0-0.17)
Treatment			
Conservative treatment	305 (36.8)	89 (14.9)	216 (92.7)
Surgery treatment	524 (63.2)	507 (85.1)	17 (7.3)

Values are median (IQR) or n (%).

SBP, stress blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-B type natriuretic peptide.

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Table S3. Association Between NT-proBNP and Clinical Outcome.

	1-Year death			30-Day death		
	No. of events/total patients (%)*	Hazard ratio (95% CI)	*P* value	No. of events/total patients (%)*	Odds ratio (95% CI)	*P* value
ln NT-proBNP	–	1.24 (1.15-1.34)	<0.001	–	1.32 (1.19-1.46)	<0.001
NT-proBNP tertiles						
T1 (≤155.0)	50/276 (18.1)	Reference	–	47/276 (17.0)	Reference	–
T2 (155.0-671.4)	90/277 (32.5)	1.91 (1.35-2.69)	<0.001	83/277 (30.0)	2.08 (1.39-3.13)	<0.001
T3 (>671.4)	116/276 (42.0)	2.56 (1.84-3.57)	<0.001	103/276 (37.3)	2.90 (1.95-4.32)	<0.001

*Values are Kaplan-Meier estimated rates.

CI, confidence interval.

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Table S4. Patient Characteristics and Outcomes According to the Treatment Strategy

	Total (N=829)	Conservative (N=305)	Surgery (N=524)
Baseline Characteristics			
Age, yrs	55.1 ± 13.1	53.7 ± 12.5	58.6 ± 13.9
Male	587 (70.8)	202 (66.2)	385 (73.5)
Heart rate	79.4 ± 18.1	81.1 ± 20.4	78.5 ± 16.6
Admission SBP (mmHg)	144.5 ± 31.9	137.9 ± 33.8	148.3 ± 30.0
Admission DBP (mmHg)	77.3 ± 19.8	75.3 ± 19.4	78.4 ± 20.0
Diabetes mellitus	40 (4.8)	14 (4.6)	26 (5.0)
Hypertension	690 (83.2)	249 (81.6)	441 (84.2)
Hyperlipidemia	180 (21.7)	57 (18.7)	123 (23.5)
Smoking	264 (31.8)	55 (18.0)	209 (39.9)
Coronary artery disease	123 (14.8)	52 (17.0)	71 (13.5)
Previous stroke	63 (7.6)	28 (9.2)	35 (6.7)
Previous aortic disease	22 (2.7)	11 (3.6)	22 (2.7)
Previous replacement of aorta valve	12 (1.4)	7 (2.3)	5 (1.0)
Syncope	61 (7.4)	34 (11.1)	27 (5.2)
Coma	14 (1.7)	13 (4.3)	1 (0.2)
Shock	35 (4.2)	35 (15.0)	0 (0)
Time from onset to admission, hrs	12.0 (7.0-24.0)	10.0 (6.0-24.0)	13.0 (7.0-24.5)
In-hospital assessment			
Left ventricular diameter, mm	49.9 ± 7.4	48.7 ± 8.5	50.6 ± 6.7
Left ventricular ejection fraction, %	58.8 ± 7.7	56.4 ± 10.4	60.1 ± 5.2
Aortic valve regurgitation	210 (25.4)	77 (25.5)	133 (25.4)
Pericardial effusion	61 (7.4)	42 (13.9)	19 (3.6)

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Artery affected			
Coronary artery	213 (27.0)	82 (30.9)	131 (25.0)
Brachiocephalic trunk	522 (66.2)	183 (69.1)	339 (64.7)
Coeliac axis	227 (28.8)	85 (32.1)	142 (27.1)
Superior mesenteric artery	198 (25.1)	67 (25.3)	131 (25.0)
Renal artery	211 (26.7)	75 (28.3)	36 (26.0)
Iliac artery	298 (37.8)	95 (35.8)	203 (38.7)
Baseline biomarkers			
NT-proBNP, pg/ml	308.0 (104.8-974.5)	524.9 (192.6-1490.5)	227.9 (82.9-722.3)
ln NT-proBNP	5.8 ± 1.6	6.3 ± 1.5	5.5 ± 1.5
Haemoglobin, g/dl	134.8 ± 19.2	131.8 ± 21.1	136.6 ± 17.8
D-dimers, mg/l	10.9 (3.8-20.0)	16.6 (6.3-20.0)	8.2 (2.9-20.0)
Creatinine, umol/L	110.9 ± 58.2	131.3 ± 75.4	99.0 ± 40.9
C-reactive protein, mg/l	11.4 (4.6-53.2)	10.0 (4.7-50.0)	11.9 (4.5-54.2)
Troponin I (TnI), ng/ml	0 (0-0.04)	0 (0-0.13)	0 (0-0.02)
Clinical Outcomes			
1-year death	256 (30.9)	226 (74.1)	30 (5.7)
30-day death	233 (28.1)	216 (70.8)	17 (3.2)

Values are median (IQR) or n (%).

Abbreviations as in Table 1.

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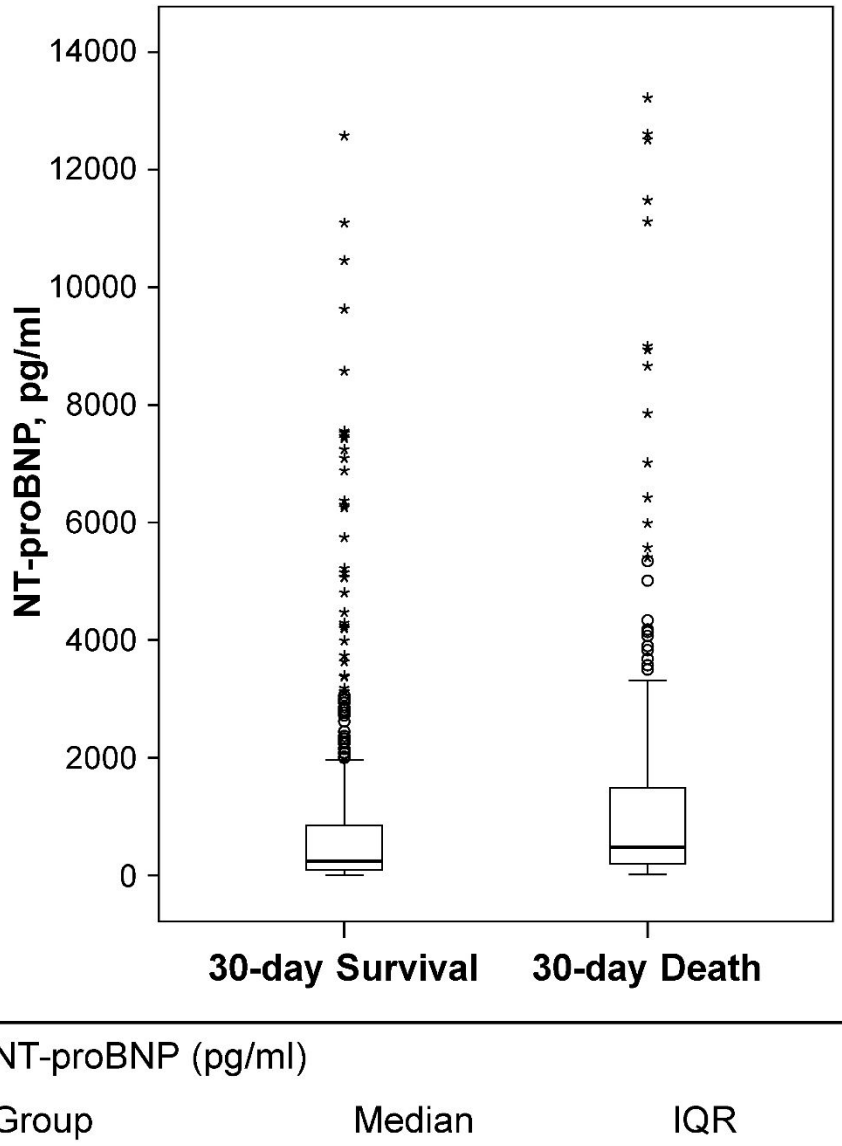
Figure S1. Baseline NT-proBNP as a predictor of 30-day outcome

Abbreviations as in Figure 1.



NT-proBNP (pg/ml)		
Group	Median	IQR
30-day Survival	248.0	91.5 to 846.5
30-day Death	482.0	195.7 to 1489.0

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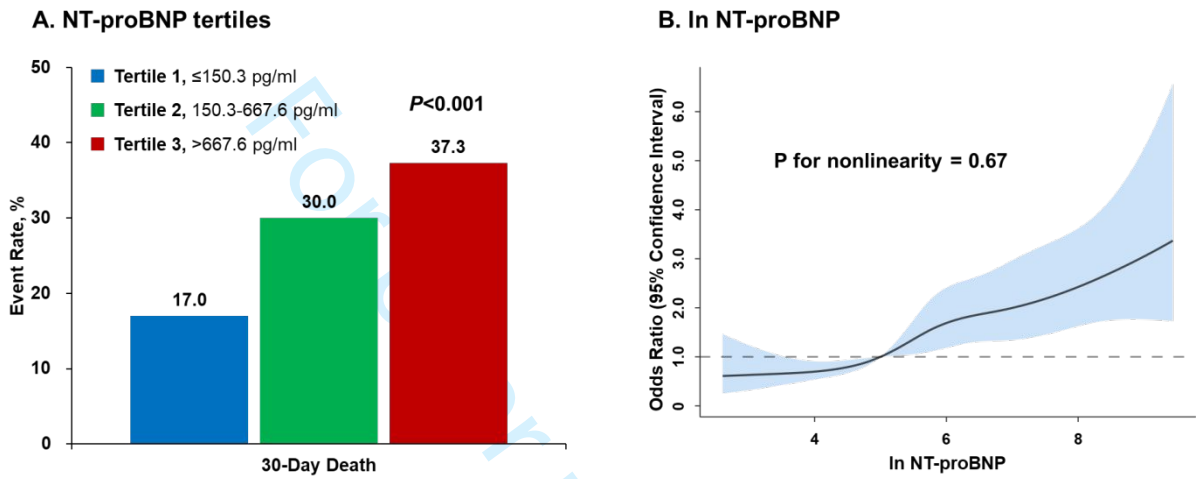
Figure S2. Death within 30 days from admission according to NT-proBNP levels

Incidence of 30-day all-cause death is presented according to (A) NT-proBNP tertiles and (B) continuous value of ln NT-proBNP among patients with acute type A aortic dissection.

CI, confidence interval; OR, odds ratio; other abbreviations as in Figure 1.



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