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Using preoperative N-terminal pro-B-type natriuretic peptide levels for predicting major adverse cardiovascular events and myocardial injury after noncardiac surgery in Chinese advanced-age patients

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ABSTRACT

BACKGROUND N-terminal pro-B-type natriuretic peptide (NT-proBNP) is often viewed as an indicator for heart failure. However, the prognostic association and the predictive utility of NT-proBNP for postoperative major adverse cardiovascular events (MACEs) and myocardial injury after noncardiac surgery (MINS) among older patients are unclear.

METHODS In this study, we included 5033 patients aged 65 years or older who underwent noncardiac surgery with preoperative NT-proBNP recorded. Logistic regression was adopted to model the associations between preoperative NT-proBNP and the risk of MACEs and MINS. The receiver operating characteristic curve was used to determine the predictive value of NT-proBNP.

RESULTS A total of 5033 patients were enrolled, 63 patients (1.25%) and 525 patients (10.43%) had incident postoperative MACEs and MINS, respectively. Analysis of the receiver operating characteristic curve indicated that the cutoff values of ln (NT-proBNP) for MACEs and MINS were 5.16 (174 pg/mL) and 5.30 (200 pg/mL), respectively. Adding preoperative ln (NT-proBNP) to the Revised Cardiac Risk Index score and the Cardiac and Stroke Risk Model boosted the area under the receiver operating characteristic curves from 0.682 to 0.726 and 0.787 to 0.804, respectively. The inclusion of preoperative NT-proBNP in the prediction models significantly increased the reclassification and discrimination.

CONCLUSIONS Increased preoperative NT-proBNP was associated with a higher risk of postoperative MACEs and MINS. The inclusion of NT-proBNP enhances the predictive ability of the preexisting models.

More than 300 million surgical procedures are performed globally each year with the rapid growth of the elderly surgical population.[1] Prior studies suggested that perioperative major adverse cardiovascular events (MACEs) occurred in 2% to 8% of all patients and were attributed to one-third of postoperative deaths.[2,3] Acute myocardial infarction (AMI) and stroke are the leading causes of MACE-induced deaths.[4] Myocardial injury after noncardiac surgery (MINS) is a complication that develops insidiously and is strongly associated with adverse short-term and long-term prognoses.[5] Additionally, because the cardiovascular systems are more fragile in older patients, they have a much higher perioperative cardiovascular risk, which requires more attention.[6] Prevention is more important than the treatment of perioperative cardiovascular complications. Previous studies have developed prediction models to assess the risk of postoperative cardiovascular complications, such as the Revised Cardiac Risk Index (RCRI) and the Cardiac and Stroke Risk Model (CSRM).[7,8] However, these pre-

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dictive models perform unfavorably in older Chinese noncardiac surgery patients.[9,10] Therefore, a more precise prediction tool for postoperative cardiovascular complications among older patients is needed.

Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) is considered to be a widely used biomarker in heart failure similar to B-type natriuretic peptide, and it is also upregulated in myocardial ischemia, arrhythmias, infections and renal insufficiency with decreased clearance.[11,12] In recent years, an increasing number of studies have been conducted to explore the predictive capability of NT-proBNP in postoperative complications.[13,14] Verwijmeren, *et al.*[15] found that it could be a strong preoperative indicator for acute kidney injury after cardiac surgery. Another prospective study indicated that preoperative NT-proBNP had better predictive performance of postoperative atrial fibrillation compared with other conventional prognostic factors in noncardiac surgery.[16] The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study found that preoperative NT-proBNP was associated with MINS, myocardial infarction, vascular death, and overall mortality.[17] However, there is still a lack of studies on NT-proBNP and cardiovascular complications after noncardiac surgery in older Chinese patients.

In this study, we aimed to determine the threshold value of preoperative NT-proBNP for predicting the occurrence of MACEs and MINS within 30 postoperative days and to evaluate the predictive capability of NT-proBNP for MACEs and MINS in Chinese advanced-age patients undergoing noncardiac surgery.

METHODS

Study Design and Population

The Ethics Committee Board of the First Medical Centre, Chinese PLA General Hospital, Beijing, China reviewed and approved this study (No.S2019-311-02). Informed consent was waived since this single-center retrospective cohort study posed minimal risk to all patients.

The included patients were inpatients of noncardiac surgery under nonlocal anesthesia and aged ≥ 65 years between January 1, 2017 and August 1, 2019 in the First Medical Centre, Chinese PLA General Hospital, Beijing, China. Patients' information was collected anonymously from the medical records database of the hospital. The exclusion criteria were as follows: (1) American Society of Anesthesiologists grade V; (2) low-risk surgery (hysteroscopic and body surface surgery);[18] (3) length of surgery ≤ 30 min; (4) short operation interval (less than three days between procedures); (5) missing data on patient characteristics; and (6) no NT-proBNP measurement seven days before surgery.

Data Acquisition

The analyzed variables of eligible patients fall into several categories, including demographic characteristics, medical history, perioperative laboratory results, pharmacological exposures, surgery-related information, and postoperative complications, such as age, sex, body mass index, smoking, drinking status, and previous history of cardiovascular and other diseases (Table 1). Surgery-related information included facility, American Society of Anesthesiologists grade, surgery duration, blood loss, crystalloid infusion, duration of intraoperative hypotension, and surgical specialty. Intraoperative hypotension was defined as a mean arterial pressure of < 65 mmHg for at least one minute.[19]

Primary Outcome

The primary outcome was MACEs occurring 30 days after noncardiac surgery. MACEs include death, AMI, and ischemic stroke.[20] Patients with postoperative MACEs were identified by extracting the corresponding information from patients' medical records. For data elements in patients' medical records, we used structured query language, a standard language for storing, manipulating, and retrieving data in databases, to find instances of data domains. We extracted the patients' postoperative biochemical tests, electrocardiograms, coronary angiograms, postoperative course descriptions, and consultation records to diagnose MACEs. A patient could have more than one MACE. The complications were independently evaluated by three experienced doctors. If there was any dispute, they discussed it and solved it through negotiation.

AMI was defined as acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of an increase or decrease in cTn val-

Table 1 Baseline characteristics of the patients with and without MACEs and MINS.

Variables	Primary outcome			Secondary outcome		
	Non-MACEs (*n* = 4970)	MACEs (*n* = 63)	*P*-value	Non-MINS (*n* = 4508)	MINS (*n* = 525)	*P*-value
Age, yrs	70.91 ± 5.13	71.62 ± 5.29	0.274	70.68 ± 4.95	72.95 ± 6.10	< 0.001
Female	2380 (47.89%)	22 (34.92%)	0.041	2185 (48.47%)	217 (41.33%)	0.002
Body mass index, kg/m^2	24.37 ± 3.59	24.17 ± 3.17	0.651	24.4 ± 3.55	24.1 ± 3.91	0.086
Smoking			0.009			0.238
Never smoker	3823 (76.92%)	40 (63.49%)		3464 (76.84%)	399 (76.00%)	
Former smoker	574 (11.55%)	15 (23.81%)		527 (11.69%)	54 (10.29%)	
Current smoker	573 (11.53%)	8 (12.70%)		517 (11.47%)	72 (13.71%)	
Drinking			0.011			0.406
Never drinker	3856 (77.59%)	40 (63.49%)		3490 (77.42%)	406 (77.33%)	
Former drinker	349 (7.02%)	10 (15.87%)		703 (15.59%)	75 (14.29%)	
Current drinker	765 (15.39%)	13 (20.63%)		315 (6.99%)	44 (8.38%)	
Hypertension	2268 (45.63%)	35 (55.56%)	0.116	2042 (45.30%)	261 (49.71%)	0.055
Cerebrovascular disease	398 (8.01%)	15 (23.81%)	< 0.001	339 (7.52%)	74 (14.10%)	< 0.001
Diabetes mellitus	1247 (25.09%)	19 (30.16%)	0.357	1122 (24.89%)	144 (27.43%)	0.204
Coronary artery disease	647 (13.02%)	22 (34.92%)	< 0.001	555 (12.31%)	114 (21.71%)	< 0.001
Cardiac intervention	191 (3.84%)	10 (15.87%)	< 0.001	156 (3.46%)	45 (8.57%)	< 0.001
Arrhythmia	547 (11.0%)	8 (12.7%)	0.670	460 (10.2%)	95 (18.1%)	< 0.001
Valvular heart disease	28 (0.56%)	0	> 0.999	23 (0.51%)	5 (0.95%)	0.328
Congestive heart failure	15 (0.30%)	4 (6.35%)	< 0.001	6 (0.13%)	13 (2.48%)	< 0.001
Chronic obstructive pulmonary disease	112 (2.25%)	1 (1.59%)	> 0.999	100 (2.22%)	13 (2.48%)	0.706
Renal insufficiency	79 (1.59%)	1 (1.59%)	> 0.999	71 (1.57%)	9 (1.71%)	0.809
Peripheral artery disease	73 (1.47%)	4 (6.35%)	0.015	65 (1.44%)	12 (2.29%)	0.136
Pre-hemoglobin, g/dL	126.82 ± 17.95	118.24 ± 23.15	0.005	127.36 ± 17.61	121.14 ± 20.65	< 0.001
Pre-hematocrit, %	0.38 (0.34–0.41)*	0.35 (0.31–0.39)*	< 0.001	0.38 (0.35–0.41)*	0.36 (0.32–0.40)*	< 0.001
Pre-serum creatine, mg/dL	69.3 (59.0–81.3)*	69.9 (62.1–80.5)*	0.528	68.9 (59.0–80.5)*	73.3 (59.6–89.5)*	< 0.001
Pre-blood glucose, mmol/L	5.90 ± 1.96	6.30 ± 2.16	0.104	5.84 ± 1.86	6.48 ± 2.59	< 0.001
Pre-sodium, mmol/L	140.98 ± 3.27	138.86 ± 4.12	< 0.001	141.12 ± 3.13	139.52 ± 4.22	< 0.001
Pre-fibrinogen, g/L	3.68 ± 1.10	4.00 ± 1.28	0.020	3.65 ± 1.07	3.94 ± 1.31	< 0.001
Pre-NT-proBNP, pg/mL	89.6 (49.1–176.1)*	175.8 (76.3–349.4)*	< 0.001	86.2 (47.7–165.2)*	155.7 (73.4–387.3)*	< 0.001
Pre-ln (NT-proBNP)	4.59 ± 1.05	5.15 ± 1.25	0.001	4.53 ± 1.01	5.18 ± 1.22	< 0.001
Angiotensin-converting enzyme inhibitors	169 (3.40%)	4 (6.35%)	0.353	154 (3.42%)	19 (3.62%)	0.809
Angiotensin receptor blocker	546 (10.99%)	8 (12.70%)	0.666	482 (10.69%)	72 (13.71%)	0.036
Statin	307 (6.18%)	8 (12.70%)	0.063	275 (6.10%)	40 (7.62%)	0.174
Diuretic	305 (6.14%)	9 (14.29%)	0.017	254 (5.63%)	60 (11.43%)	< 0.001
Anticoagulant	508 (10.22%)	16 (25.40%)	< 0.001	445 (9.87%)	79 (15.05%)	< 0.001
Antiplatelet	445 (8.95%)	8 (12.70%)	0.302	384 (8.52%)	69 (13.14%)	< 0.001
Beta-blockers	477 (9.60%)	8 (12.70%)	0.407	410 (9.09%)	75 (14.29%)	< 0.001
Calcium channel blocker	1311 (26.38%)	18 (28.57%)	0.695	1192 (26.44%)	137 (26.10%)	0.865
American Society of Anesthesiologists			< 0.001			< 0.001
I	52 (1.05%)	1 (1.59%)		47 (1.04%)	6 (1.14%)	

Continued

Variables	Primary outcome			Secondary outcome		
	Non-MACEs (*n* = 4970)	MACEs (*n* = 63)	*P*-value	Non-MINS (*n* = 4508)	MINS (*n* = 525)	*P*-value
II	3799 (76.44%)	27 (42.86%)		3547 (78.68%)	279 (53.14%)	
III	1059 (21.31%)	31 (49.21%)		884 (19.61%)	206 (39.24%)	
IV	60 (1.21%)	4 (6.35%)		30 (0.67%)	34 (6.48%)	
Facility (urgent)	193 (3.88%)	7 (11.11%)	0.009	136 (3.02%)	64 (12.19%)	< 0.001
Revised Cardiac Risk Index high risk surgery	3063 (61.6%)	44 (69.8%)	0.229			
Surgery duration, per hour	2.5 (1.67–3.58)*	3.47 (1.92–4.58)*	< 0.001	2.42 (1.61–3.50)*	3.23 (2.05–4.55)*	< 0.001
Surgical speciality			< 0.001			< 0.001
Other abdominal surgery	327 (6.6%)	1 (1.6%)		301 (6.7%)	26 (5.0%)	
Ear, nose, throat	55 (1.1%)	2 (3.2%)		51 (1.1%)	6 (1.1%)	
Bariatric, stomach, esophagus	497 (10.0%)	13 (20.6%)		439 (9.7%)	71 (13.5%)	
Brain	93 (1.9%)	4 (6.3%)		76 (1.7%)	21 (4.0%)	
Intestine (not rectum)	330 (6.6%)	2 (3.2%)		292 (6.5%)	40 (7.6%)	
Liver, pancreas, spleen	1535 (30.9%)	17 (27.0%)		1388 (30.8%)	164 (31.2%)	
Obstetrics, gynecology, breast	79 (1.6%)	1 (1.6%)		79 (1.8%)	1 (0.2%)	
Orthopedic (lower extremity, pelvis)	971 (19.5%)	9 (14.3%)		883 (19.6%)	97 (18.5%)	
Orthopedic (upper extremity, shoulder)	44 (0.9%)	0		44 (1.0%)	0	
Spine	447 (9.0%)	3 (4.8%)		421 (9.3%)	29 (5.5%)	
Thoracic (non-esophageal)	201 (4.0%)	0		188 (4.2%)	13 (2.5%)	
Urology	263 (5.3%)	5 (7.9%)		240 (5.3%)	29 (5.5%)	
Vascular (carotid endarterectomy)	4 (0.1%)	1 (1.6%)		0	3 (0.6%)	
Vascular (aorta)	14 (0.3%)	1 (1.6%)		10 (0.2%)	5 (1.0%)	
Vascular (thoracic endovascular aneurysm repair)	0	1 (1.6%)		3 (0.1%)	0	
Vascular (endovascular aneurysm repair)	18 (0.4%)	2 (3.2%)		17 (0.4%)	3 (0.6%)	
Vascular (other)	45 (0.9%)	1 (1.6%)		34 (0.8%)	12 (2.3%)	
Other surgery	47 (0.9%)	0		42 (0.9%)	5 (1.0%)	
Colloid infusion, mL/kg per hour	2.31 (0–3.84)*	2.4 (1.23–4.21)*	0.278	2.25 (0–3.82)*	2.67 (1.36–4.06)*	< 0.001
Crystalloid infusion, mL/kg per hour	10.25 (7.71–13.57)*	9.28 (6.55–12.20)*	0.032	10.31 (7.76–13.68)*	9.78 (7.36–12.68)*	0.001
Urine volume, mL	300 (100–600)*	300 (100–800)*	0.097	300 (100–600)*	400 (200–600)*	< 0.001
Blood loss, mL	100 (50–200)*	200 (100–500)*	< 0.001	100 (50–200)*	200 (100–400)*	< 0.001
Duration of hypotension, min	10 (0–20)*	20 (5–45)*	0.001	10 (0–20)*	15 (5–35)*	< 0.001
Intraoperative hypoxemia	1121 (22.56%)	10 (15.87%)	0.207	999 (22.16%)	132 (25.14%)	0.121

Data are presented as means ± SD or *n* (%). *Presented as median (interquartile range). MACEs: major adverse cardiovascular events; MINS: myocardial injury after noncardiac surgery; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

ues with at least one value above the 99th percentile upper reference limit and at least one of the following: (1) symptoms of myocardial ischemia; (2) new ischemic electrocardiogram changes; (3) development of pathological Q waves; (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; and (5) identification of a coronary thrombus by angiography or autopsy. Death was defined as any death during the 30 days after noncardiac surgery. Ischemia stroke was defined as an embolic or thrombotic event lasting at least 30 min with or without persistent residual motor, sensory, or cognitive dysfunction; if the neurological symp-

toms continued for > 24 h, a person was diagnosed with stroke.

Secondary Outcome

MINS was defined as myocardial injury due to ischemia that occurred 30 days after noncardiac surgery. MINS was defined as at least one postoperative high-sensitivity troponin T (hs-TnT) of 20–65 ng/L with an absolute change of ≥ 5 ng/L or a hs-TnT concentration ≥ 65 ng/L due to a presumed ischemic etiology regardless of the presence or absence of clinical symptoms and electrocardiographic changes.[3] Elevated hs-TnT concentrations caused by nonischemic mechanisms, including pulmonary embolism, sepsis and renal failure, cannot be considered MINS.[5] The value of postoperative hs-TnT was also extracted and judged through structured query language, which was also manually reviewed.

Statistical Analysis

Continuous variables are presented as the mean ± SD for variables with a normal distribution and the median [interquartile range (IQR)] for those variables with skewed data. Categorical variables are shown as counts (percentages). Continuous variables were compared using the independent Student's *t*-test or the Mann-Whitney *U* test. Categorical variables were analyzed using the Pearson's chi-squared test or Fisher's exact probability test. Pearson correlation analysis was applied to analyze the correlation between ln (NT-proBNP) and other clinical and biochemical indices, and an absolute value of $r < 0.5$ was considered to be weakly correlated.[21]

Univariable logistic regression analysis was performed for the potential risk factors for postoperative MACEs and MINS. The variables examined include those with statistically significant differences between groups in the univariate logistic regression analysis and variables considered significant in clinical practice. Because of the skewed distribution, a logarithmic transformation [ln (NT-proBNP)] was performed. The variables with *P*-value < 0.05 and clinically significant in the univariate logistic regression analysis were identified as potential risk factors and were adjusted in the multivariate logistic regression analysis. Regression results are presented as the odds ratio (OR) with the 95% confidence interval (CI). The optimum cutoff value of ln (NT-proBNP) was defined based on the highest diagnostic accuracy according to the receiver operating characteristic (ROC) curve.

Based on the RCRI and CSRM models, the ln (NT-proBNP) level variable was added for each of these two models for MACEs. The ROC curves of the models before and after the addition of ln (NT-proBNP) levels were plotted. The area under the curve (AUC) of ROC curve and its 95% CI were calculated to evaluate the predictive discrimination ability of each model. Additionally, the change in AUC before and after the addition of the ln (NT-proBNP) level was calculated separately. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were adopted to evaluate the predictive and discriminatory ability of the previous and enhanced models with the addition of ln (NT-proBNP) levels.

Two-sided *P*-value < 0.05 were considered statistically significant. Statistical analysis was performed using R statistical software 4.0.2 (http://www.r-proje ct.org).

RESULTS

A total of 16,521 patients aged 65 years or older who underwent noncardiac surgery were screened, and 5033 patients remained in this study. A flowchart of the exclusion process is described below and shown in Figure 1.

Overall, 63 patients (1.25%) and 525 patients (10.43%) had postoperative 30-day MACEs and MINS, respectively. There were 33 cases (0.7%) of AMI, 5 cases (0.1%) of death, and 25 cases (0.5%) of ischemic stroke in this study. Preoperative levels of NT-proBNP were positively correlated with preoperative levels of serum creatine ($r = 0.03$), fibrinogen ($r = 0.175$), and glucose ($r = 0.055$) and were negatively correlated with body mass index ($r = -0.131$), hematocrit ($r = -0.295$), and serum sodium ($r = -0.120$). The correlation between NT-proBNP and other laboratory variables was generally weaker. Patients with MACEs and MINS were more likely to have a history of cerebrovascular and cardiovascular diseases than patients who did not have MACEs and MINS. Other characteristics evaluated, including sex, smoking, and drinking status, were also significantly different between the MACEs group and non-MACEs gr-

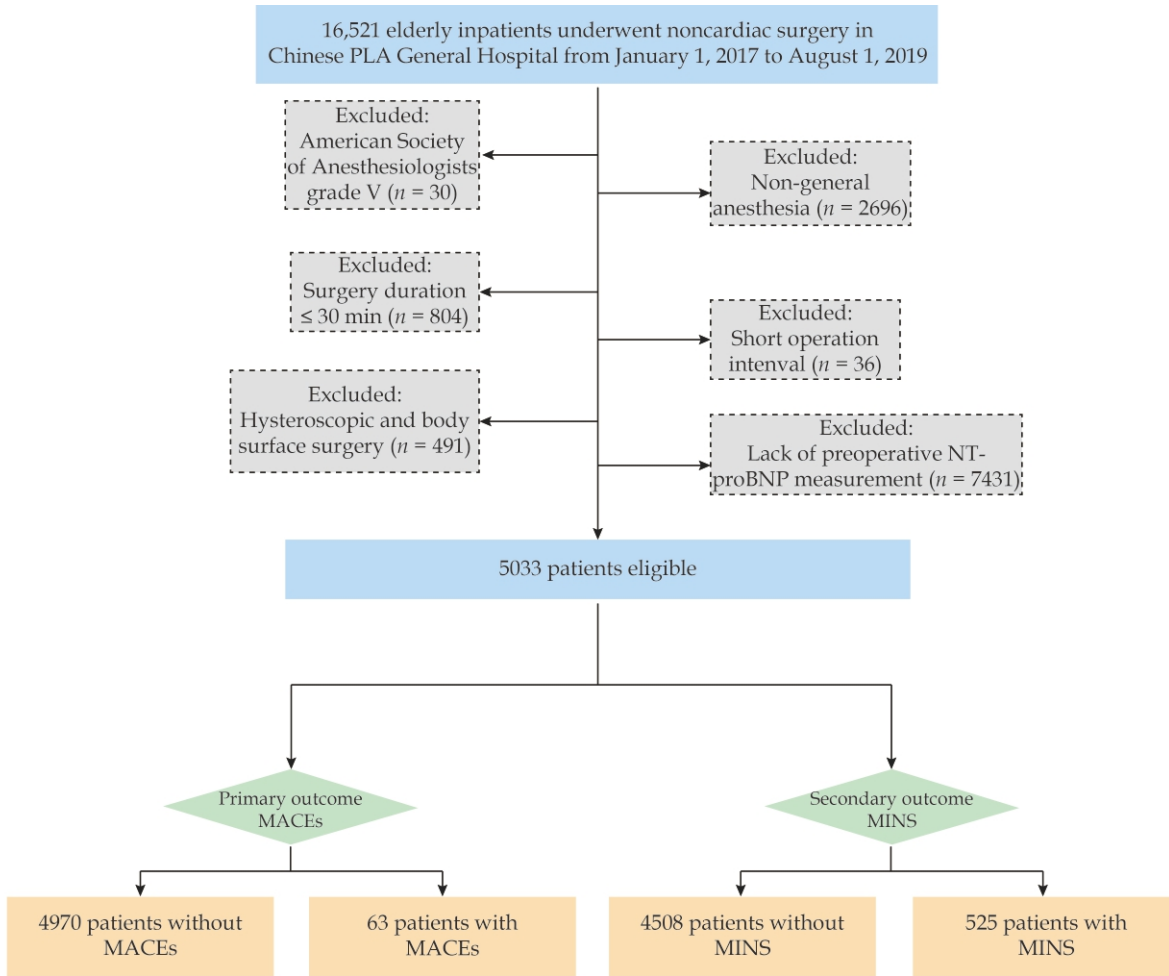

Figure 1 Flowchart of participants selection. MACEs: major adverse cardiovascular events; MINS: myocardial injury after noncardiac surgery; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

oup ($P < 0.05$). For the MINS group, the proportion of patients of higher age was significantly higher than that in the non-MINS group. The baseline characteristics of patients in the two groups with or without postoperative MACEs and MINS are presented in Table 1.

Univariate Regression Analysis and Multivariate Logistic Regression Analysis

In the results of univariate regression analysis, ln (NT-proBNP) was associated with MACEs (OR = 1.561, 95% CI: 1.267–1.923). The median level of NT-proBNP in the MACEs group was significantly increased compared with that in the non-MACEs group [175.8 (76.3–349.4) pg/mL *vs.* 89.6 (49.1–176.1) pg/mL, $P < 0.001$]. In addition to ln (NT-proBNP), other variables, such as coronary heart disease (OR = 3.585, 95% CI: 2.122–6.058), cardiac intervention (OR = 4.721, 95% CI: 2.365–9.422) and cerebrovascular disease (OR = 3.583, 95% CI: 1.963–6.542), were significantly associated with a higher rate of MACEs. ln (NT-proBNP) was also associated with MINS (OR = 1.729, 95% CI: 1.592–1.877). The median level of NT-proBNP in the MINS group was also significantly higher than that in the non-MINS group [155.7 (73.4–387.3) pg/mL *vs.* 86.2 (47.7–165.2) pg/mL, $P < 0.001$]. Patients with a history of cerebrovascular disease (OR = 2.018, 95% CI: 1.541–2.642) and coronary artery disease (OR = 1.976, 95% CI: 1.576–2.476) were more likely to experience MINS. See other details in Table 2.

Table 2 also shows risk factors for postoperative MACEs and MINS in the multivariate model. Preoperative ln (NT-proBNP) was significantly associated with postoperative MACEs (OR = 1.392, 95% CI: 1.105–1.755) and MINS (OR = 1.401, 95% CI: 1.264–1.553), respectively. In addition to ln (NT-proBNP), medi-

Table 2 Univariate and multivariate logistic regression analysis for the risk factors associated with MACEs and MINS.

Variables	MACEs			MINS		
	Univariate analysis OR (95% CI)	Multivariable analysis OR (95% CI)	*P*-value	Univariate analysis OR (95% CI)	Multivariable analysis OR (95% CI)	*P*-value
Age				1.079 (1.062–1.096)	1.057 (1.037–1.078)	< 0.001
Cerebrovascular disease	3.590 (1.992–6.468)	3.583 (1.963–6.542)	< 0.001	2.018 (1.541–2.642)	1.768 (1.284–2.434)	0.001
Coronary artery disease	3.585 (2.122–6.058)	2.981 (1.711–5.194)	< 0.001	1.976 (1.576–2.476)	1.478 (1.078–2.028)	0.015
Cardiac intervention	4.721 (2.365–9.422)			2.615 (1.853–3.692)	1.707 (1.048–2.782)	0.032
Congestive heart failure	22.395 (7.217–69.496)	10.127 (2.856–35.905)	< 0.001	19.051 (7.210–50.339)	5.509 (1.837–16.520)	0.002
Peripheral artery disease	4.548 (1.610–12.850)					
Anticoagulant	2.990 (1.683–5.312)			1.617 (1.249–2.094)		
Pre-hemoglobin	0.976 (0.963–0.988)			0.982 (0.977–0.986)		
Pre-hematocrit	1.545 (1.005–2.374)			1.470 (1.171–1.846)		
Pre-fibrinogen	1.244 (1.036–1.494)			1.235 (1.149–1.328)		
Pre-sodium	0.864 (0.816–0.914)		< 0.001			
ln (NT-proBNP)	1.561 (1.267–1.923)	1.392 (1.105–1.755)	0.005	1.729 (1.592–1.877)	1.401 (1.264–1.553)	< 0.001
Pre-serum creatine				1.012 (1.008–1.016)	1.009 (1.004–1.014)	< 0.001
Facility (urgent)	3.094 (1.392–6.877)			4.463 (3.266–6.098)	1.913 (1.218–3.005)	0.005
American Society of Anesthesiologists						
I	Reference			Reference		
II	0.370 (0.049–2.771)			0.616 (0.261–1.454)		
III	1.522 (0.204–11.368)			1.825 (0.770–4.327)		
IV	3.467 (0.376–32.000)			8.878 (3.327–23.686)		
Blood loss	1.091 (1.056–1.128)	1.001 (1.000–1.001)	0.002	1.118 (1.095–1.141)	1.001 (1.000–1.001)	< 0.001
Surgery duration	1.335 (1.179–1.512)	1.229 (1.060–1.425)	0.006	1.357 (1.288–1.430)	1.445 (1.329–1.572)	< 0.001
Crystalloid infusion	1.051 (1.024–1.078)			0.970 (0.952–0.988)	1.027 (1.004–1.050)	0.021
Duration of hypotension	1.012 (1.007–1.017)			1.012 (1.009–1.015)	1.004 (1.000–1.007)	0.042
Surgical speciality						
Other abdominal surgery	Reference			Reference		
Bariatric, stomach, esophagus	8.527 (1.110–65.497)			1.872 (1.167–3.004)		
Ear, nose, throat	11.855 (1.057–132.968)					
Brain	14.022 (1.548–126.974)			3.199 (1.708–5.992)		
Vascular (carotid endarterectomy)	81.500 (4.300–1544.650)			17.365 (2.776–108.634)		
Vascular (aorta)	23.286 (1.384–391.818)			5.788 (1.840–18.205)		
Vascular (thoracic endovascular aneurysm repair)	163.000 (7.337–3621.438)					
Vascular (endovascular aneurysm repair)	36.222 (3.135–418.462)					
Vascular (other)				4.086 (1.891–8.829)		

CI: confidence interval; MACEs: major adverse cardiovascular events; MINS: myocardial injury after noncardiac surgery; NT-proBNP: N-terminal pro-B-type natriuretic peptide; OR: odds ratio.

cal history, including congestive heart failure (OR = 10.127, 95% CI: 2.856–35.905), coronary heart disease (OR = 2.981, 95% CI: 1.711–5.194), and cerebrovascular disease (OR = 3.583, 95% CI: 1.963–6.542), significantly increased the risk of MACEs. Several intraoperative factors, including surgery duration (OR = 1.229, 95% CI: 1.060–1.425) and blood loss (OR = 1.001, 95% CI: 1.00–1.001), were also indicated to be risk factors for MACEs. On multivariate logistic regression analysis for the outcome of MINS, in addition to ln (NT-proBNP), age (OR = 1.057, 95% CI: 1.037–1.078), history of cerebrovascular disease (OR = 1.768, 95% CI: 1.284–2.434), history of coronary artery disease (OR = 1.478, 95% CI: 1.078–2.028), history of ca-

rdiac intervention (OR = 1.707, 95% CI: 1.048–2.782), history of congestive heart failure (OR = 5.509, 95% CI: 1.837–16.520), emergency surgery (OR = 1.913, 95% CI: 1.218–3.005), surgery duration (OR = 1.445, 95% CI: 1.329–1.572), crystalloid infusion (OR = 1.027, 95% CI: 1.004–1.050), serum creatine (OR = 1.009, 95% CI: 1.004–1.014) and blood loss (OR = 1.001, 95% CI: 1.000–1.001) were also risk factors for MINS.

Predictive Value of Preoperative NT-proBNP

The ROC curve indicated that the cutoff value of ln (NT-proBNP) was 5.16 (NT-proBNP = 174 pg/mL) for MACEs (Figure 2A) and 5.30 (NT-proBNP = 200 pg/mL) for MINS (Figure 2C). The incidence of MACEs and MINS based on the cutoff value of ln (NT-proBNP) is shown in Figure 2B and Figure 2D. The incidence of postoperative MACEs was 2.7% when ln (NT-proBNP) ≥ 5.16 and 1.1% when ln (NT-proBNP) < 5.16, while the incidence of MINS was 21.3% when ln (NT-proBNP) ≥ 5.30 and 7.4% when ln (NT-proBNP) < 5.30.

The ROC curves showed that the addition of NT-proBNP resulted in better fitting models for postoperative MACEs prediction (Figure 3A & 3B). For MACEs, the RCRI and CSRM were used to predict perioperative cardiovascular complications in prior studies. The RCRI showed low discriminative power (AUC = 0.682) in our study. The addition of ln (NT-proBNP)

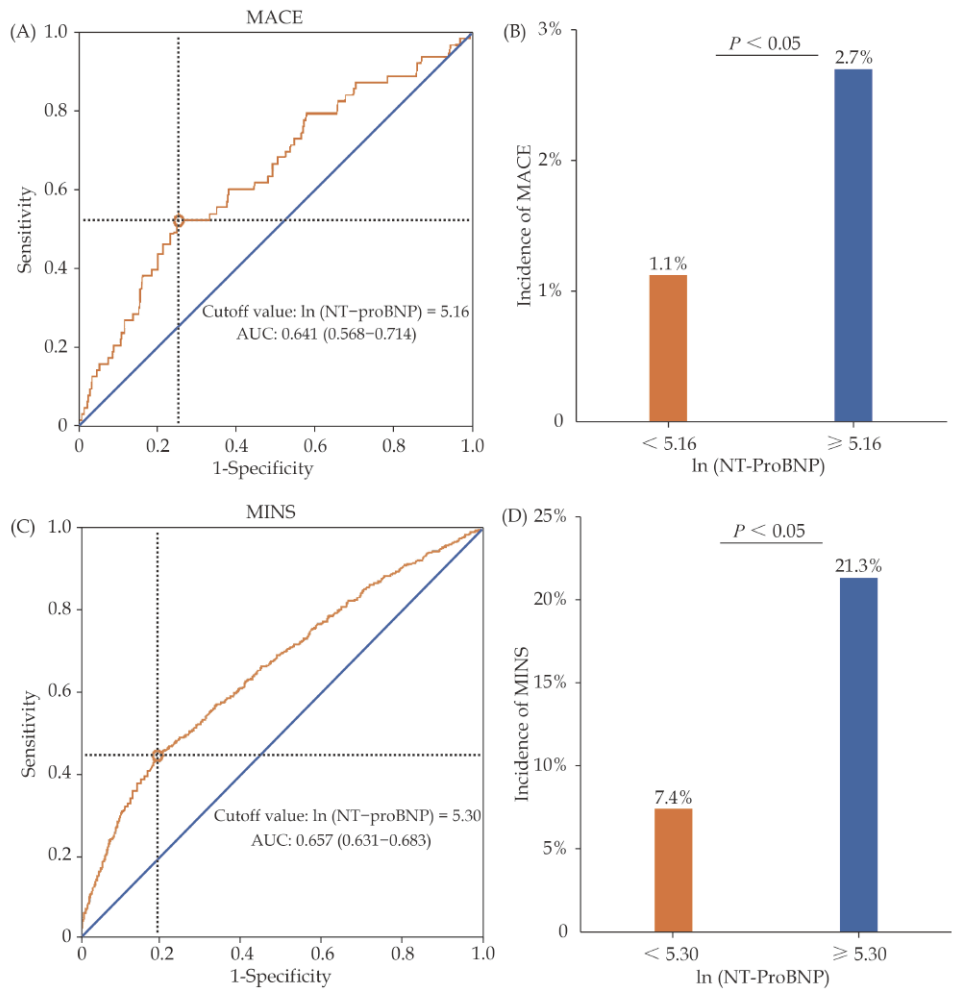

Figure 2 The relationship between ln (NT-proBNP) and postoperative MACEs and MINS. (A): The receiver operating characteristic curve for the cutoff value of ln (NT-proBNP) level and postoperative MACEs; (B): the incidence of MACEs between the two groups based on the cutoff value of ln (NT-proBNP); (C): the receiver operating characteristic curve for the cutoff value of ln (NT-proBNP) level and postoperative MINS; and (D): the incidence of MINS between the two groups based on the cutoff value of ln (NT-proBNP). MACEs: major adverse cardiovascular events; MINS: myocardial injury after noncardiac surgery; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

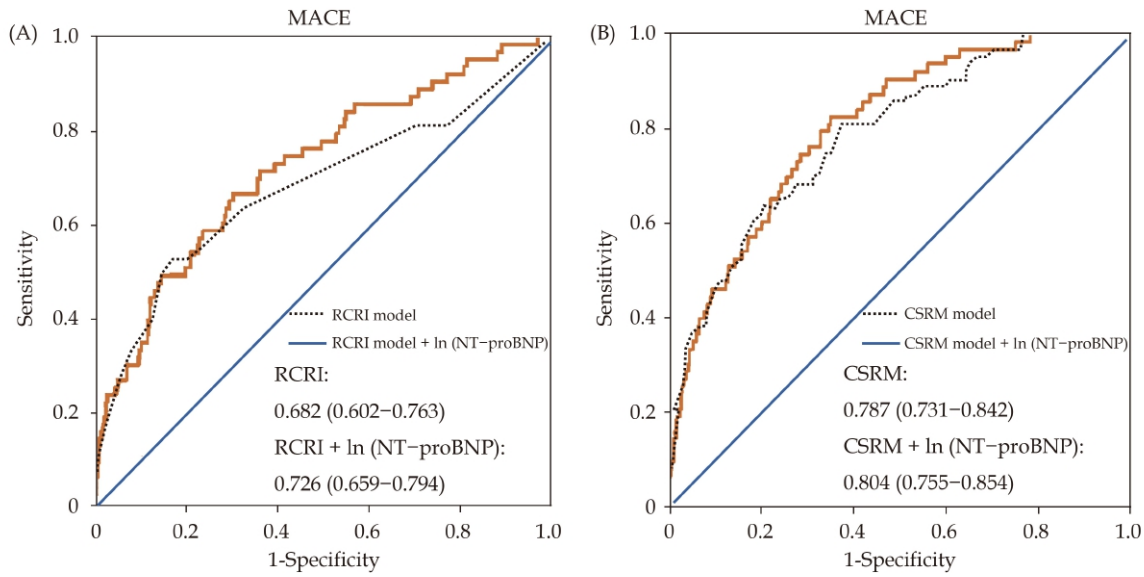

Figure 3 The AUC of receiver operating characteristic curve comparison for MACEs and MINS models with or without ln (NT-proBNP). (A): The AUC for the RCRI model with or without ln (NT-proBNP) for MACEs; and (B): the AUC for the CSRM model with or without ln (NT-proBNP) for MACEs. AUC: area under the curve; CSRM: Cardiac and Stroke Risk Model; MACEs: major adverse cardiovascular events; MINS: myocardial injury after noncardiac surgery; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RCRI: Revised Cardiac Risk Index.

improved its predictive power (AUC = 0.726). When using the CSRM model in our study, there was also a lower predictive efficiency (AUC = 0.787) compared to adding just the ln (NT-proBNP) level (AUC = 0.804). To assess the improvement of the proposed models, the NRI and IDI were further evaluated and were shown in Table 3. After adding ln (NT-proBNP) to the RCRI and CSRM, the continuous NRI increased 0.288 (-0.038–0.557) and 0.142 (-0.049–0.484), respectively.

DISCUSSION

In our study, we proved that the elevated level of preoperative NT-proBNP was an independent indicator for postoperative MACEs and MINS. Using ROC curve analysis, the level of 174 pg/mL of NT-proBNP [ln (NT-proBNP) = 5.16] and the level of 200 pg/mL of NT-proBNP [ln (NT-proBNP) = 5.30] were identified as the cutoff values to predict postoperative MACEs and MINS. Furthermore, our findings indicated the importance of NT-proBNP in optimizing postoperative MACEs risk assessments for older patients after noncardiac surgery.

In recent years, NT-proBNP has been used to predict perioperative complications. Feringa, *et al.*[22] found that NT-proBNP of ≥ 319 pg/mL could predict 6-month mortality after vascular surgery. Three observational studies have shown that preoperative NT-proBNP was closely related to postoperative kidney injury.[15,23,24] Yun, *et al.*[25] found that preoperative NT-proBNP was an independent predictor for perioperative cardiovascular events (cardiac death, ischemic heart disease, acute pulmonary edema or nonfatal stroke) in Korea. However, the relationship between NT-proBNP and perioperative cardiovascular complications in Chinese advanced-age patients needs further study. Ma, *et al.*[26] investigated the relationship between preoperative NT-proBNP and postoperative MACEs in older Chinese patients undergoing emergency noncardiac surgery and discovered that elevated NT-proBNP (917 pg/mL) increased the risk of postoperative MACEs. However, our study included a wide range of surgery types, including general surgery, hepatobiliary surgery, major vascular surgery, thoracic surgery, otolaryngology, urology, obstetrics and gynecology, orthopedics, neurosurgery and ophthalmology, in advanced-age patients undergoing noncardiac surgery (both emergency and elective) to validate the predictive value of NT-proBNP for MACEs and MINS. In our study, NT-proBNP showed a robust association with MACEs and MINS in the multivariate logistics analysis.

Table 3 Predictive values of MACEs with and without ln (NT-proBNP).

Variables	RCRI *vs.* RCRI + ln (NT-proBNP)		CSRM *vs.* CSRM + ln (NT-proBNP)	
	Change value	95% CI	Change value	95% CI
ΔAUC	0.044	0.003–0.085	0.017	0.001–0.035
Categorical NRI				
NRI	-0.018	-0.121–0.094	0.006	-0.075–0.135
NRI for event	-0.032	-0.132–0.114	0.016	-0.074–0.149
NRI for nonevent	0.014	-0.031–0.039	0.01	-0.015–0.016
Continuous NRI				
NRI	0.288	-0.038–0.557	0.142	-0.049–0.484
NRI for event	0.079	-0.123–0.258	-0.016	-0.190–0.238
NRI for nonevent	0.208	0.009–0.298	0.158	-0.071–0.283
IDI				
IDI, %	0.266	-0.325–0.858	-0.080	-0.433–0.274
Relative IDI, %	10.044	-12.27–32.357	-2.010	-10.925–6.905

AUC: area under the curve; CSRM: Cardiac and Stroke Risk Model; IDI: integrated discrimination improvement; MACEs: major adverse cardiovascular events; NRI: net reclassification improvement; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RCRI: Revised Cardiac Risk Index.

Although NT-proBNP has been researched in predicting perioperative cardiovascular complications, the threshold of NT-proBNP remains inconsistent. We found a significant increase in the incidence of MACEs and MINS with NT-proBNP of > 174 pg/mL and 200 pg/mL, which suggests to clinicians that NT-proBNP > 174 pg/mL might be the threshold where clinical intervention is needed. The threshold of NT-proBNP was 917 pg/mL in study by Ma, *et al.*[26] Farzi, *et al.*[27] found that preoperative NT-proBNP ≥ 725 pg/mL was associated with a higher risk of cardiac complications in emergency surgery. Chong, *et al.*[28] found preoperative NT-proBNP > 842 pg/mL was an independent predictor of a higher risk of in-hospital cardiac complications. This may result from the preoperative laboratory results of patients undergoing emergency surgery being higher than those of patients undergoing elective surgery, which explains why the value of NT-proBNP in older patients in our research is much lower than in studies with patients receiving emergency surgery. The VISION study[17] found that preoperative NT-proBNP ≥ 200 pg/mL was associated with postoperative cardiac risk in noncardiac surgery, which was similar to our study. We have confirmed the reliability of their findings using different study populations.

The American Heart Association and American College of Cardiology recommended that perioperative cardiovascular evaluation of noncardiac surgery should be considered an easy-to-use tool designed to guide preoperative investigation and treatment.[29] This tool requires consideration of both the patients' physical condition and the surgery risks. Such requirements are equally necessary for cardiac risk assessment for noncardiac surgery in the Chinese geriatric population. NT-proBNP is certainly a good candidate due to its simplicity and cost-effectiveness. If NT-proBNP is to be used as a routine screening indicator for noncardiac surgical cardiovascular events in older Chinese patients, an accurate and uniform threshold in these patients is also urgently needed. Our thresholds also provided a reference point for serious adverse events such as myocardial infarction and cardiovascular death, and relatively asymptomatic complications such as MINS.

Kopec, *et al.*[30] suggested that the addition of high-sensitivity cardiac troponin T and NT-proBNP to the RCRI significantly improved the prediction of perioperative myocardial infarction after major noncardiac surgery, with an increased AUC from 0.590 to 0.716 and 0.66 of NRI. Choi, *et al.*[31] found the inclusion of both NT-proBNP and C-reactive protein levels had better predictive power in perioperative major cardiac events than RCRI (AUC: 0.772 ± 0.017 *vs.* 0.592 ± 0.019). To verify the predictive va-

lue of NT-proBNP for MACEs in the older noncardiac surgery population, the classical predictive model RCRI and the cardiovascular complication model CSRM were used. The performance of predictive models was compared using AUC and reclassification measures (NRI and IDI). The addition of ln (NT-proBNP) increased the AUC of RCRI (0.682 *vs.* 0.726) and CSRM (0.787 *vs.* 0.804). We also found that the predictive power of the models improved effectively by observing changes in continuous NRI for predictive models. Through the results, it was found that the addition of ln (NT-proBNP) improved the predictive power of the model for nonoutcome events more significantly. It can be seen that NT-proBNP as a continuous variable in the model is more accurate in predicting the occurrence of postoperative MACEs and MINS.

LIMITATIONS

There are several limitations that must be noted. Firstly, our study was a retrospective single-center cohort study, and further external validation of the NT-proBNP threshold and model prediction effects is needed for extrapolation. Secondly, preoperative NT-proBNP tests were applied for patients who underwent high cardiovascular risk surgeries or patients with preoperative serious comorbidities in the First Medical Centre, Chinese PLA General Hospital. Therefore, to some extent, bias existed in this study. Further prospective observational or interventional studies are urgently needed to verify the prognostic efficiency of NT-proBNP. Last but not least, the incidence of MACEs and MINS was lower than that previously reported. Perhaps because this study was a retrospective study, missing medical records and laboratory results can influence the integrity and accuracy of the extracted data.

CONCLUSIONS

In conclusion, preoperative NT-proBNP was independently associated with the risk of MACEs and MINS. The addition of NT-proBNP increases the preoperative prediction of MACEs after noncardiac surgery. However, the decision to use NT-proBNP as a tool to screen for perioperative cardiovascular events in Chinese advanced-age patients undergoing noncardiac surgery still requires more prospective observational or interventional studies.

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