Preoperative N-terminal pro-B-type natriuretic peptide for prediction of acute kidney injury after non-cardiac surgery: A retrospective cohort study

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Research

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Abstract

Background Acute kidney injury (AKI) is associated with poor outcomes after non-cardiac surgery. Whether preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) predicts AKI after non-cardiac surgery is unclear.

Methods We conducted a retrospective study on patients whose NT-proBNP concentrations were measured before non-cardiac surgery at a tertiary academic hospital between 2008 and 2018. Multivariable logistic regression was used to investigate the predictive role of preoperative NT-proBNP on postoperative AKI defined by the Kidney Disease: Improving Global Outcomes creatinine criteria.

Results Some 6.1% (444 of 7248) of patients developed AKI within 1 week after surgery. Preoperative NT-proBNP was an independent predictor of AKI after adjustment for clinical variables (odd ratio comparing top to bottom quintiles 2.29, 95% confidence interval [CI] 1.47-3.65, p<0.001 for trend; odd ratio per 1-unit increment in natural log transformed NT-proBNP 1.27, 95% CI 1.16-1.39). Compared with clinical variables alone, the addition of NT-proBNP modestly improved the discrimination (change in area under the curve from 0.764 to 0.773, p=0.005) and reclassification (continuous net reclassification improvement 0.210, 95% CI 0.111-0.308; integrated discrimination improvement 0.0044, 95% CI 0.0016-0.0072) of AKI and non-AKI cases.

Conclusions Preoperative NT-proBNP concentrations provided predictive information for AKI in a cohort of patients undergoing non-cardiac surgery, independent of and incremental to conventional risk factors. Prospective studies are required to confirm this finding and examine its clinical impact.

Background

Acute kidney injury (AKI) is a common and important complication in patients undergoing non-cardiac surgery. A systematic review reported a 13.4% pooled incidence of AKI following major abdominal surgery [1]. Similar incidences were reported in orthopaedic and thoracic surgery [2, 3]. Postoperative increases in serum creatinine have been associated with increased morbidity, mortality, length of hospital stay and health care costs [2, 4–6], even those not meeting the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines consensus criteria for AKI diagnosis [7].

Early identification of patients at high risk of postoperative AKI is a prerequisite for developing strategies to ameliorate or prevent perioperative renal injury. In the past decade, several preoperative risk prediction models for AKI following non-cardiac surgery were developed [2, 8–13]. These models are all based solely on conventional clinical and laboratory-based variables. Recent studies have associated cardiac biomarkers B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) with risk of AKI in several medical settings [14–18] and in cardiac surgery [19]. Moreover, natriuretic peptides are established and guideline-recommended biomarkers for perioperative cardiovascular risk assessment in patients with elevated baseline risks undergoing non-cardiac surgery [20–25]. However, whether preoperative NT-proBNP could help to predict postoperative AKI in these patients is less clear.

Considering the complex interactions between cardiac and renal dysfunction [26], we hypothesised that preoperative NT-proBNP could be associated with the development of AKI after mixed types of non-cardiac surgery and could improve AKI prediction beyond conventional clinical risk factors. This study aims to test the hypothesis to provide evidence for the use of NT-proBNP in assessing AKI risk before non-cardiac surgery.

Methods

This retrospective cohort study was conducted in Southern Medical University Nanfang Hospital, a tertiary academic hospital in Guangzhou, China. The institutional review board approved the study and waived the informed consent (NFEC-2019-081). The study was conducted following a predefined protocol and statistical plan. The protocol was preregistered in Chinese Clinical Trial Registry (ChiCTR1900024056); however, the statistical plan was not published before data analysis. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Table S1) [27].

Patients

The study cohort was identified using the hospital's perioperative data warehouse, built as a collaborative program between Southern Medical University Nanfang Hospital and Shanghai Lejiu Healthcare Technology Co., Ltd. It contains deidentified demographic, medical, surgical and laboratory information for all patients undergoing surgery in Department of Anaesthesiology since the implementation of electronic health records system. For this study, all consecutive adult (age ≥ 18 y) patients who had a serum creatinine and NT-proBNP measurement within 30 preoperative days and at least one serum creatinine measurement within seven days after surgery between February 2008 and May 2018 were identified. For patients who had multiple surgeries, only the first surgery in the study period was included. The exclusion criteria were: (1) patients underwent cardiac, vascular, urological, neurological, transplant or obstetric procedures; (2) surgery lasted < 1 hour; (3) patients had end-stage renal disease, defined as an estimated glomerular filtration rate < 15 $ml.min^{-1}.1.73\ m^{-2}$, or history of renal replacement therapy or kidney transplantation; and (4) patients had evidence of preoperative AKI.

Variables

Baseline information included patients' demographics (age, sex, body mass index), medical history (hypertension, diabetes mellitus, coronary heart disease, stroke or transient ischaemic attack, congestive heart failure, ascites, use of renin-angiotensin-aldosterone system inhibitors), routine preoperative laboratory tests (estimated glomerular filtration rate, proteinuria, haemoglobin, serum albumin), surgical characteristics (urgency, type and duration of surgery, type of anaesthesia, blood pressure before anaesthesia), and American Society of Anesthesiologists (ASA) physical status. Preoperative estimated glomerular filtration rate was calculated based on serum creatinine concentration using a modified Modification of Diet in Renal Disease equation that has been validated in Chinese patients [28]. Serum NT-proBNP has been clinically measured using Roche Elecsys NT-proBNP assay (Roche Diagnostics,

Shanghai, China) in the hospital's Laboratory Medicine Centre since 2008. For patients who had multiple preoperative NT-proBNP measurements, the most recent value was used.

The primary outcome was AKI, defined according to the creatinine criteria of the KDIGO guidelines (increase in serum creatinine of ≥ 26.5 μmol.l^{-1} within 48 hours or ≥ 1.5 times baseline within 7 days after surgery) [29]. The most recent serum creatinine value before surgery was used as the baseline. Severe AKI (defined by KDIGO stage 2 or 3: increase in serum creatinine to ≥ 2 times baseline or ≥ 353.6 μmol.l^{-1} or initiation of renal replacement therapy) was the secondary outcome.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges and were compared using Mann-Whitney U test. Categorical variables are presented as counts and percentages and were compared using χ^2 or the Fisher exact test, as appropriate.

Patients with NT-proBNP concentrations below the limit of detection (n = 90) were assigned a value of 2.5 pg.ml^{-1} (0.5 × the lower limit of detection). Natural logarithmic (ln) transformation was performed for NT-proBNP concentrations due to their skewed distribution. We conducted multiple linear regression analysis to search for predictors of ln(NT-proBNP). Pearson product moment correlation coefficients (r) were calculated as a measure of linear association between clinical variables and ln(NT-proBNP). R-squared, expressing explained variation/total variation, was also computed.

To examine the association between preoperative NT-proBNP and postoperative AKI, we treated NT-proBNP both as a categorical (in quintiles) and as a continuous (ln-transformed) variable, and conducted univariable and multivariable logistic regression analysis. We adjusted all aforementioned baseline variables in the multivariable model as they had an established or putative role as risk factors for postoperative AKI. Results are reported by odds ratio and 95% confidence interval (CI). The shape of the multivariable association between preoperative NT-proBNP and AKI was further assessed by fitting restricted cubic splines to the continuous model.

To assess the added predictive value of preoperative NT-proBNP beyond conventional AKI risk factors, we used the χ^2 likelihood ratio test to determine whether the multivariable logistic regression model that included ln(NT-proBNP) provided a better fit than the one without it [30]. Furthermore, the models' ability to discriminate between AKI cases and non-cases was compared by testing the change in area under the receiver operating characteristic curves (AUC) using DeLong's method [31]. The risk reclassification ability of preoperative NT-proBNP was assessed by the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) indices [32, 33]. We used the continuous NRI version for the primary analysis because it is considered the more objective way to compare across studies and because there are no widely accepted risk thresholds for postoperative AKI. Nevertheless, we performed a sensitivity analysis with categorical NRI using cutoffs (< 2, 2–10, 10–20, and > 20%) that have been used in an AKI prediction model [13]. In additional analyses, we tested the predictive value of NT-proBNP over a model including the conventional risk factors and left ventricular ejection fraction (LVEF) in the 3827

patients who had transthoracic echocardiography before surgery. We also determined whether preoperative NT-proBNP could improve the predictive ability of two AKI preoperative prediction models that were developed and validated in non-cardiac surgical patients, i.e. the weighted General Surgery AKI (GS-AKI) risk index [9] and the Simple Postoperative AKI Risk (SPARK) index [13], respectively.

We did not calculate the sample size for this study and planned to analyse all eligible patients to maximise statistical power. Multiple imputation with chained equations was used for observations with missing data for 1 or more variables in logistic regression models, with 20 data sets being imputed, averaging predictions, and taking into account uncertainty owing to imputation [34]. Those variables with missing data in 1 or more observations included body mass index (number of observations with missing data n = 234), preoperative haemoglobin (n = 31), serum albumin (n = 16), urine dipstick test results (n = 73), urgency of surgery (n = 62), and blood pressure before anaesthesia (n = 408).

Statistical analyses were performed using the R statistical software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were 2-tailed.

Results

Characteristics of the study cohort

The patient selection process is shown in Fig. 1. Of the 7248 patients eligible for analysis, some 6.1% (444 of 7248) developed AKI within 1 week after surgery, most commonly stage 1 AKI (354 of 444, 79.7%). Characteristics of the study cohort, overall and stratified by the presence of postoperative AKI, are shown in Table 1. Patients who developed AKI were older and more likely to be male and to have more baseline comorbidity.

Table 1
Baseline characteristics of the study patients according to the occurrence of postoperative acute kidney injury.

Variables *	Overall (n = 7248)	No AKI (n = 6804, 93.9%)	AKI (n = 444, 6.1%)	p value
Age; year	63 (53–71)	62 (52–71)	70 (62–76)	< 0.001
Male sex	4017 (55.4)	3746 (55.1)	271 (61.0)	0.016
Body mass index; $kg.m^{-2}$	23 (20–25)	23 (20–25)	23 (21–26)	0.375
Medical history				
Hypertension	1984 (27.4)	1767 (26)	217 (48.9)	< 0.001
Diabetes	1294 (17.9)	1167 (17.2)	127 (28.6)	< 0.001
Coronary heart disease	375 (5.2)	324 (4.8)	51 (11.5)	< 0.001
Stroke	327 (4.5)	291 (4.3)	36 (8.1)	< 0.001
Congestive heart failure	305 (4.2)	256 (3.8)	49 (11.0)	< 0.001
Ascites	59 (0.8)	52 (0.8)	7 (1.6)	0.091
Use of RAAS inhibitors	773 (10.7)	675 (9.9)	98 (22.1)	< 0.001
Preoperative laboratory findings				
eGFR; $ml.min^{-1}.1.73\ m^{-2}$	93 (78, 111)	94 (78, 112)	83 (62, 108)	< 0.001
Proteinuria (≥ 1+)	408 (5.7)	343 (5.1)	65 (14.7)	< 0.001
Haemoglobin; $g.l^{-1}$	125 (109, 138)	125 (110, 138)	115 (96, 130)	< 0.001
Serum albumin; $g.l^{-1}$	38 (35, 41)	38 (35, 41)	36 (32, 39)	< 0.001
NT-proBNP; $pg.ml^{-1}$	67 (34–162)	64 (33–150)	154 (69–497)	< 0.001
Surgical characteristics				

* Categorical variables were shown as counts (percentages) and continuous variables as medians (interquartile ranges).

† Hypertensive was defined by systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg before anaesthesia; hypotensive was defined by preoperative systolic BP < 90 mmHg and diastolic BP < 60 mmHg before anaesthesia; other BPs were categorised as normotensive.

Abbreviations: AKI = acute kidney injury, ASA = American Society of Anesthesiologists, BP = blood pressure, eGFR = estimated glomerular filtration rate, IQR = interquartile range, NT-proBNP = N-terminal pro- B-type natriuretic peptide, RAAS = renin-angiotensin-aldosterone system.

Variables *	Overall (n = 7248)	No AKI (n = 6804, 93.9%)	AKI (n = 444, 6.1%)	p value
Elective surgery	6764 (94.1)	6376 (94.5)	388 (88.8)	< 0.001
Type of surgery				
General	2534 (35)	2306 (33.9)	228 (51.4)	< 0.001
Orthopaedic	2394 (33.0)	2244 (33.0)	150 (33.8)	
Thoracic	1972 (27.2)	1923 (28.3)	49 (11.0)	
Gynecological	101 (1.4)	97 (1.4)	4 (0.9)	
Others	247 (3.4)	234(3.4)	13(2.9)	
Surgery duration; hour	2 (2, 3)	2 (2, 3)	3 (2, 4)	< 0.001
Type of anaesthesia				
General	6067 (83.7)	5690 (83.6)	377 (84.9)	0.520
Regional	1181 (16.3)	1114 (16.4)	67 (15.1)	
BP before anaesthesia; mmHg				
Systolic BP	133 (119, 147)	132 (119, 147)	138 (122, 152)	< 0.001
Diastolic BP	76 (69, 83)	76 (69, 83)	76 (69, 85)	0.194
Normotensive †	3746 (52.7)	3563 (52.4)	183 (41.2)	< 0.001
Hypertensive †	2479 (34.2)	2293 (33.7)	186 (41.9)	
Hypotensive †	415 (5.7)	387 (5.7)	28 (6.3)	
ASA physical status				
1	1135 (15.7)	1107 (16.3)	28 (6.3)	< 0.001
2	4805 (66.3)	4549 (66.9)	256 (57.7)	
3	1023 (14.1)	894 (13.1)	129 (29.1)	

* Categorical variables were shown as counts (percentages) and continuous variables as medians (interquartile ranges).

† Hypertensive was defined by systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg before anaesthesia; hypotensive was defined by preoperative systolic BP < 90 mmHg and diastolic BP < 60 mmHg before anaesthesia; other BPs were categorised as normotensive.

Abbreviations: AKI = acute kidney injury, ASA = American Society of Anesthesiologists, BP = blood pressure, eGFR = estimated glomerular filtration rate, IQR = interquartile range, NT-proBNP = N-terminal pro- B-type natriuretic peptide, RAAS = renin-angiotensin-aldosterone system.

Variables *	Overall (n = 7248)	No AKI (n = 6804, 93.9%)	AKI (n = 444, 6.1%)	p value
4	101 (1.4)	83 (1.2)	18 (4.1)	
* Categorical variables were shown as counts (percentages) and continuous variables as medians (interquartile ranges).				
† Hypertensive was defined by systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg before anaesthesia; hypotensive was defined by preoperative systolic BP < 90 mmHg and diastolic BP < 60 mmHg before anaesthesia; other BPs were categorised as normotensive.				
Abbreviations: AKI = acute kidney injury, ASA = American Society of Anesthesiologists, BP = blood pressure, eGFR = estimated glomerular filtration rate, IQR = interquartile range, NT-proBNP = N-terminal pro- B-type natriuretic peptide, RAAS = renin-angiotensin-aldosterone system.				

The median preoperative NT-proBNP was 67 $pg.ml^{-1}$ (interquartile range 34 to 162 $pg.ml^{-1}$). NT-proBNP concentrations correlated positively with age (r = 0.39) and ASA physical status score (r = 0.37), and negatively with haemoglobin (r = − 0.43), serum albumin (r = − 0.45) and estimated glomerular filtration rate (r = − 0.21). The correlation of ln(NT-proBNP) with other baseline variables was generally modest to weak (Table S2). A linear regression model combining all these clinical variables yielded a 0.40 R-squared value, i.e., it explained only 40% of total NT-proBNP variation.

Associations between NT-proBNP and AKI

Preoperative NT-proBNP concentrations were markedly higher in patients who developed versus did not develop AKI after surgery (median 154 versus 64 $pg.ml^{-1}$, p < 0.001, Table 1). Besides, the risk of AKI increased across quintiles of NT-proBNP (p for trend < 0.001, Figure S1), with a more than 6-times higher odds of AKI for the highest compared with the lowest quintile (Table 2). This relationship was attenuated after adjustment for patient demographics, medical history, laboratory findings, and surgical characteristics in a logistic regression model. Nevertheless, quintiles 4 and 5 remained independently associated with postoperative AKI. When included continuously in the logistic model, preoperative NT-proBNP was also significantly and independently associated with AKI risk (adjusted odds ratio per 1-unit increment in ln(NT-proBNP) 1.27, 95% confidence interval [CI] 1.16–1.39, p < 0.001, Table 2). Figure 2 depicts the multivariable-adjusted odds ratios from the restricted cubic spline models for postoperative AKI by preoperative NT-proBNP value in the study cohort.

Table 2
Associations of preoperative N-terminal pro-B-type natriuretic peptide with acute kidney injury after non-cardiac surgery

	Categorized NT-proBNP (quintiles *)					p trend value	Continuous ln(NT-proBNP) (per 1-unit increment)	p value
	< 29	29–51	51–90	90–215	> 215			
Unadjusted OR (95% CI)	1 (reference)	1.62 (1.03–2.60)	2.29 (1.50–3.59)	4.07 (2.75–6.24)	6.87 (4.71–10.38)	< 0.001	1.64 (1.53–1.75)	< 0.001
Adjusted OR † (95% CI)	1 (reference)	1.20 (0.75–1.94)	1.42 (0.91–2.27)	2.01 (1.31–3.16)	2.29 (1.47–3.65)	< 0.001	1.27 (1.16–1.39)	< 0.001

* The number of patients per quintile is as follows: quintile 1, n = 1449; quintile 2, n = 1449; quintile 3, n = 1450; quintile 4, n = 1450; and quintile 5, n = 1450.

† Adjusted for age (per year), sex, body mass index, ASA physical status, hypertension, diabetes mellitus, coronary heart disease, stroke, congestive heart failure, ascites, use of renin-angiotensin-aldosterone system inhibitors, non-elective surgery, surgery type, surgery duration, anaesthesia type, blood pressure before anaesthesia (in categories: normotensive, hypertensive and hypotensive), estimated glomerular filtration rate, proteinuria, haemoglobin and serum albumin.

Abbreviations: AKI = acute kidney injury, ASA = American Society of Anesthesiologists, CI = confidence interval, ln = natural log-transformed, NT-proBNP = N-terminal pro- B-type natriuretic peptide, OR = odds ratio.

Additive value of NT-proBNP in risk prediction

Likelihood ratio test showed that addition of NT-proBNP resulted in a significantly better fitting model for AKI prediction ($\chi^2 = 24.3$, $p < 0.001$). The discrimination measure AUC was 0.694 (95% CI 0.668–0.720) for the prediction model containing only NT-proBNP as a continuous variable, and 0.764 (95% CI 0.741–0.786) for the logistic regression model containing clinical risk factors but not NT-proBNP. The addition of NT-proBNP to the base model moderately increased the AUC by 0.009 (p for change = 0.005, Table 3). It also improved reclassification by 5.9% (95% CI − 3.3%-15.1%) for patients who developed postoperative AKI and by 15.1% (95% CI 12.7%-17.5%) for those who did not, resulting in a significant overall improvement in net reclassification (continuous NRI 0.210, 95% CI 0.111–0.308, $p < 0.001$). The absolute and relative IDI was 0.0044 (95% CI 0.0016–0.0072) and 6.27% (95% CI 2.05%-10.48%), respectively. The categorical NRI analysis also showed significant overall improvement in risk reclassification (categorial NRI 0.088, 95% CI 0.047–0.129, $p < 0.001$; Table S3). In additional analyses including only 3827 patients who had preoperative transthoracic echocardiography, the addition of NT-proBNP to the base model that included both conventional risk factors and LVEF significantly improved the model performance (Table S4).

Table 3

Performance metrics of acute kidney injury prediction models with and without preoperative N-terminal pro-B-type natriuretic peptide.

	Base model	Base model and NT-proBNP *
Multivariable logistic regression model † as the base model		
AUC	0.764 (95% CI 0.741–0.786)	0.773 (95% CI 0.749, 0.796)
ΔAUC	Reference	0.009, p = 0.005
NRI for event	Reference	0.059 (95% CI − 0.033, 0.151)
NRI for non-event	Reference	0.151 (95% CI 0.127, 0.175)
NRI	Reference	0.210 (95% CI 0.111, 0.308)
IDI	Reference	0.0044 (95% CI 0.0016, 0.0072)
Relative IDI; %	Reference	6.27 (95% CI 2.05, 10.48)
Weighted General Surgery AKI risk index as the base model		
AUC	0.704 (95% CI 0.680–0.728)	0.735 (95% CI 0.712, 0.759)
ΔAUC	Reference	0.031, p < 0.001
NRI for event	Reference	0.135 (95% CI 0.037, 0.233)
NRI for non-event	Reference	0.256 (95% CI 0.231, 0.280)
NRI	Reference	0.391 (95% CI 0.289, 0.492)
IDI	Reference	0.0137 (95% CI 0.0090, 0.0183)
Relative IDI; %	Reference	39.86 (95% CI 25.81, 53.91)
Simple Postoperative AKI Risk index as the base model		
AUC	0.714 (95% CI 0.689–0.739)	0.740 (95% CI 0.717, 0.763)
ΔAUC	Reference	0.026, p < 0.001

* Natural log-transformed NT-proBNP.

† Adjusted for age (per year), sex, body mass index, ASA physical status, hypertension, diabetes mellitus, coronary heart disease, stroke, congestive heart failure, ascites, use of renin-angiotensin-aldosterone system inhibitors, non-elective surgery, surgery type, surgery duration, anaesthesia type, blood pressure before anaesthesia (in categories: normotensive, hypertensive and hypotensive), estimated glomerular filtration rate, proteinuria, haemoglobin and serum albumin.

Abbreviations: AKI = acute kidney injury, ASA = American Society of Anesthesiologists, AUC = area under the curve, CI = confidence interval, ΔAUC = change in area under the curve, IDI = integral discrimination improvement, NT-proBNP = N-terminal pro- B-type natriuretic peptide, NRI = net reclassification improvement.

	Base model	Base model and NT-proBNP *
NRI for event	Reference	0.124 (95% CI 0.029, 0.220)
NRI for non-event	Reference	0.225 (95% CI 0.201, 0.249)
NRI	Reference	0.350 (95% CI 0.252, 0.447)
IDI	Reference	0.0110 (95% CI 0.0066, 0.0154)
Relative IDI; %	Reference	22.64 (95% CI 12.36, 32.92)
* Natural log-transformed NT-proBNP.		
† Adjusted for age (per year), sex, body mass index, ASA physical status, hypertension, diabetes mellitus, coronary heart disease, stroke, congestive heart failure, ascites, use of renin-angiotensin-aldosterone system inhibitors, non-elective surgery, surgery type, surgery duration, anaesthesia type, blood pressure before anaesthesia (in categories: normotensive, hypertensive and hypotensive), estimated glomerular filtration rate, proteinuria, haemoglobin and serum albumin.		
Abbreviations: AKI = acute kidney injury, ASA = American Society of Anesthesiologists, AUC = area under the curve, CI = confidence interval, ΔAUC = change in area under the curve, IDI = integral discrimination improvement, NT-proBNP = N-terminal pro- B-type natriuretic peptide, NRI = net reclassification improvement.		

The addition of preoperative NT-proBNP to the weighted GS-AKI risk index or the SPARK index both resulted in significant improvement in model performance, as demonstrated by the increased AUC, the continuous NRI and the IDI indices (Table 3), but the GS-AKI and SPARK indices also had lower predictive ability than the multivariable logistic regression model in our primary analysis.

Preoperative NT-proBNP and severe AKI

We also analysed the relationship between preoperative NT-proBNP and severe AKI after non-cardiac surgery. Similarly, preoperative NT-proBNP was independently associated with severe AKI (adjusted odds ratio comparing top to bottom quintiles 3.94, 95% CI 1.41–14.10, p for trend = 0.005; adjusted odds ratio per 1-unit increment in ln(NT-proBNP) 1.27, 95% CI 1.05–1.53; Table S5, Figures S2 and S3). However, the added value of NT-proBNP to clinical variables for severe AKI prediction was inconclusive (likelihood ratio test for model fit, χ^2 = 6.02, p = 0.014; change in AUC from 0.809 to 0.821, p = 0.050; continuous NRI 0.395, 95% CI 0.188–0.602; IDI 0.0007, 95% CI − 0.0038–0.0053; Table S6).

Discussion

In this study of 7248 non-cardiac surgical patients with preoperative NT-proBNP measurement for perioperative risk assessment, we found that raised preoperative NT-proBNP concentration was an independent predictor for AKI. The addition of NT-proBNP to conventional AKI risk factors, such as demographic, medical, laboratory and surgical variables, modestly improved risk discrimination and reclassification. These findings inform the role of NT-proBNP in optimal preoperative AKI risk stratification for these patients.

NT-proBNP and BNP are well established predictive markers for adverse cardiac events after non-cardiac surgery [20–23]. Guidelines on perioperative cardiac risk assessment recommended measuring preoperative NT-proBNP/BNP in patients with confirmed cardiovascular diseases or with cardiovascular risk factors to achieve better risk stratification [24, 25]. However, the relationship between NT-proBNP/BNP and postoperative AKI in these patients has not been elucidated. A recent study reported that preoperative NT-proBNP is useful for predicting AKI after elective lung cancer surgery [3]. Our study extends the finding of that study and suggests that preoperative NT-proBNP is independently associated with AKI in patients undergoing mixed types of non-cardiac surgery. This result is in accordance with observations in previous studies showing that NT-proBNP/BNP concentrations were associated with risk of AKI after cardiac surgery [19] and in other acute care settings [14–18].

In addition, we found that adding preoperative NT-proBNP to conventional risk factors improved AKI risk prediction, and the improvements remained even when LVEF was included in the base model. Because the incidence of AKI after non-cardiac surgery is relatively low, and because conventional risk factors have good prediction performance for postoperative AKI, even biomarkers with an independent association with AKI (such as BNP) may not improve the discrimination ability of existing clinical models [17]. Despite these challenges, in our study, NT-proBNP offered modest but statistically significant improvements in the AUC, the continuous and categorical NRI, and the IDI. The magnitude of improvements was comparable to that of NT-proBNP for cardiovascular diseases prediction in other cohort studies [35]. Besides, the relative IDI indicates that the strength of NT-proBNP is larger than the average strength of risk factors in the base model [33]. These data have some possible clinical implications. Following major guidelines on perioperative cardiac risk assessment [24, 25], NT-proBNP/BNP measurements are being incorporated in the workup for at-risk patients scheduled for major surgery by more and more institutions, and their concentrations are increasingly readily available to surgeons and anaesthesiologists before surgery. NT-proBNP/BNP concentrations should be considered carefully, along with other clinical risk factors, to achieve a more precise preoperative AKI risk stratification for these patients.

A predictive biomarker is clinically useful when it can help to identify high-risk patients in whom preventive strategies could be implemented to improve their outcomes [36]. Several renal biomarkers have been developed and used in recent years [37]. The urinary cell cycle arrest biomarkers insulin-like growth factor-binding protein 7 and tissue inhibitor of metalloproteinase-2, for example, have shown their ability to guide the implementation of KDIGO care bundle (volume optimization, blood pressure maintenance, and avoidance of nephrotoxins) to reduce the incidence and severity of postoperative AKI [38, 39]. However, these biomarkers only start to increase postoperatively after the kidney damage has occurred allowing early detection but not preoperative prediction of AKI. Whether NT-proBNP/BNP-based preoperative risk prediction and prevention could yield greater efficacy in reducing postoperative AKI is currently unknown, and this needs to be tested in prospective trials.

The pathophysiologic mechanisms involved in the relationship between NT-proBNP and postoperative AKI is unclear. Serum NT-proBNP concentrations are able to reflect small changes in ventricular function

in patients who mostly had no evidence of clinically significant cardiac dysfunction. In addition, NT-proBNP concentrations are also associated with other non-cardiac factors contributing to the development of AKI such as aging, renal dysfunction and inflammation [40, 41]. NT-proBNP concentrations seem to provide information not contained in other clinical and laboratory-based variables, as suggested by the lack of strong predictors of preoperative NT-proBNP concentrations in our linear regression analysis.

Several limitations of this study must be addressed. First of all, this study used a retrospective cohort from a single tertiary academic hospital. The clinical indication and timing for preoperative NT-proBNP tests were not standardised because they reflected real-time clinical care. We included patients with NT-proBNP tests within 30 days before surgery. Although the clinical indication for NT-proBNP measurement in each patient was not recorded, the majority were believed to be ordered for perioperative cardiac risk assessment in this timeframe. Given the fact that patients needed to have both NT-proBNP and pre- and postoperative serum creatinine tests to be included, the study cohort represents patients with higher baseline cardiovascular and renal risk burden than the overall non-cardiac surgical population. Importantly, the study reflected real world scenarios where NT-proBNP/BNP measurements would only be performed in patients with elevated perioperative risks rather than in the general surgical population. This is in accordance with guidelines on use of cardiac biomarkers in non-cardiac surgical setting [24, 25]. Nevertheless, the reduced generalisability was an inherent limitation of our study due to the retrospective design. Prospective studies evaluating use of NT-proBNP/BNP in this population would be beneficial.

As with any observational study, our analyses are susceptible to residual confounding. We cannot exclude that other factors not routinely measured preoperatively, such as novel markers of kidney injury and inflammation, may be more strongly associated with postoperative AKI than NT-proBNP. We were also unable to account for the change in clinical care following NT-proBNP measurement because the providers were not blinded to the test results. Another limitation is that the incidence of severe postoperative AKI (KDIGO stage 2 or 3) in this cohort was low (n = 90, 1.2%), making our analyses for these outcomes less reliable. Finally, in this study we focused on the preoperative identification of patients at risk of AKI, so we did not investigate the predictive role of postoperative NT-proBNP, nor did we include intraoperative and postoperative variables in the logistic regression model. Postoperative NT-proBNP concentrations may have better predictive ability for AKI. However, the clinical utility of that prediction may also be lower.

Conclusions

In this retrospective cohort study of 7248 patients undergoing non-cardiac surgery, preoperative NT-proBNP concentrations were independently associated with the risk of postoperative AKI. NT-proBNP improved the predictive ability of a logistic regression model based on conventional clinical risk factors as well as that of currently available AKI prediction indices. These findings need to be validated in prospective studies, and further trials are required to assess whether NT-proBNP-based preoperative evaluation and treatment could reduce the incidence of postoperative AKI.

Abbreviations

AKI = acute kidney injury, ASA = American Society of Anesthesiologists, AUC = area under the receiver operating characteristic curves, BNP = B-type natriuretic peptide, CI = confidence interval, IDI = integrated discrimination improvement, KDIGO = Kidney Disease: Improving Global Outcomes, ln = Natural logarithmic, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro- B-type natriuretic peptide, NRI = net reclassification improvement, SMUNH = Southern Medical University Nanfang Hospital.

Declarations

Ethics approval and consent to participate

The institutional review board of Southern Medical University Nanfang Hospital approved the study (NFEC-2019-081) and waived the informed consent due to the retrospective study design.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

B.C.Z., W.F.L. and K.X.L. designed the study. B.C.Z., P.P.Z and S.H.L. collected the data, performed statistical analysis and drafted the manuscript. X.Y., S.D.Q., C.L., W.F.L. and K.X.L. critically revised the manuscript. All authors provided intellectual content of critical importance to the work described and approved the final version. B.C.Z., P.P.Z and S.H.L. contributed equally to this work.

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Figures

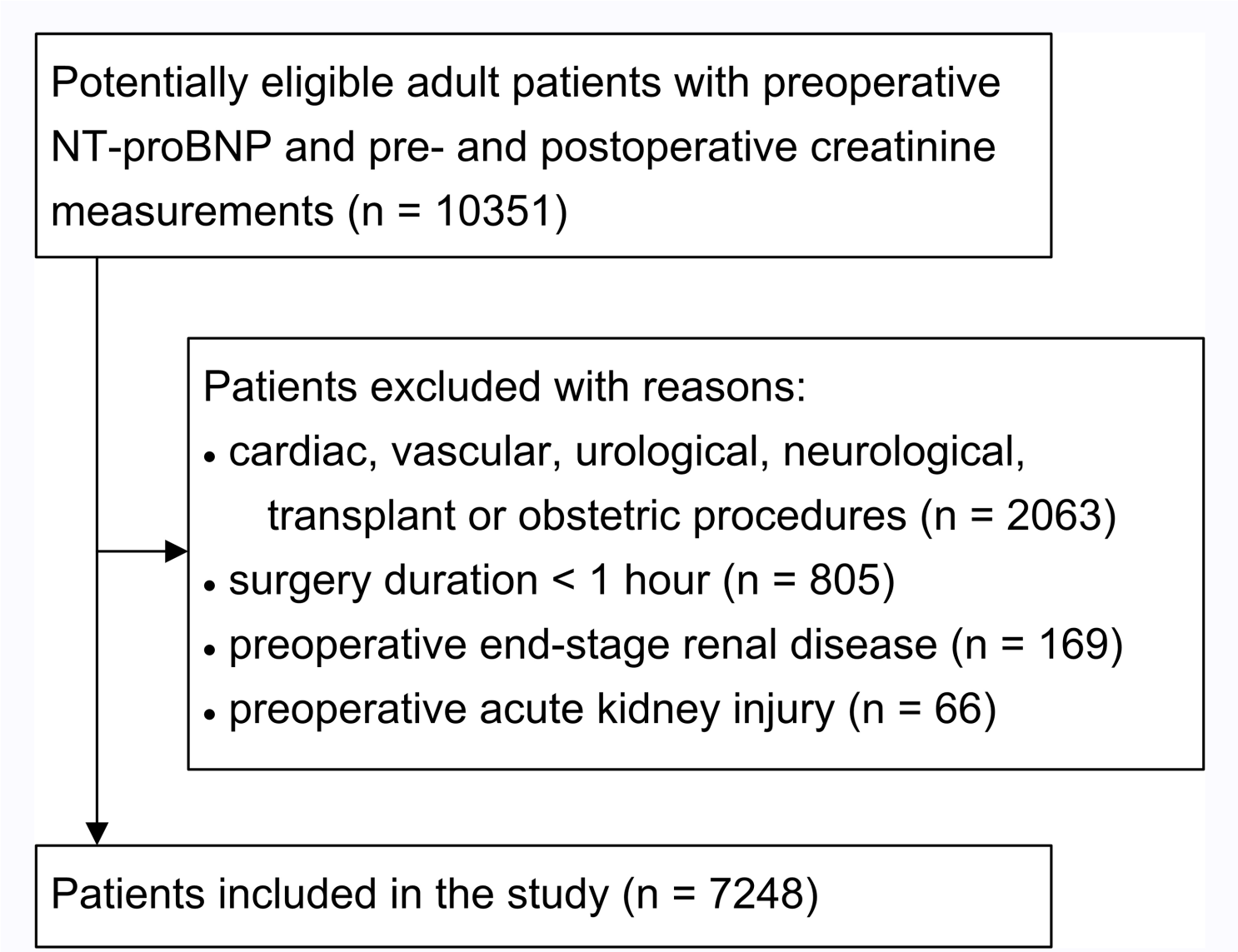

Figure 1

Flow chart for patient selection. Abbreviations: NT-proBNP = N-terminal pro-B-type natriuretic peptide.

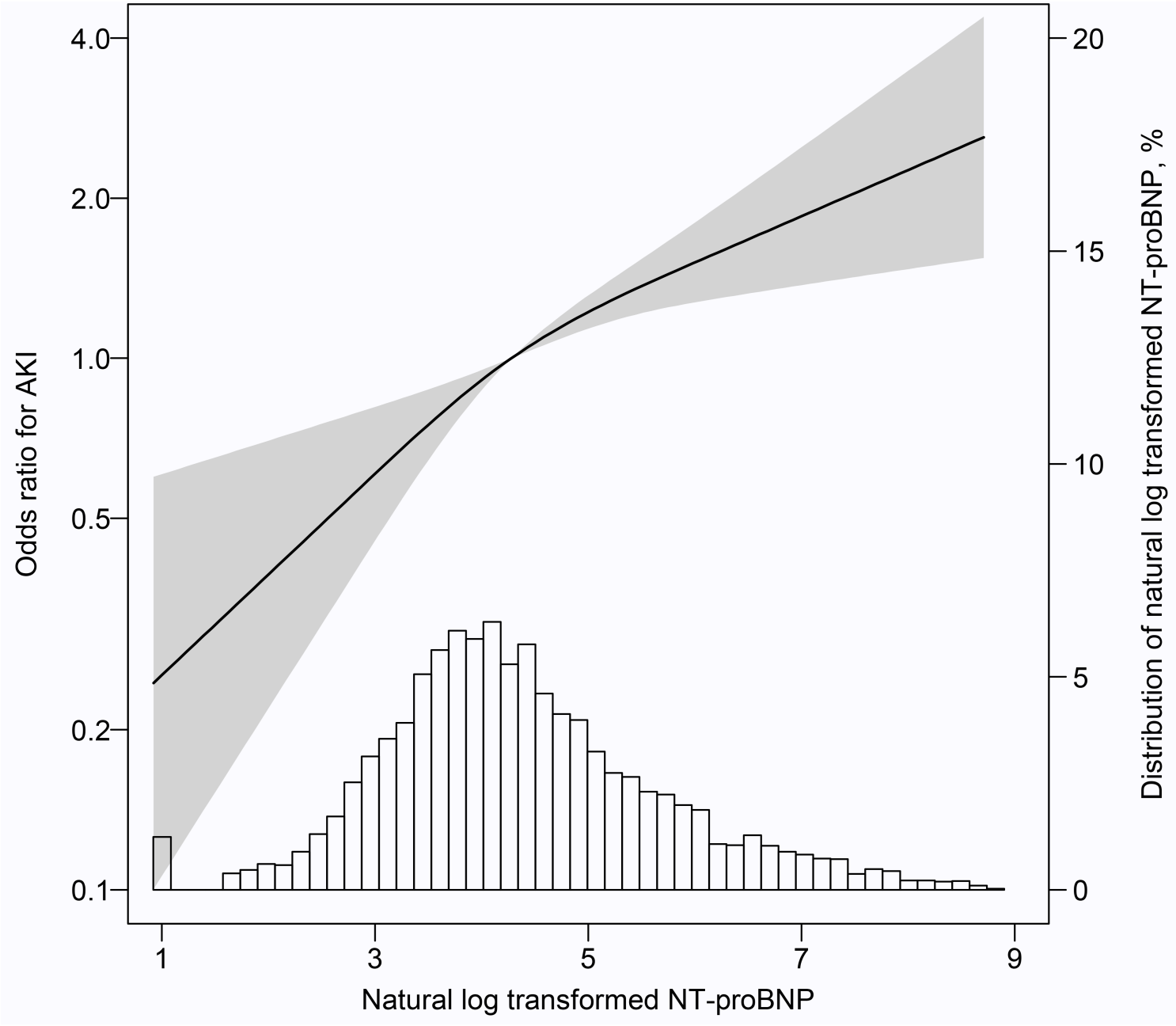

Figure 2

Multivariable-adjusted restricted cubic spline regression models for the association between NT-proBNP and postoperative acute kidney injury. The reference value for the odds ratio was 4.2 for natural log-transformed NT-proBNP. The shadow area indicates 95% confidence interval. Three knots were used, located at the 5th, 50th, and 95th percentiles of the natural log-transformed NT-proBNP (2.5, 4.2 and 6.9). The histogram represents the distribution of the natural log-transformed preoperative NT-proBNP concentrations. Abbreviations: NT-proBNP = N-terminal pro-B-type natriuretic peptide.

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