



Correlation of N-terminal-pro-brain natriuretic peptide with postoperative outcomes of older patients undergoing transcatheter aortic valve replacement

Ying-Ching Huang^a, Hsiao-Huang Chang^b, Po-Lin Chen^b, Chi-Ming Chu^c, Jen-Chen Tsai^a, Kwua-Yun Wang^{a,c,d,e,*}

^aCollege of Nursing, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; ^bDivision of Cardiovascular Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; ^cSchool of Public Health, National Defense Medical Center, Taipei, Taiwan, ROC; ^dDepartment of Nursing, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; ^eSchool of Nursing, National Defense Medical Center, Taipei, Taiwan, ROC

Abstract

Background: Patients undergoing transcatheter aortic valve replacement surgery (TAVR) are typically older adults with multiple chronic diseases and therefore have a high surgical risk. The N-terminal of brain natriuretic peptide (BNP) and pro-BNP, referred to as NT-pro-BNP, is an easily measurable biomarker of heart failure. Studies on correlation between higher NT-pro-BNP levels and adverse prognoses after TAVR have yielded inconsistent results. Here, we investigated whether preoperative NT-pro-BNP levels are correlated with outcomes among older adults undergoing TAVR.

Methods: This retrospective study included older adults with severe aortic stenosis (AS) who received TAVR from a medical center between January 2013 and June 2017. The patients' demographics, preoperative laboratory data, postoperative complications, and 1-year mortality were recorded. They were divided into two groups based on their preoperative NT-pro-BNP levels. The post-TAVR outcomes in the two groups were analyzed using a multivariate logistic regression analysis of the binary results.

Results: Of the 132 patients included (mean age: 81.5 ± 8.1 years; 47% men), 96 (72.7%) had preoperative NT-pro-BNP levels ≤ 4853 ng/L, and 36 (27.3%) had preoperative NT-pro-BNP levels > 4853 ng/L. The postoperative outcomes were significantly better in the NT-pro-BNP ≤ 4853 group than in the NT-pro-BNP > 4853 group: postoperative extracorporeal membrane oxygenation fittings (4.2% vs 16.7%, $p = 0.025$), number of days in hospital (17.5 ± 21.0 vs 27 ± 17.0, $p = 0.009$), in-hospital mortality (4.2% vs 16.7%, $p = 0.025$), and 1-year mortality (11.5% vs 38.9%, $p = 0.001$); the significant differences persisted after controlling for other variables.

Conclusion: For older patients undergoing TAVR with NT-pro-BNP levels > 4853 ng/L, their postoperative outcomes and 1-year mortality were correlated. Thus, NT-pro-BNP is useful for the risk assessment of patients undergoing TAVR and should be regarded as a biomarker in future risk assessments.

Keywords: Natriuretic peptide; NT-pro-BNP; Postoperative complications; Transcatheter aortic valve replacement

1. INTRODUCTION

In recent years, transcatheter aortic valve implantation surgery (TAVR) has become the primary surgical treatment for severe aortic stenosis (AS).^{1,2} Patients undergoing TAVR tend to be older and have multiple chronic illnesses, making them high-risk patients. Approximately 30% to 40% of high-risk surgical patients are unsuitable for surgical aortic valve replacement, but

whether they receive surgical treatment is correlated with their risk of death.^{1,3} Among patients who receive only conservative drug treatments and no surgical treatment, the 1-year mortality rate is >30% and the 2-year mortality rate increases to 50%.⁴ Conversely, after TAVR, the 30-day mortality rate is 10% and the 2-year mortality rate remains under 20%.⁵

Medical work often involves encountering complex, severe, and rapidly changing conditions that require early and accurate assessments and close monitoring afterward; such conditions range from acute coronary syndrome and heart failure in cardiac surgery to septic shock in internal medicine and include respiratory failure, renal failure, and even multiple organ failure. An objective analysis tool, preferably one that is noninvasive and capable of point-of-care testing, is essential to the entire process. In addition to reducing the risks inherent in testing, such a tool should be able to provide rapid results. Many biomarkers have been discussed, especially brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP)—two crucial biomarkers of heart failure that have gradually become increasingly discussed in critical care medicine.^{6,7}

*Address correspondence. Dr. Kwua-Yun Wang, Department of Nursing, National Yang Ming Chiao Tung University, 155, Section 2, Linong Street, Taipei 112, Taiwan ROC. E-mail address: kywang7@vghtpe.gov.tw (K.-Y. Wang).

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BNP was isolated from porcine brain tissue in 1988 and was found to be secreted by cardiomyocytes in the heart ventricles. BNP is a prohormone composed of 134 amino acids and then split into a prohormone with 108 amino acids. In the circulation, this prohormone is further split into NT-pro-BNP with 76 amino acids and BNP with 32 amino acids. Between the two, BNP is more biologically active, while NT-pro-BNP is more stable. NT-pro-BNP has a longer half-life of approximately 120 min, while BNP has a half-life of only approximately 20 minutes. Consequently, testing for BNP must be completed within 20 minutes after blood is drawn, whereas NT-pro-BNP has a more stable circulation concentration, and its detection can therefore be used for early diagnosis.⁷

NT-pro-BNP has been found to have strong correlations with mortality and rehospitalization rates relating to heart failure and favorable prognostic predictive abilities; however, this has been limited to known cardiovascular diseases.⁸ For older and high-risk surgical patients undergoing TAVR, no assessment system that can rapidly identify the risk of death has been developed. Furthermore, research in recent years indicates that among older adults with severe AS, the predictive value of NT-pro-BNP in clinical prognoses and short-term mortality after TAVR has been inconsistent.⁹ Few studies from Asia have examined the correlations between NT-pro-BNP values and clinical results after TAVR.¹⁰⁻¹² Consequently, using objective test items to assess risks among older adults with severe AS has become imperative. Therefore, this study investigated whether preoperative NT-pro-BNP values can predict the prognosis of older adults undergoing TAVR.

2. METHODS

2.1. Study design and participants

This retrospective study was approved by the Institutional Review Board (2017-12-013CC). Data on patients with AS who underwent treatment at a medical center in northern Taiwan between January 2013 and June 2017 were collected. The inclusion criteria were patients with severe AS recommended for TAVR by the TAVR team (which includes a cardiologist, imaging cardiologist, thoracic surgeon, radiologist, and anesthesiologist) who were ≥ 65 years old and had an aortic valve area ≤ 1 cm². Patients with previous valve surgery or infective endocarditis were excluded. Data collected in this study include demographic variables, laboratory data (include preoperative serum NT-pro-BNP data), cardiac ultrasound data, surgery records, postoperative complications, the number of days in hospital, and the time of death.

NT-pro-BNP analysis is part of the institution's standard preoperative blood tests. The effects of preoperative NT-pro-BNP levels are analyzed based on published research.^{13,14} According to determine the cutoff value by receiver operating characteristic curve analysis and Youden's index of their serum NT-pro-BNP levels, the patients were divided into two groups (NT-pro-BNP levels ≤ 4853 vs >4853).

2.2. Statistical analysis

Statistical analysis was performed using SPSS version 24 (IBM, Armonk, NY, USA). Continuous variables are expressed as mean \pm standard deviation, and categorical variables are expressed as frequency and percentages. Inferential statistics involve comparisons of differences between two groups based on the nature of the research variables; among the continuous variables, normally distributed variables were tested using independent t tests and nonnormally distributed variables were tested using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square test; if the cross tabulations contained expected values smaller than 5, it was then analyzed using Fisher's exact test. Finally, we performed univariate and multivariate logistic regression analysis of binary results to fit the model and to estimate

and adjust the influences of NT-pro-BNP levels ≤ 4853 vs >4853 on postoperative clinical outcomes: postoperative extracorporeal membrane oxygenation (ECMO) machine, number of days in hospital, and in-hospital and 1-year mortality. All reported P values for the logistic regression model, odds ratios, corresponding 95% confidence intervals, and *p* values (Wald test) were two-sided; *p* < 0.05 was set as statistically significant. In addition, we provided a figure to compare the cumulative overall survival rates between patients with high and those with low serum NT-pro-BNP levels by using the Kaplan-Meier method.

3. RESULTS

3.1. Baseline parameters

This study included 132 patients. The preoperative NT-pro-BNP values had a mean of 6579 ng/L and a median of 1936 ng/L. Using the Youden's index value 4853 ng/L as the cutoff point, the patients were divided into two groups: the NT-pro-BNP ≤ 4853 group and the NT-pro-BNP >4853 group. The research participants comprised 96 patients in the NT-pro-BNP ≤ 4853 group (72.7%) and 36 patients in the NT-pro-BNP >4853 group (27.3%). The ages of the members in the NT-pro-BNP >4853 group were significantly higher than those of NT-pro-BNP ≤ 4853 group; the two groups did not demonstrate significant differences in the other demographic variables, such as gender and BMI. In terms of lab data, the preoperative NT-pro-BNP >4853 group had significantly lower mean hemoglobin levels (11.8 ± 1.6 g/dL vs 10.1 ± 1.6 g/dL, *p* < 0.001), indicating anemia. This group also demonstrated higher mean levels of blood urea nitrogen (BUN) (23.5 ± 11.3 vs 40.6 ± 27.0 mg/dL, *p* = 0.001) and creatinine (1.08 ± 0.4 vs 2.7 ± 2.7 mg/dL, *p* = 0.001), indicating impaired renal function. In terms of disease characteristics, the patients in the NT-pro-BNP >4853 group had significantly more preexisting conditions than patients in the NT-pro-BNP ≤ 4853 group, including diabetes (33.3% vs 52.8%, *p* = 0.04) and dialysis treatments (0% vs 16.7%, *p* < 0.001).

No significant differences were present between the two groups based on the Charlson comorbidity index and other variables. As for the cardiac ultrasound tests, the NT-pro-BNP >4853 group had significantly more patients with left ventricular ejection fraction (LVEF) < 45% than the NT-pro-BNP ≤ 4853 group (30.6% vs 10.4%, *p* = 0.005) (Table 1).

3.2. Perioperative complications

The NT-pro-BNP >4853 group was more likely to require a postoperative ECMO machine (4.2% vs 16.7%, *p* = 0.025). Significant differences were not observed between the two groups in operation length and postoperative implantation of artificial cardiac pacemakers (Table 2).

3.3. Outcome

The NT-pro-BNP >4853 group had significantly longer hospital stay (27 days) than the NT-pro-BNP ≤ 4853 group (18 days) (*p* < 0.009). However, significant differences were not present in the number of days in the intensive care unit. Significant between-group differences were observed in in-hospital mortality (4.2% vs 16.7%, *p* = 0.025) and 1-year mortality (11.5% vs 38.9%, *p* = 0.001) but not for 30-day mortality (Table 3).

3.4. Multivariable regression analysis

After adjustment for factors such as age, gender, hemoglobin, serum albumin, diabetes, dialysis, LVEF < 45%, and preoperative NT-pro-BNP levels (NT-pro-BNP ≤ 4853 ng/L vs NT-pro-BNP >4853 ng/L), a multivariate logistic model was used to analyze postoperative ECMO installations, number of days in hospital,

Table 1
Baseline characteristics and approach according to NT-pro-BNP groups

Variable	Total (n = 132, 100%)		NT-pro-BNP ≤ 4853 (n = 96, 72.7%)		NT-pro-BNP >4853 (n = 36, 27.3%)		p
Demographic characteristic							
Age, y, mean (SD)	81.5	8.1	80.2	8.5	85.1	6.0	0.002
Male, n (%)	62	47	41	42.7	21	58.3	0.109
Body mass index, mean (SD)	23.8	3.9	24.1	4.1	23.1	3.1	0.171
Laboratory							
Hemoglobin (g/dL), mean (SD)	11.4	1.8	11.8	1.6	10.1	1.6	<0.001
BUN (mg/dL), mean (SD)	28.2	18.6	23.5	11.3	40.6	27.0	<0.001
Creatinine (mg/dL), mean (SD)	1.5	1.6	1.1	0.4	2.7	2.7	<0.001
Serum albumin (g/L), mean (SD)	3.6	0.46	3.8	0.4	3.3	0.4	<0.001
eGFR, mean (SD)	57.3	23.6	64.0	20.1	39.4	23.4	<0.001
Disease characteristics							
Hypertension, n (%)	94	71.2	67	69.8	27	75.0	0.55
Diabetes mellitus, n (%)	51	38.6	32	33.3	19	52.8	0.041
COPD, n (%)	15	11.4	12	12.5	3	8.3	0.759
Dialysis, n (%)	6	4.5	0	0	6	16.7	<0.001
Prior malignancy, n (%)	18	13.6	13	13.5	5	13.9	1.0
Prior cerebrovascular disease, n (%)	11	8.3	6	6.3	5	13.9	0.157
Atrial fibrillation, n (%)	28	21.2	18	18.8	10	27.8	0.258
Coronary artery disease, n (%)	63	47.7	44	45.8	19	52.8	0.477
Prior coronary bypass, n (%)	8	6.1	6	6.3	2	5.6	1.0
CCI							
<3	126	95.5	93	96.9	33	91.7	0.201
≥3	6	4.5	3	3.1	3	8.3	
Echocardiogram							
LEVF							
≥45%	111	84.1	86	89.6	25	69.4	0.005
<45%	21	15.9	10	10.4	11	30.6	
RVSP							
≤40	69	52.3	55	57.3	14	38.9	0.059
>40	63	47.7	41	42.7	22	61.6	

BUN = blood urea nitrogen; CCI = Charlson comorbidity index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LEVF = left ventricular ejection fraction; NT-pro-BNP = N-terminal-pro-brain natriuretic peptide; RVSP = right ventricular systolic pressure.

Table 2
Perioperative complication according to NT-pro-BNP groups

Variable	Total (n = 132, 100%)		NT-pro-BNP ≤ 4853 (n = 96, 72.7%)		NT-pro-BNP > 4853 (n = 36, 27.3%)		p
Operation time, mean (SD)	146.6	108.1	148.1	118.0	142.7	77.1	0.449
Postoperative ECMO, n (%)	10	7.6	4	4.2	6	16.7	0.025
Postoperative pacemaker, n (%)	5	3.8	4	4.2	1	2.8	1.00

ECMO = extracorporeal membrane oxygenation; NT-pro-BNP = N-terminal-pro-brain natriuretic peptide.

and 1-year mortality. The results indicate a visible statistical significance regarding grouping the patients by NT-pro-BNP (Table 4).

3.5. Kaplan–Meier method

Use the Kaplan–Meier method (log-rank test) to verify the survival curves of two groups. Mortality at 1 year was significantly different between the two groups ($p < 0.001$; Fig. 1). Cumulative survival of patients NT-pro-BNP>4853 showed a statistically significant higher 1-year mortality rate than patients NT-pro-BNP ≤ 4853 ng/L (log-rank < 0.001).

4. DISCUSSION

The research results indicate that preoperative NT-pro-BNP levels of >4853 ng/L can independently predict adverse prognoses

and in-hospital and 1-year mortality after TAVR. Older patients with severe AS had higher NT-pro-BNP values (median: 1936 ng/L, IQR: 553–4988), consistent with Elhmedi et al.¹³ This may be due to the patients' advanced ages, increased left ventricular load, and impaired myocardial function, resulting in poor postoperative survival.¹⁵ Our results revealed that older adults with preoperative NT-pro-BNP > 4853 ng/L who underwent TAVR typically had severe comorbidities: (1) lower hemoglobin and serum albumin levels; (2) impaired renal function, indicated by visibly higher BUN, Cr, and estimated glomerular filtration rate (eGFR) levels; (3) more chronic diseases, such as diabetes or need for hemodialysis; and (4) poorer left ventricular function. Pathophysiological mechanisms can be used to explain the high correlations with the high NT-pro-BNP level engendered by heart failure.^{16,17} Furthermore, patients with higher NT-pro-BNP values have higher chances of adverse prognoses and requiring

Table 3
Hospital stay and mortality rates according to NT-pro-BNP groups

Variable	Total (n = 132, 100%)		NT-pro-BNP ≤ 4853 (n = 96, 72.7%)		NT-pro-BNP > 4853 (n = 36, 27.3%)		p
Hospital stay (d), mean (SD)	20.1	20.3	17.5	21.0	27.0	17.0	0.009
Intensive care unit stay (d), mean (SD)	6.0	15.2	5.4	17.1	7.6	8.2	0.371
In-hospital mortality, n (%)	10	7.6	4	4.2	6	16.7	0.025
30-d mortality, n (%)	6	4.5	3	3.0	3	10.0	0.344
1-y mortality, n (%)	25	18.9	11	11.5	14	38.9	0.001

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

Table 4
Uni- and multivariable logistic regression analysis

Dependent variable	95% CI	p
Postoperative ECMO		
NT-pro-BNP ≤ 4853 vs NT-pro-BNP > 4853 (unadjusted)	1.388-20.064	0.025
NT-pro-BNP ≤ 4853 vs NT-pro-BNP > 4853 (adjusted)	1.604-94.109	0.016
20-d Cutting hospital stay (d)		
NT-pro-BNP ≤ 4853 vs NT-pro-BNP > 4853 (unadjusted)	3.734-22.073	<0.001
NT-pro-BNP ≤ 4853 vs NT-pro-BNP > 4853 (adjusted)	1.851-18.122	0.003
In-hospital mortality		
NT-pro-BNP ≤ 4853 vs NT-pro-BNP > 4853 (unadjusted)	1.388-20.064	0.025
NT-pro-BNP ≤ 4853 vs NT-pro-BNP > 4853 (adjusted)	0.391-12.516	0.369
1-y mortality		
NT-pro-BNP ≤ 4853 vs NT-pro-BNP > 4853 (unadjusted)	1.509-9.469	0.001
NT-pro-BNP ≤ 4853 vs NT-pro-BNP > 4853 (adjusted)	1.378-15.259	0.013

Multivariable logistic regression: controlled for age, gender, hemoglobin, serum albumin, DM, dialysis, LEVF < 45%. Hospital stay cutoff value by mean (20 days). ECMO = extracorporeal membrane oxygenation; LEVF = left ventricular ejection fraction; NT-pro-BNP = N-terminal-pro-brain natriuretic peptide.

an ECMO; the main cause may be the patient demonstrating unstable hemodynamics in the later stage of developing AS, resulting in higher risks of worsening hemodynamics during the operation period and ultimately culminating in the use of ECMO as an emergency strategy for surgical complications.¹⁸ Research reported that end-stage renal disease, pulmonary hypertension, and postoperative complications are predictors of prolonged hospital stays and that patients undergoing TAVR with higher preoperative NT-pro-BNP levels have a higher complexity of disease and severity of complications, leading to prolonged hospital stays. This study also indicates that patients with higher degrees of myocardial damage and disease complexity due to elevated NT-Pro-BNP require longer hospital stay.¹⁹

NT-pro-BNP can predict the 30-day mortality of patients who undergo TAVR.^{20,21} However, consistent with Elmidi et al,¹³ our results also did not reveal a correlation between NT-pro-BNP values and 30-day mortality rates; this may be because the NT-pro-BNP value in this study for sorting patients into groups (NT-pro-BNP > 4853 ng/L) was relatively close to the NT-pro-BNP value in Elmidi et al (NT-pro-BNP ≥ 4691 ng/L). We did observe a correlation between NT-pro-BNP levels and 1-year mortality, consistent with Huang et al⁸; in their study, patients with heart failure in the high NT-pro-BNP group had significantly more comorbidities and higher in-hospital and 1-year all-cause mortality rates than those in the low NT-pro-BNP group.⁸ This result is closely related to left ventricular systolic and diastolic dysfunction, arterial hypertension, and valve diseases; and hemodynamics in the ventricles affects long-term survival.^{9,13}

Even after adjustment for age, gender, hemoglobin, serum albumin, diabetes, dialysis, and LVEF < 45%, the between-group differences were still identified in postoperative ECMO installations, number of days in hospital, and 1-year mortality. Therefore, NT-pro-BNP can be expected to have prognostic value for older adults with severe AS who underwent TAVR.

NT-pro-BNP may be considered a more integrated reference value with major prognostic significance.

NT-pro-BNP data may have clinical significance in the prognoses of patients with severe AS undergoing TAVR.^{22,23} Our findings also highlighted that NT-pro-BNP levels can serve as predictors of risks in older adults. NT-pro-BNP tests are also cheaper than other cardiac examinations. Therefore, we recommend incorporating NT-pro-BNP tests into the risk assessment procedure for older adults with severe AS during their outpatient follow-up and preoperative assessment. However, other studies have warned that using NT-pro-BNP, a single plasma value, to predict patient prognoses requires careful assessments.^{24,25} In patients with highly severe and complex diseases that require accurate diagnoses and rapid treatments, even though preoperative NT-pro-BNP assessment may not be able to completely replace conventional, invasive examinations, if properly used to complement other tests, it may provide rapid and comprehensive information, leading to a higher quality of care for critically ill patients.

First, this was a single-center retrospective study with a relatively small sample size. Second, 1-year mortality is affected by multiple external factors, affecting the predictive ability of NT-pro-BNP. Therefore, large-scale prospective studies are required to verify the prognostic value of preoperative NT-pro-BNP levels among patients undergoing TAVR and evaluate correlations between specific adverse TAVR outcomes and NT-pro-BNP levels.

In conclusion, compared with older patients undergoing TAVR using preoperative NT-pro-BNP, those with preoperative NT-pro-BNP > 4853 ng/L had severe comorbidities, higher likelihoods of being fitted with an ECO machine, long hospital stay, and 1-year mortality. Older adults undergoing TAVR should maintain healthy preparations before surgery. Our data indicate that NT-pro-BNP (>4853 ng/L) is a useful preoperative

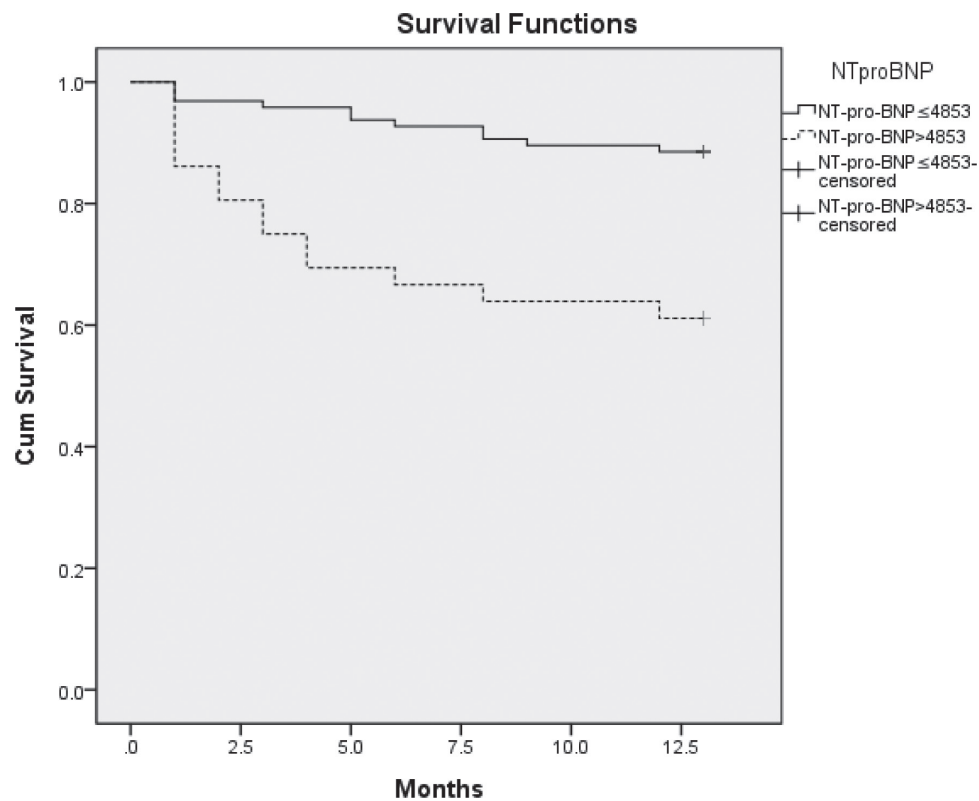


Fig. 1 Cumulative survival of the two groups. Mortality at 1 year was significantly different between the two groups (log-rank < 0.001).

indicator of potentially poor postoperative outcomes, with as a possible preoperative lab marker that can be used to improve preoperative risk assessments and select the best treatment strategy.

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