

# Predictors and Prognostic Effects of Perioperative Myocardial Injury After Transcatheter Aortic Valve Replacement According to VARC-3 Criteria

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**Purpose:** The impact of periprocedural myocardial injury (PPMI) according to VARC-3 criteria in patients undergoing transcatheter aortic valve replacement (TAVR) remains unclear. This study aimed to investigate the incidence, risk factors, and prognosis of PPMI in patients with severe aortic who underwent TAVR in China.

**Materials and Methods:** Between September 2012 and November 2021, 516 patients with severe aortic stenosis who underwent TAVR at the Fuwai Hospital were consecutively enrolled. PPMI was defined according to the VARC-3 criteria as a 70-fold increase of upper reference limit in cardiac troponin I (cTnI) levels. We compared the baseline characteristics, perioperative conditions, and in-hospital and long-term endpoints between the PPMI and non-PPMI groups. Logistic regression analysis was used to determine the predictors of PPMI. Survival probabilities for outcomes between the PPMI and non-PPMI groups were estimated using the Kaplan-Meier method.

**Results:** Of the enrolled patients (mean age: 75.5±7.2 years, 57.5% male), the incidence of PPMI was 20.5%. The median cTnI was 24.9 (interquartile range: 11.4–60.2) times the upper reference limit. After multivariable adjustment, female sex (odds ratio [OR]: 3.01, 95% confidence interval [CI]: 1.88–4.82,  $P < 0.001$ ), anticoagulant use (OR: 0.27, 95% CI: 0.08–0.96,  $P = 0.043$ ), balloon-expandable valve (OR: 0.27, 95% CI: 0.09–0.79,  $P = 0.017$ ), and secondary valve implantation (OR: 2.66, 95% CI: 1.40–5.03,  $P = 0.003$ ) were significantly associated with PPMI. Patients with PPMI had short- and long-term outcomes similar to those without PPMI.

**Conclusion:** Female sex and secondary valve implantation are predictors of an increased risk of PPMI, whereas baseline anticoagulant use and the use of balloon-expandable valves are protective factors. The presence of PPMI does not seem to indicate poor short- or long-term prognosis in patients undergoing TAVR.

**Keywords:** aortic stenosis, transcatheter aortic valve replacement, myocardial injury, risk factor, prognosis

## Introduction

Transcatheter aortic valve replacement (TAVR) has emerged as the frontline treatment comparable to surgical aortic valve replacement for patients with severe aortic stenosis (AS).<sup>1</sup> Periprocedural myocardial injury (PPMI) is common during cardiac surgery or interventional procedure and in general has been associated with poor outcomes.<sup>2,3</sup> The incidence of PPMI varies due to differences in selected biomarkers, diagnostic criteria, and study populations.<sup>4–12</sup> Previous studies have shown contradictory results regarding the impact of PPMI on post-TAVR outcomes.<sup>4–9</sup> Compared with the Valve Academic Research Consortium (VARC)-2, the updated VARC-3 criteria further raised the criterion of PPMI to 70 times the upper reference limit (URL), aiming at improve the discriminative ability to predict long-term outcomes.<sup>13,14</sup> Two

recent studies demonstrated that PPMI defined by the VARC-3 criteria could be used to predict adverse outcomes post-TAVR.<sup>15,16</sup> However, given the significant heterogeneity of the TAVR population and the controversial prognostic value of PPMI, it is necessary to extensively discuss this finding across different TAVR populations.

The clinical characteristics and aortic valve anatomy of Chinese patients with severe AS, including high proportion of bicuspid aortic valve (BAV), excessive calcification, and complex complications, may potentially contributed to PPMI.<sup>17,18</sup> Compared to tricuspid aortic valve, patients with BAV exhibit distinct leaflet and left ventricular remodeling, posing potential risk factors for PPMI.<sup>6,19</sup> Excessive calcification may also cause debris to dislodge into the coronary arteries during bioprosthesis deployment, leading to myocardial ischemia.<sup>20,21</sup> In addition, patients with multiple underlying conditions and frailty are also more prone to developing PPMI.<sup>22</sup> However, there is insufficient information regarding the incidence and risk factors of PPMI in such patients. Therefore, expanding these studies to include different patient populations could provide additional information for a comprehensive understanding of PPMI.

In light of the complicated condition and special aortic valve anatomy among Chinese patients with severe AS, this study aimed to determine the incidence and risk factors of PPMI according to the VARC-3 criteria among patients undergoing TAVR and investigate the impact of PPMI on short- and long-term prognosis.

## Methods and Materials

### Study Design and Population

This study retrospectively included patients who underwent TAVR for symptomatic severe aortic stenosis at the Fuwai Hospital between September 2012 and November 2021. The exclusion criteria were as follows: (1) patients without information about cardiac troponin at baseline or within 48 h post-TAVR; (2) patients who received valve-in-valve (TAVR-in-surgical aortic valve replacement/TAVR-in-TAVR) treatment; and (3) patients with coronary obstruction or transfer to open surgery. We initially included 589 patients and excluded 73. This study included 516 patients ([Supplementary Figure S1](#)). All patients underwent preoperative multidisciplinary team discussions to determine the TAVR indications and approach. TAVR procedures were performed according to standard clinical practice. The prosthesis size was based on preoperative computerized tomography measurements and the manufacturer's recommendations. The data were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The study was approved by the Ethics Review Committee of Fuwai Hospital, National Center for Cardiovascular Diseases (Approval No. 2020–1290). Written informed consent was obtained from all patients. This study was conducted in accordance with the principles of the Declaration of Helsinki.

### Measurement of Periprocedural Myocardial Injury

Levels of cardiac troponin I (cTnI) were measured using chemiluminescent immunoassay kits (Access AccuTnI, Beckman Coulter, California, Abbott Diagnostic Architect STAT) at the Quality Control Laboratory of Fuwai Hospital. The URL for cTnI was established on the basis of the 99th percentile value in a healthy population. According to the VARC-3 criteria, PPMI was defined as an increase in cTnI levels to  $\geq 70$  times the URL within 48 h post-TAVR in patients with normal baseline cTnI or an absolute increment exceeding the levels recommended for patients with elevated baseline cTnI.<sup>14</sup>

### Echocardiography and Computed Tomography

Experienced echocardiographers conducted echocardiographic assessments following the American Society of Echocardiography Guidelines.<sup>23</sup> Measurements the mean pressure gradient, aortic valve flow velocity, effective orifice area of the aortic valve, and left ventricular ejection fraction (LVEF) (measured using the biplane Simpson's method) were measured for all patients. Left ventricular diastolic diameter, intraventricular septum diastolic diameter, and posterior wall thickness were measured in two dimensions in the parasagittal view. The relative wall thickness and left ventricular mass index were calculated.<sup>24</sup> The classification of left ventricular remodeling was defined according to guideline recommendations.<sup>24</sup> Prosthesis function parameters obtained from the echocardiogram included mean transprosthetic pressure gradient and paravalvular leakage. All CT images were assessed using a 3mensio workstation

(3mensio Structural Heart, version 10.0; 3mensio Medical Imaging BV, the Netherlands). Imaging analysis was conducted by the core laboratories of the Fuwai Hospital. Details of the CT acquisition protocol are provided in [Supplementary Methods S1](#).

## Follow-Up and Endpoint

All patients were followed up at 1 month, 3 months, 6 months, 1 year, and each subsequent year after discharge via telephone interviews or outpatient visits. The endpoints were all-cause mortality and major adverse cardiovascular events (MACE). MACE were defined as a composite of cardiac death, non-fatal myocardial infarction, and non-fatal stroke.

## Data Collection and Definition

All baseline demographic and clinical treatment data for the patients were retrospectively collected using an electronic data capture system and subjected to dual verification for accuracy and reliability. All comorbidities were defined based on ICD-10 codes according to medical diagnosis. Large oversizing of the prosthesis was defined as a perimeter oversizing of  $> 9.5\%$  or an area oversizing of  $> 20\%$ .<sup>25</sup> Blood biomarkers, including N-terminal brain natriuretic peptide (NT-proBNP), creatinine, and lipid profile, were analyzed in a quality-controlled laboratory at Fuwai Hospital. Renal function was estimated using the estimated glomerular filtration rate (eGFR), calculated using the CKD Epidemiology Collaboration equation. Medication details upon discharge were documented.

## Statistical Analyses

Continuous data are presented as mean  $\pm$  SD or median (Q1-Q3), and categorical variables are expressed as numbers and percentages. Baseline data comparisons were conducted using Student's *t*-test or Mann-Whitney *U*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables to determine significant differences between the two groups (PPMI and non-PPMI).

Logistic regression analysis was used to determine the predictors of PPMI with odds ratios (ORs) and 95% confidence intervals (CIs). Multivariable logistic regression was performed using forward stepwise analysis with *P*-value of 0.10. Cox proportional hazards models were used to examine the association between baseline information and all-cause mortality with hazard ratios (HRs) and 95% CIs. All Cox regression models assessed the proportionality hazard assumption and the results were satisfactory. The change in LVEF from baseline to the one-year follow-up was analyzed using a paired-sample Student's *t*-test. Changes in NT-proBNP levels over the same period were evaluated using a paired-sample Wilcoxon rank-sum test. Survival probabilities for outcomes were estimated using Kaplan-Meier curves and Log rank tests. Statistical significance was set at a two-tailed *P*-value of  $< 0.05$ . All analyses were performed using Stata 15.0 (StataCorp LLC, College Station, TX, USA) and R version 4.0.2 (The R Project for Statistical Computing, Vienna, Austria).

## Results

### Baseline Characteristics

Baseline information, echocardiography findings, and medication use are shown in [Table 1](#). According to the VARC-3 criteria, the incidence of PPMI was 20.5% in all the patients. The distribution of cTnI levels before and post-TAVR is shown in [Figure 1](#). The mean age of the cohort was 75.5 (standard deviation: 7.2) years, with 57.5% being male. The median cTnI was 24.9 (interquartile range: 11.4–60.2) times that of the URL, and the median EuroSCORE II was 2.94 (IQR: 1.84–4.82). Patients in the PPMI group were more likely to be female, non-smokers, and to have higher total cholesterol levels. A higher mean aortic valve gradient, peak velocity, and lower left ventricular diastolic diameter were also observed in the PPMI group.

### Periprocedural Condition

Perioperative details are presented in [Table 2](#). The proportion of the BAV was higher in the PPMI group, whereas the annulus diameter and height of the right coronary artery were lower. The frequencies of self-expanding valve use and

**Table 1** Baseline Information

	<b>All (n=516)</b>	<b>Non-PPMI (n=410)</b>	<b>PPMI (n=106)</b>	<b>P value</b>
Fold of cTnl	24.90 (11.45–60.23)	18.47 (9.09–35.46)	119.09 (93.29–173.23)	<0.001
<b>Demographics and medical history</b>				
Age, years	75.54 ± 7.20	75.50 ± 7.12	75.68 ± 7.55	0.817
Male, %	297 (57.56%)	257 (62.68%)	40 (37.74%)	<0.001
BMI, kg/m <sup>2</sup>	23.60 ± 3.56	23.59 ± 3.67	23.65 ± 3.10	0.865
NYHA class ≥ III, %	381 (73.84%)	306 (74.63%)	75 (70.75%)	0.418
Hypertension, %	324 (62.79%)	259 (63.17%)	65 (61.32%)	0.725
Hyperlipemia, %	329 (63.76%)	260 (63.41%)	69 (65.09%)	0.748
Coronary heart disease, %	227 (43.99%)	182 (44.39%)	45 (42.45%)	0.720
Prior myocardial infarction, %	38 (7.36%)	34 (8.29%)	4 (3.77%)	0.112
Prior PCI, %	69 (13.37%)	59 (14.39%)	10 (9.43%)	0.181
Prior CABG, %	20 (3.88%)	17 (4.15%)	3 (2.83%)	0.531
Chronic heart failure, %	191 (37.02%)	160 (39.02%)	31 (29.25%)	0.063
Atrial fibrillation, %	84 (16.28%)	74 (18.05%)	10 (9.43%)	0.032
Prior stroke, %	63 (12.21%)	51 (12.44%)	12 (11.32%)	0.754
Prior permanent pacemaker, %	16 (3.10%)	12 (2.93%)	4 (3.77%)	0.654
Chronic kidney disease, %	42 (8.14%)	38 (9.27%)	4 (3.77%)	0.065
Diabetes mellitus, %	117 (22.67%)	101 (24.63%)	16 (15.09%)	0.037
Smoking, %	197 (38.18%)	168 (40.98%)	29 (27.36%)	0.010
EuroSCORE II, %	2.94 (1.84–4.82)	2.95 (1.85–4.86)	2.84 (1.76–4.27)	0.458
<b>Biomarker</b>				
eGFR, mL/min/1.73m <sup>2</sup>	63.31 ± 17.98	62.70 ± 17.61	65.66 ± 19.28	0.132
LDL-C, mmol/L	2.55 ± 0.98	2.51 ± 0.95	2.71 ± 1.09	0.060
NT-proBNP, pg/mL	1868.50 (782.00–5010.75)	1946.00 (746.00–5433.00)	1724.00 (883.00–3896.00)	0.560
<b>Echocardiography</b>				
LVEF, %	55.46 ± 13.49	54.66 ± 13.72	58.56 ± 12.16	0.008
LVMI, g/m <sup>2</sup>	142.05 ± 40.87	143.20 ± 41.42	137.33 ± 38.39	0.205
LVDD, mm	51.35 ± 8.16	51.98 ± 8.35	48.94 ± 6.90	<0.001
Left ventricular remodeling, %				0.058
Normal	34 (6.59%)	29 (7.07%)	5 (4.72%)	
Eccentric hypertrophy	151 (29.26%)	130 (31.71%)	21 (19.81%)	
Concentric remodeling	52 (10.08%)	40 (9.76%)	12 (11.32%)	
Concentric hypertrophy	279 (54.07%)	211 (51.46%)	68 (64.15%)	
Aortic valve mean gradient, mmHg	56.55 ± 17.54	55.75 ± 17.51	59.55 ± 17.56	0.048
Aortic valve peak velocity, m/s	4.71 ± 0.69	4.60 (4.20–5.10)	4.80 (4.50–5.19)	0.006
Aortic valve area, cm <sup>2</sup>	0.63 ± 0.22	0.65 ± 0.23	0.57 ± 0.18	0.010
Aortic stenosis pathology, %				0.259
Rheumatic	18 (3.49%)	16 (3.90%)	2 (1.89%)	
Degenerated	418 (81.01%)	335 (81.71%)	83 (78.30%)	
Congenital	80 (15.50%)	59 (14.39%)	21 (19.81%)	

(Continued)

Table 1 (Continued).

	All (n=516)	Non-PPMI (n=410)	PPMI (n=106)	P value
<b>Medication</b>				
Aspirin, %	390 (75.58%)	306 (74.63%)	84 (79.25%)	0.325
P2Y12 inhibitor, %	417 (80.81%)	322 (78.54%)	95 (89.62%)	0.010
Anticoagulant, %	41 (7.95%)	37 (9.02%)	4 (3.77%)	0.075
Statin, %	402 (77.91%)	321 (78.29%)	81 (76.42%)	0.678

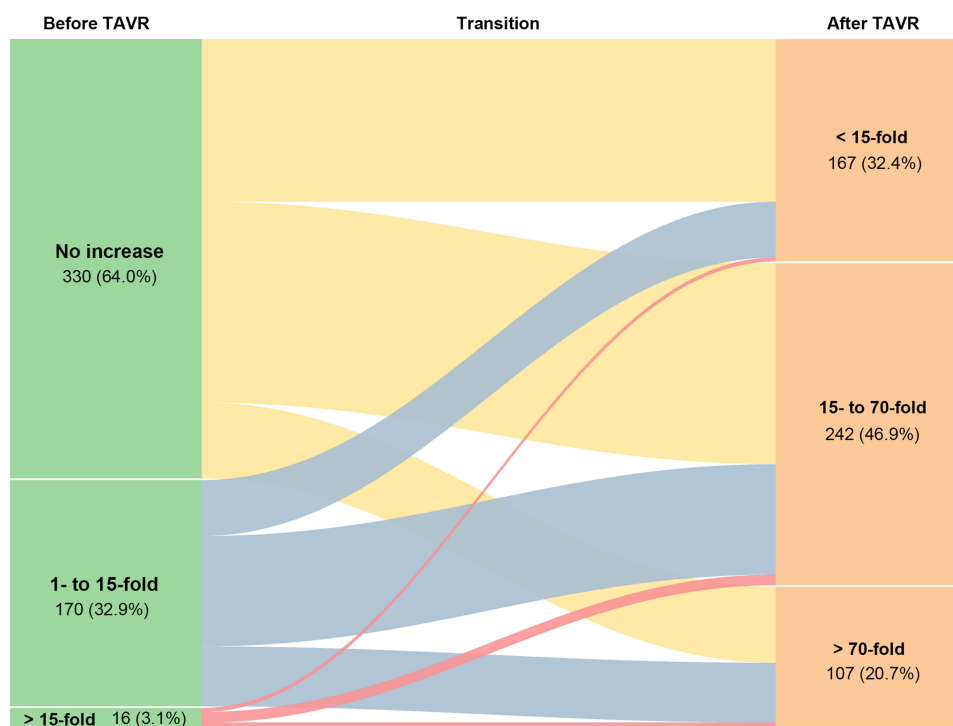
**Notes:** Data are presented as the mean  $\pm$  SD, median (interquartile range), or n (%). Comparison between non-PPMI and PPMI patients.

**Abbreviations:** BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal brain natriuretic peptide; cTnI, cardiac troponin I; LVEF, left ventricular ejection fraction; LVDD, left ventricular diastolic diameter; LVMI, left ventricular mass index; NYHA, New York Heart Association; ACEIs, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blocker; PPMI, periprocedural myocardial injury.

secondary valve implantation were higher in the PPMI group. Valve function assessments, including mean transprosthetic gradient and paravalvular leakage, showed no significant differences between the groups. The incidence of major bleeding events was slightly higher in the PPMI group ( $P = 0.042$ ), whereas there were no significant differences in other events.

## Predictors of Periprocedural Myocardial Injury

As shown in Table 3, multivariate logistic regression analysis identified female sex (odds ratio [OR]: 3.01, 95% confidence interval [CI]: 1.88–4.82,  $P < 0.001$ ) and secondary valve implantation (OR: 2.66, 95% CI: 1.40–5.03,  $P = 0.003$ ) as risk factors for PPMI, whereas baseline anticoagulant use (OR: 0.27, 95% CI: 0.08–0.96,  $P = 0.043$ ) and balloon-expandable valve (OR: 0.27, 95% CI: 0.09–0.79,  $P = 0.017$ ) were protective factors for PPMI.



**Figure 1** Transition of troponin I folds pre- and post-TAVR.

**Abbreviation:** TAVR, transcatheter aortic valve replacement.

**Table 2** Perioperative Conditions

	<b>All (n=516)</b>	<b>Non-PPMI (n=410)</b>	<b>PPMI (n=106)</b>	<b>P value</b>
<b>Procedure detail</b>				
Type of aortic valve, %				0.022
Bicuspid aortic valve	171 (33.1%)	126 (30.73%)	45 (42.45%)	
Tricuspid aortic valve	345 (66.9%)	284 (69.27%)	61 (57.55%)	
Annulus diameter, mm	24.42 ± 2.70	24.61 ± 2.71	23.67 ± 2.49	0.002
Coronary height, mm				
Left coronary artery	13.93 ± 3.66	14.00 ± 3.73	13.66 ± 3.34	0.402
Right coronary artery	16.79 ± 3.13	16.96 ± 3.16	16.12 ± 2.92	0.017
Calcium volume at HU 850, mm <sup>3</sup>	442.65 (222.20–787.88)	433.00 (221.20–774.80)	463.00 (266.70–897.80)	0.259
Large oversizing, %	217 (43.23%)	172 (42.89%)	45 (44.55%)	0.763
Approach, %				>0.999
Femoral	506 (98.06%)	401 (97.80%)	105 (99.06%)	
Carotid	3 (0.58%)	3 (0.73%)	0 (0.00%)	
Aortic	7 (1.36%)	6 (1.46%)	1 (0.94%)	
Anesthesia, %				0.385
Local/conscious sedation	317 (61.43%)	248 (60.49%)	69 (65.09%)	
General anesthesia	199 (38.57%)	162 (39.51%)	37 (34.91%)	
Prosthesis type, %				0.009
Self-expanding valve	460 (89.15%)	358 (91.46%)	102 (96.23%)	
Balloon-expandable valve	56 (10.85%)	52 (8.54%)	4 (3.77%)	
Secondary valve implantation, %	63 (12.21%)	41 (10.00%)	22 (20.75%)	0.003
Pre-dilatation, %	482 (93.59%)	383 (93.64%)	99 (93.40%)	0.926
Post-dilatation, %	89 (17.25%)	73 (17.80%)	16 (15.09%)	0.510
Concomitant PCI, %	82 (15.89%)	61 (14.88%)	21 (19.81%)	0.216
Mean transprosthetic pressure gradient, mmHg	12.47 ± 5.98	12.36 ± 5.51	12.76 ± 6.82	0.521
Moderate or severe perivalvular leakage, %	11 (2.13%)	7 (1.71%)	4 (3.77%)	0.189
<b>In-hospital events, %</b>				
Death	1 (0.19%)	1 (0.24%)	0 (0.00%)	>0.999
Stroke	4 (0.78%)	3 (0.73%)	1 (0.94%)	>0.999
Acute kidney injury	3 (0.58%)	1 (0.24%)	2 (1.89%)	0.109
Major bleeding	2 (0.39%)	0 (0.00%)	2 (1.89%)	0.042
Major vessel complication	16 (3.10%)	14 (3.41%)	2 (1.89%)	0.419
Length of admission, day	11 (9–15)	11 (9–15)	12 (8–15)	0.793

**Abbreviations:** PPMI, periprocedural myocardial injury; PCI, percutaneous coronary intervention; HU, Hounsfield unit.

## Association Between Periprocedural Myocardial Injury and Cardiac Function and Long-Term Prognosis

A total of 374 patients (72.5%) underwent echocardiographic assessment at one year, and NT-proBNP results were available for 255 patients (49.4%). In the matched analyses, a significant improvement in LVEF at one year post-TAVR was observed in both the PPMI and non-PPMI groups in the overall population (Figure 2 and [Supplementary Table S1](#)). Over a median follow-up period of 3.5 (2.2–4.6) years, 77 cases (14.9%) experienced all-cause mortality and 38 cases (7.4%) experienced MACE. The cumulative incidence of all-cause mortality and MACE in the PPMI versus non-PPMI groups is depicted in Figure 3 and detailed in [Supplementary Table S2](#). No significant differences were observed between PPMI and non-PPMI groups. The results of the multivariate Cox regression analysis also supported these findings ([Supplementary Tables S3](#) and [S4](#)).

**Table 3** Predictors of Periprocedural Myocardial Injury

	Univariable Model		Multivariable Model	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, per 1-y increase	1.00 (0.97–1.03)	0.816	-	-
Female	2.77 (1.78–4.31)	<0.001	3.01 (1.88–4.82)	<0.001
BMI, per 1 kg/m <sup>2</sup> increase	1.00 (0.95–1.07)	0.867	-	-
NYHA class ≥ III	0.82 (0.51–1.32)	0.418	-	-
Hypertension	0.92 (0.59–1.43)	0.725	-	-
Hyperlipemia	1.08 (0.69–1.68)	0.748	-	-
Coronary heart disease	0.92 (0.60–1.42)	0.720	-	-
Prior myocardial infarction	0.43 (0.15–1.25)	0.122	-	-
Prior PCI	0.62 (0.30–1.26)	0.185	-	-
Prior CABG	0.67 (0.19–2.34)	0.534	-	-
Chronic heart failure	0.64 (0.41–1.03)	0.064	-	-
Atrial fibrillation	0.47 (0.23–0.95)	0.036	-	-
Prior stroke	0.90 (0.46–1.75)	0.754	-	-
Prior permanent pacemaker	1.30 (0.41–4.12)	0.655	-	-
Chronic kidney disease	0.38 (0.13–1.10)	0.075	-	-
Diabetes mellitus	0.54 (0.30–0.97)	0.039	0.57 (0.31–1.05)	0.072
Smoking	0.54 (0.34–0.87)	0.011	-	-
LDL-C, per 1 mmol/L increase	1.21 (0.99–1.49)	0.063	-	-
NT-proBNP, per 1000 pg/mL increase	0.97 (0.93–1.01)	0.114	-	-
LVEF, per 5% increase	1.02 (1.01–1.04)	0.009	1.02 (1.00–1.04)	0.055
LVDD, per 1 mm increase	0.95 (0.92–0.98)	0.001	-	-
Concentric remodeling/hypertrophy	1.38 (1.07–1.77)	0.012	1.63 (0.94–2.82)	0.081
Bicuspid vs tricuspid aortic valve	1.66 (1.07–2.58)	0.023	1.61 (0.99–2.60)	0.054
Aortic valve mean gradient, per 1 mmHg increase	1.01 (1.00–1.02)	0.050	-	-
Left coronary artery height, per 1 mm increase	0.97 (0.91–1.04)	0.401	-	-
Right coronary artery height, per 1 mm increase	0.91 (0.85–0.98)	0.018	-	-
Calcium volume at HU 850, mm <sup>3</sup>	1.02 (0.98–1.06)	0.385	-	-
Large oversizing	1.03 (0.67–1.58)	0.895	-	-
Balloon-expandable vs self-expanding valve	0.27 (0.09–0.76)	0.014	0.27 (0.09–0.79)	0.017
Pre-dilation	0.96 (0.40–2.27)	0.926	-	-
Post-dilation	0.82 (0.45–1.48)	0.511	-	-
Secondary valve implantation	2.36 (1.33–4.17)	0.003	2.66 (1.40–5.03)	0.003
Concomitant PCI	1.27 (0.74–2.17)	0.378	-	-
Antiplatelet agents	2.30 (0.89–5.98)	0.086	-	-
Anticoagulant	0.39 (0.14–1.13)	0.085	0.27 (0.08–0.96)	0.043

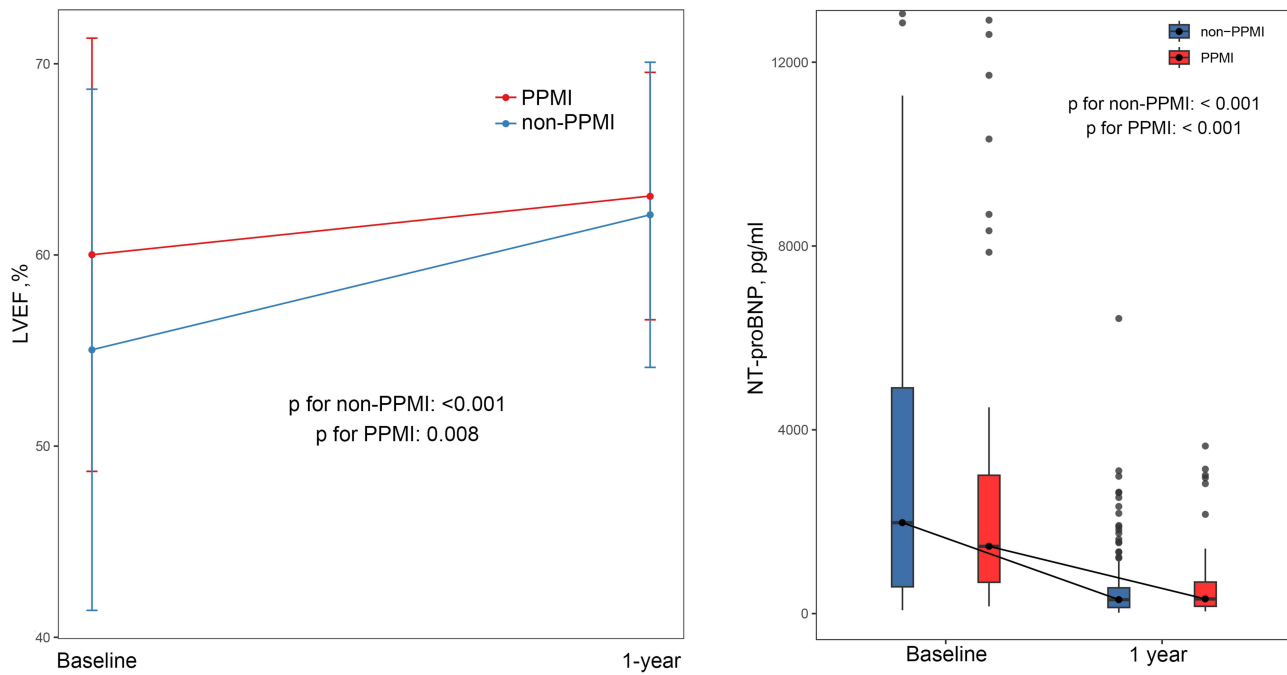
**Abbreviations:** PPMI, periprocedural myocardial injury; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVDD, left ventricular diastolic diameter; NYHA, New York Heart Association; OR, odds ratio; CI, confidence interval.

## Discussion

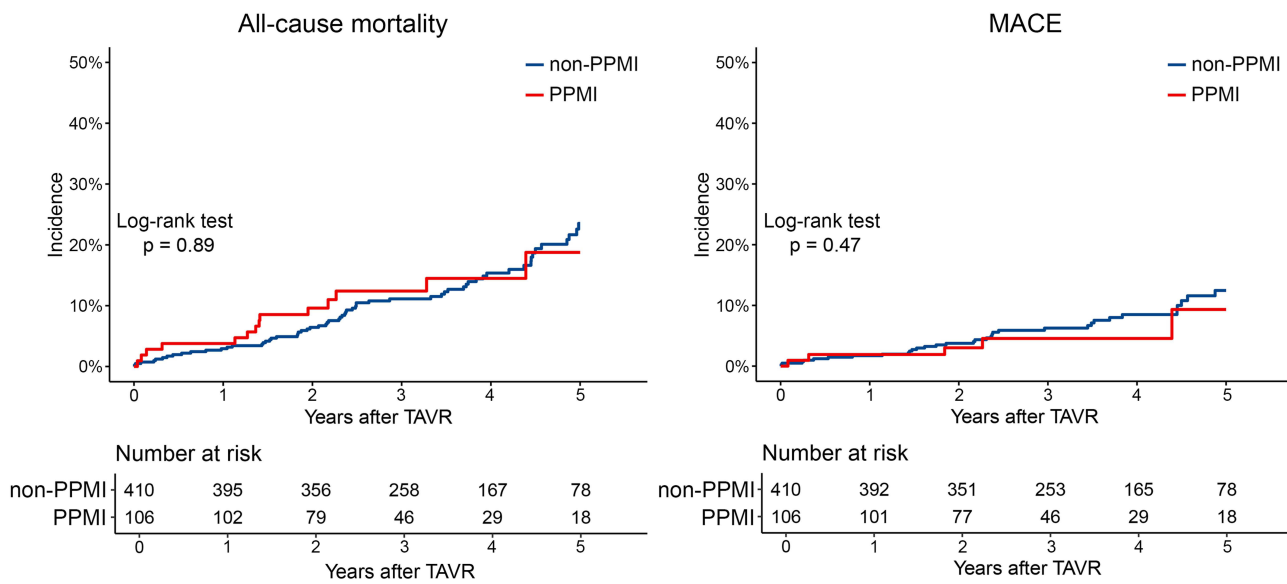
This study indicated that the incidence of PPMI in Chinese patients undergoing TAVR, as defined by the VARC-3 criteria, was 20.5%. Female sex and second valve implantation were predictors of an increased risk of PPMI, whereas baseline anticoagulant use and the use of balloon-expandable valves were protective factors. Concomitant PCI during TAVR did not increase the incidence of PPMI. The PPMI was not associated with cardiac dysfunction or long-term prognosis after TAVR.

With advancements in TAVR, the incidence of myocardial infarction due to coronary artery occlusion has substantially decreased. However, procedure-related PPMI remain an inevitable complication. PPMI, which is distinct from perioperative myocardial infarction, is primarily characterized by elevated cardiac biomarkers without fulfilling other





**Figure 2** Cardiac function at baseline and 1-year follow-up according to the presence and absence of PPMI.  
**Abbreviations:** LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal brain natriuretic peptide; PPMI, periprocedural myocardial injury.



**Figure 3** Kaplan-Meier estimates for all-cause mortality and MACE according to the presence and absence of PPMI.  
**Abbreviations:** PPMI, periprocedural myocardial injury; MACE, major adverse cardiovascular event.

diagnostic criteria for myocardial infarction. Previous studies employing the VARC-2 criteria have reported PPMI incidence rates ranging from 27.9% to 79.0%.<sup>5-8,12,26</sup> Two recent studies based on the VARC-3 criteria in patients receiving bioprosthesis implantation reported a PPMI incidence of approximately 14%, which was lower than the 21% observed in our study.<sup>15</sup> This discrepancy may be attributed to the higher prevalence of BAV, the complexity of the procedures, and the predominant use of self-expanding valves in our patient cohort.<sup>12,26,27</sup> In addition, we found that 26% of the population with elevated preoperative TnI developed PPMI, compared to 17% in the population with normal



preoperative TnI, each of which accounted for half of the total PPMI cases. This finding suggests that patients with preoperative myocardial injury are more likely to develop PPMI after TAVR.

Previous studies examining risk factors for PPMI have investigated both demographic characteristics and comorbidities and have focused on perioperative techniques.<sup>7,8,10</sup> Female sex and use of self-expanding valves are independent predictors of PPMI, consistent with previously published studies.<sup>6,10,12</sup> Furthermore, we found that secondary valve implantation was associated with an increased incidence of PPMI, whereas anticoagulant use was associated with a decreased trend. Secondary valve implantation usually involves a more complex procedure requiring more rapid pacing, longer operative time, and higher risk of aortic valve debris falling off. This also confirms why early inexperience and first-generation valve use are some procedural risk factors.<sup>10</sup> The protective effect of anticoagulation on PPMI may be by reducing microembolic particle formation during TAVR, improving coronary mismatch of oxygen supply demand and avoiding the risk of coronary thrombosis.

In our study, the incidence of concomitant PCI during TAVR was 16%, but this was not a risk factor for PPMI. PCI during TAVR is mainly used for coronary artery protection or resolution of existing severe coronary stenosis. The current strategies for treating AS with coronary artery disease are not clearly recommended. However, our study found that concomitant PCI did not increase the risk of PPMI, suggesting that this strategy is safe for patients with coronary complications.

The impact of PPMI on post-TAVR outcomes remains a subject of debate.<sup>4-6,28</sup> Some studies have suggested that PPMI using the VARC-2 definition is a strong predictor of short- and medium-term mortality.<sup>4,28</sup> However, some studies have argued that PPMI does not confer additional prognostic value.<sup>6-8,12</sup> Recent studies using the VARC-3 criteria for PPMI found that PPMI was associated with poor outcome 1-year post-TAVR.<sup>15,16</sup> Notably, the low incidence of PPMI in both studies improved specificity in identifying patients at high risk for poor prognosis.<sup>15,16</sup> However, as mentioned in some insights, PPMI may be only one indicator of procedural complexity, and there are many factors that influence it.<sup>8,26</sup> Different TAVR systems, patient characteristics, and operative procedures may have different rates of PPMI.<sup>8,26</sup> Our study suggests that adopting a PPMI defined by VARC-3 may not result in delayed cardiac complexity. This may be due to differences in patient cohorts, anatomical lesion characteristics, and procedural details. This supports the previous view that PPMI may be merely an experiential process,<sup>29</sup> but we cannot ignore the associated risk of potentially adverse outcomes, as some patients may still be alerted to PPMI. Since most patients with severe aortic stenosis (AS) present with heart failure with preserved ejection fraction, which is characterized by compensatory left ventricular hypertrophy and diastolic dysfunction caused by pressure overload, these changes can be detected by echocardiography. Our study found that left ventricular concentric remodeling or hypertrophy might be associated with PPMI, although it was not statistically significant in multivariate analysis. Previous studies have shown that left ventricular dysfunction is a residual risk in TAVR patients.<sup>30</sup> Exercise stress echocardiography is capable of detecting left ventricular dysfunction, and evidence indicates that it provides additional prognostic insights for AS and TAVR patients.<sup>31,32</sup> Thus, further studies should be designed to evaluate whether exercise stress echocardiography might help identify additional echocardiographic predictors of PPMI after TAVR.

Our study has several advantages. First, to our knowledge, this study is one of the few larger survival studies reported in Chinese TAVR patients, with a longer follow-up period of up to 5 years, which has unique value in determining the long-term prognosis of PPMI. Second, we excluded patients with acute coronary occlusion or intraoperative conversions to surgery from our study population, as elevations in cTnI levels in these cases were not solely attributable to PPMI and were complicated. We created conditions for studying the long-term effects of the PPMI. Third, most of the included patients underwent TAVR via the femoral artery approach, circumventing confounding myocardial injury from transapical access. However, our study has some limitations. First, during the study period, cTnI assays evolved to include both standard and high-sensitivity assays. This was due to the iteration of cTnI measurement techniques. However, PPMI assessment for each patient in our study was based on the corresponding URL of the assay kit. Second, as patient inclusion began in 2012, first-generation prosthesis products were predominantly used, possibly leading to a higher proportion of secondary valve implantations than those in other studies. However, this also indirectly highlights anatomical complexity and operational difficulty. Third, future studies with longer follow-up time are needed to confirm

our conclusions. Finally, because this was a single-center study with a limited sample size, the generalizability of our findings to other settings requires further investigation.

## Conclusions

In summary, PPMI is relatively common in severe AS patients undergoing TAVR. In addition to some baseline features (sex and anticoagulant use), some procedural details (secondary valve implantation and type of bioprosthesis) are also associated with the occurrence of PPMI. PPMI did not affect the cardiac function or long-term outcomes in these patients. Further studies are needed to confirm the findings.

## Ethics Approval and Consent to Participate

The study was approved by the Ethics Review Committee of Fuwai Hospital, National Center for Cardiovascular Diseases (Approval No. 2020-1290). Written informed consent was obtained from all patients.

## Acknowledgments

We would like to thank all the participants included in the study.

## Funding

This work was supported by the Beijing Natural Science Foundation (7244395), the National Key R&D Program of China (2020YFC2008100), the CAMS Innovation Fund for Medical Sciences (2022-I2M-C&T-B-044), and the National High Level Hospital Clinical Research Funding (2023-GSP-GG-38).

## Disclosure

The authors report no conflicts of interest in this work.

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