Original papers

# Neutrophil-to-lymphocyte ratio and prognostic nutritional index in predicting composite endpoint of early safety following transcatheter aortic valve replacement

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## Abstract

**Background.** The incidence of composite endpoint of early safety (CEES) after transcatheter aortic valve replacement (TAVR) has been a topic of focus within the cardiovascular field due to its impact on long-term patient outcomes. Timely prophylactic interventions are crucial for patients identified as high risk for CEES through preoperative risk stratification.

**Objectives.** This study aimed to explore the connection between inflammatory and nutritional markers, specifically the neutrophil-to-lymphocyte ratio (NLR) and prognostic nutritional index (PNI), and CEES occurrence.

**Materials and methods.** A cohort of 134 patients undergoing TAVR in a single center was studied. The study endpoint was the occurrence of CEES, which was defined according to the Valve Academic Research Consortium 3.

**Results.** The CEES was reached in 25.4% of patients at 30 days. A high NLR was associated with a 5.55-fold increased risk of CEES (95% confidence interval (95% CI): 1.52–20.29; $p < 0.05$), while a low PNI was linked to a 4.43-fold increased risk (95% CI: 1.55–12.65; $p < 0.01$). Combining NLR and PNI provided additional risk stratification for high-risk patients (hazard ratio (HR), 95% CI: 2.24–43.37; $p < 0.005$).

**Conclusions.** A high NLR and low PNI were shown to be significant predictors of CEES following TAVR. These findings underscore the significance of NLR and PNI in the risk assessment of TAVR patients, offering valuable insights for preventive measures.

**Key words:** prognostic nutritional index, neutrophil-to-lymphocyte ratio, transcatheter aortic valve replacement

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# Background

In recent years, there has been a significant focus on clinical endpoints observed in patients who undergo transcatheter aortic valve replacement (TAVR). The concept of composite endpoints was initially introduced in the Valve Academic Research Consortium (VARC) Consensus Report in 2011.[1] With the continuous accumulation of TAVR experience and advancements in related studies, the indications for TAVR have broadened to include low-risk patients,[2,3] and the latest definition of composite endpoints was introduced in the VARC-3 in 2021.[4] Within this definition, the composite endpoint of early safety (CEES) at 30 days serves as a measure of the procedure's early safety and effectiveness, encompassing a variety of adverse events that can have a significant impact on patient outcomes.[5–9] Consequently, an early prediction of these adverse events and the implementation of prophylactic interventions are crucial for improving patient outcomes.

In the development and occurrence of atherosclerosis and calcific aortic valve disease, inflammation is a crucial factor.[10–12] The neutrophil-to-lymphocyte ratio (NLR), an emerging inflammatory biomarker, has gained widespread attention in the past decade due to its inexpensiveness and easy accessibility. Several studies have illustrated a significant correlation between elevated preoperative NLR levels and increased postoperative mortality as well as acute kidney injury (AKI) in patients undergoing TAVR.[13,14]

Furthermore, malnutrition also has an adverse impact on the prognosis following TAVR. Elderly patients comprise a considerable proportion of the population undergoing TAVR treatment, and malnutrition is particularly prevalent in this group. Previous studies have indicated that malnourished patients have higher mortality rates following TAVR procedures.[15] The prognostic nutritional index (PNI) is a useful indicator for assessing nutritional status and has been validated for its predictive value in cardiovascular diseases such as heart failure and acute coronary syndromes.[16–19] Recent research has also suggested that PNI exhibits good predictive ability for post-TAVR survival.[20]

Neutrophil-to-lymphocyte ratio and PNI serve as predictors of post-TAVR complications by reflecting the systemic inflammatory status and nutritional level. However, there is currently a lack of research demonstrating the predictive value of these 2 indicators for composite endpoints such as CEES.

# Objectives

This research aimed to investigate the impact of the systemic inflammatory response and nutritional status on the CEES after TAVR, specifically looking at NLR and PNI. Additionally, the study assessed the predictive accuracy of NLR and PNI in identifying the occurrence of post-TAVR complications.

# Materials and methods

## Study design

The study retrospectively gathered common inflammatory and nutritional indicators for the study population. Baseline characteristics for the entire population and differences between subgroups divided according to the occurrence of CEES were analyzed. The prognostic significance of inflammatory and nutritional indicators in predicting CEES following TAVR was studied.

## Study patients

This retrospective and observational study included 145 consecutive patients who underwent TAVR at the Second Affiliated Hospital of Nanchang University (Nanchang, China) between January 2018 and February 2023. Eleven individuals were excluded from the study because of a preoperative red blood cell transfusion, cancer, sick sinus syndrome, and high-degree atrioventricular block. As this was a retrospective study, the need for informed consent was not required.

## Data collection

Demographic characteristics, clinical concomitant diseases, laboratory parameters, and pre-procedural imaging parameters were collected. Furthermore, the preprocedural Society of Thoracic Surgeons (STS) scores were calculated. In terms of inflammation parameters, we calculated the NLR, platelet-to-lymphocyte ratio (PLR) and monocyte-to-high-density lipoprotein ratio (MHR). Neutrophil-to-lymphocyte ratio is calculated as the ratio of neutrophils to lymphocytes, PLR as the ratio of platelets to lymphocytes, and MHR as the ratio of monocytes to high-density lipoprotein concentrations. For nutritional parameters, we calculated the body mass index (BMI) and the PNI. Prognostic nutritional index is measured as follows: (10 × serum albumin [g/dL]) + (0.005 × total lymphocytes [1000/μL]).[21]

## TAVR procedure

The multidisciplinary Heart Team in our center evaluated all patients and formulated operation plans after ruling out definite contraindications. Preoperative transthoracic echocardiography and multidetector computed tomography (MDCT) were performed to assess the anatomy of the aortic valve and root. Based on the anatomical parameters and clinical characteristics, a suitable valve type and size were selected. All valves in this study used self-expanding valves and included the VENUS-A (Venus MedTech, Hangzhou, China) and VitaFlow (MicroPort, Shanghai, China) valves. All patients underwent general anesthesia by endotracheal intubation in the cardiac catheterization laboratory and monitoring using transesophageal echocardiography.

The preferred access for TAVR was transfemoral with other alternative accesses, including transcarotid or transaxillary. Following the procedure, all patients were transferred to the cardiac intensive care unit for observation.

## Endpoint

The endpoint of this study was the occurrence of the CEES at 30 days, which was defined with VARC-3. This comprises all-cause mortality; stroke; VARC type 2–4 bleeding; major vascular, access-related, or cardiac structural complications; acute kidney injury stage 3 or 4; moderate or severe aortic regurgitation; new permanent pacemaker placement due to procedure-related conduction abnormalities; surgery or intervention related to the device.

## Statistical analyses

The data analysis was performed using IBM SPSS v. 26.0 software (IBM Corp., Armonk, USA). Medians (interquartile ranges) or means ± standard deviations (±SD) were used to represent continuous variables, while frequencies (percentages) were used for categorical variables. Statistical significance was defined as a p-value of less than 0.05. Continuous variables were compared using t-tests or Mann–Whitney U tests, while categorical variables were compared using the $\chi^2$ test or Fisher's test. The risk factors associated with the study endpoints were identified through univariate and multivariate logistic regression analyses conducted in sequence. For multivariate analysis, we adjusted for age, gender, STS score, New York Heart Association (NYHA) classification, hypertension, diabetes mellitus, coronary heart disease (CHD), atrial fibrillation, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), hemoglobin, platelet, hematocrit, red blood cell distribution width (RDW), mean platelet volume (MPV), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), non-high-density lipoprotein cholesterol (NHDL-c), lipoprotein(a) (Lp(a)), B-type natriuretic peptide (BNP), serum creatinine, left ventricular ejection fraction (LVEF), peak aortic jet velocity, annulus diameter, left ventricular outflow tract diameter, and ascending aorta diameter. The results were presented in terms of odds ratios (ORs) along with their corresponding 95% confidence intervals (95% CIs). A receiver operating characteristic (ROC) curve was generated to assess the predictive value of the risk factor for the occurrence of CEES, and the optimal cutoff values for NLR and PNI were identified.

# Results

## Baseline characteristic

A total of 134 patients undergoing TAVR at our center were included in this study. Among this cohort, the mean age was 71.39 ±6.92 years, with 38.8% of the population being female. The median (range) STS score was 2.36 (1.60, 3.90) and the median (range) LVEF was 56.5 (43.75, 64). Thirty-one patients (23.1%) were classified as a NYHA class IV. The occurrence of CEES at 30 days in all patients was 25.4% (34/134). We also analyzed the differences between patients who experienced CEES and those who did not. Compared to the non-CEES group, patients in the CEES group tended to have higher STS scores and BNP levels. Additionally, these patients had a higher proportion of NYHA class IV (41.2%) and intraoperative use of mechanical circulatory support devices (26.5%), but a lower baseline LVEF. In terms of inflammatory markers, the CEES group had higher NLR and MHR values compared to the non-CEES group, although PLR showed no significant differences. Regarding nutritional markers, patients in the CEES group had a lower PNI compared to the non-CEES group, but there was no significant difference in BMI between the groups. Further details are outlined in Table 1.

## Comparison of baseline characteristics according to NLR/PNI binaries

Based on the ROC curve analysis for CEES incidence, the optimal NLR and PNI cutoff values were established at 2.27 and 42.9, respectively. Subsequently, patients were divided into 2 groups according to NLR and PNI binaries, and the baseline characteristics were analyzed (Table 2). Notably, the patients with high NLR values or low PNI values had a higher incidence of CEES and exhibited higher STS scores, BNP levels, PLR values, and RDW values, but had lower LVEF measurements. Additionally, higher NLR levels were associated with higher baseline creatinine levels, as well as a higher prevalence of hypertension and diabetes. On the other hand, patients with low PNI levels had lower baseline levels of hemoglobin and high-density lipoprotein cholesterol, a higher proportion of NYHA class IV, and a higher requirement rate of intraoperative mechanical circulatory support.

## Prognostic significance in CEES

The levels of NLR or PNI were associated with the occurrence of CEES (Table 3). The risk of CEES in patients with a high NLR or low PNI was 5.55 (95% CI: 1.52–20.29) and 4.43 (95% CI: 1.55–12.65), respectively, compared to the patients with a low NLR or high PNI. To investigate whether the combination of NLR and PNI provides additional prognostic value, we further divided the patients into 3 groups: 1) NLR-low and PNI-high, 2) NLR-high or PNI-low and 3) NLR-high and PNI-low. We included the new categorical variables in the model for analysis. This simple and effective stratification successfully categorized patients into low-, intermediate- (OR = 4.07, (95% CI: 1.06–15.68)), and

**Table 1.** Demographic, clinical and procedural characteristics

| Variable | Total population | CEES | | |
|---|---|---|---|---|
| | | CEES group (n = 34) | Non-CEES group (n = 100) | p-value |
| Age [years] | 71.39 ±6.92 | 69.68 ±8.26 | 71.97 ±6.34 | 0.146 |
| Female, n (%) | 52 (38.8) | 11 (32.4) | 41 (41) | 0.371 |
| BSA [m$^2$] | 1.57 ±0.16 | 1.60 ±0.17 | 1.56 ±0.16 | 0.213 |
| BMI [kg/m$^2$] | 22.08 (20.29–24.06) | 21.76 (19.81–25.02) | 22.24 (20.31–23.90) | 0.988 |
| STS score | 2.36 (1.60–3.90) | 3.13 (1.80–5.57) | 2.22 (1.59–3.35) | 0.028 |
| NYHA class IV, n (%) | 31 (23.1) | 14 (41.2) | 17 (17) | 0.004 |
| Hypertension, n (%) | 70 (52.2) | 21 (61.8) | 49 (49) | 0.198 |
| Diabetes mellitus, n (%) | 17 (12.7) | 5 (14.7) | 12 (12) | 0.682 |
| CHD, n (%) | 35 (26.1) | 9 (26.5) | 26 (26.0) | 0.957 |
| Atrial fibrillation, n (%) | 19 (14.2) | 7 (20.6) | 12 (12) | 0.215 |
| CVD, n (%) | 16 (11.9) | 2 (5.9) | 14 (14) | 0.207 |
| COPD, n (%) | 14 (10.4) | 3 (8.8) | 11 (11.0) | 0.720 |
| CKD, n (%) | 15 (11.2) | 5 (14.7) | 10 (10) | 0.530 |
| Laboratory index | | | | |
| RBC [×10$^9$/L] | 4.11 ±0.55 | 4.02 ±0.55 | 4.14 ±0.55 | 0.307 |
| Hemoglobin [g/L] | 124.79 ±16.05 | 121.91 ±17.47 | 125.77 ±15.50 | 0.227 |
| Platelet count [×10$^9$/L] | 167 (132.75–198.25) | 168.00 (140.75–199.25) | 160.5 (131.25–197.25) | 0.476 |
| NLR | 2.96 (2.11–4.61) | 3.74 (2.65–7.03) | 2.71 (1.99–4.13) | 0.001 |
| PLR | 129.13 (94.41–162.65) | 149.82 (94.41–193.81) | 124.44 (93.01–161.06) | 0.161 |
| MHR | 0.37 (0.27–0.57) | 0.48 (0.31–0.70) | 0.36 (0.26–0.55) | 0.027 |
| Hematocrit [%] | 38.12 ±4.49 | 37.54 ±5.14 | 38.32 ±4.25 | 0.379 |
| RDW [%] | 13.30 (12.58–14.30) | 13.70 (12.60–14.65) | 13.2 (12.5–14.08) | 0.122 |
| MPV [fL] | 11.05 (10.40–11.83) | 11.15 (10.48–11.93) | 11.0 (10.2–11.78) | 0.350 |
| HDL-c [mmol/L] | 1.18 (0.99–1.43) | 1.15 (0.86–1.43) | 1.18 (1.02–1.43) | 0.597 |
| LDL-c [mmol/L] | 2.27 (1.68–3.09) | 1.95 (1.54–3.01) | 2.34 (1.77–3.10) | 0.093 |
| NHDL-c [mmol/L] | 3.04 (2.30–3.72) | 2.74 (2.15–3.56) | 3.07 (2.36–3.78) | 0.121 |
| Lp (a) [mg/L] | 159.25 (78.08–355.85) | 159.25 (62.13–375.65) | 160.25 (83.00–315.10) | 0.904 |
| PNI | 45.87 ±5.26 | 43.28 ±6.25 | 46.74 ±4.59 | 0.005 |
| BNP [pg/mL] | 679.72 (261.88–1811.09) | 1203.26 (252.00–5000) | 664.57 (259.96–1520.77) | 0.034 |
| Creatinine [µmol/L] | 81.70 (70.69–110.58) | 87.60 (74.43–127.70) | 81.10 (68.95–106.08) | 0.146 |
| Baseline echocardiographic parameters | | | | |
| Aortic regurgitation ≥moderate, n (%) | 18 (13.4) | 4 (11.8) | 14 (14) | 0.741 |
| LVEDD [mm] | 52.00 (46.00–59.00) | 54.5 (45.5–64.25) | 50.5 (46.0–57.0) | 0.083 |
| LVESD [mm] | 36.0 (29.75–44.0) | 42.00 (29.75–54.50) | 36.00 (29.25–42.00) | 0.031 |
| LVEF [%] | 56.5 (43.75–64) | 49.5 (31.25–61.00) | 58.00 (45.25–64.00) | 0.018 |
| Peak aortic jet velocity [m/s] | 4.43 (3.98–5.01) | 4.33 (3.90–4.82) | 4.49 (4.02–5.08) | 0.390 |
| Baseline MDCT parameters | | | | |
| Annulus diameter [mm] | 24.93 ±2.65 | 25.56 ±2.90 | 24.71 ±2.55 | 0.108 |
| Annulus area [mm$^2$] | 477.97 ±102.25 | 25.56 ±2.90 | 24.71 ±2.55 | 0.153 |
| LVOT diameter [mm] | 25.65 (23.68, 28.9) | 26.75 (23.25, 30.13) | 25.55 (23.70, 28.60) | 0.284 |
| Ascending aorta diameter [mm] | 37.85 ±4.56 | 38.70 ±5.63 | 37.56 ±4.13 | 0.209 |
| Procedural details | | | | |
| Circulatory support, n (%) | 9 (6.7) | 9 (26.5) | 0 (0) | <0.001 |
| Valve size >26 mm, n (%) | 50 (37.3) | 14 (41.2) | 36 (36) | 0.590 |
| 2$^{nd}$ valve needed, n (%) | 34 (25.4) | 10 (29.4) | 24 (24) | 0.531 |

Values are presented as counts (percentages) or median (IQR). CEES – composite endpoints of early safety; BSA – body surface area; STS – Society of Thoracic Surgery Risk Score; NYHA – New York Heart Association; CHD – coronary heart disease; CVD – cerebrovascular disease; COPD – chronic obstructive pulmonary disease; CKD – chronic kidney disease; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; MHR – monocyte-to-high density lipoprotein cholesterol ratio; RDW – red blood cell distribution width; MPV – mean platelet volume; HDL-c – high-density lipoprotein cholesterol; LDL-c – low-density lipoprotein cholesterol; NHDL-c – non-high-density lipoprotein cholesterol; Lp(a) – lipoprotein(a); PNI – prognostic nutritional index; BNP – B-type natriuretic peptide; LVEDD – left ventricular end-diastolic dimension; LVESD – left ventricular end-systolic dimension; LVEF – left ventricular ejection fraction; MDCT – multidetector computed tomography; LVOT – left ventricular outflow tract.

Table 2. Demographic, clinical and procedural characteristics and outcomes in patients according to NLR and PNI

| Variable | NLR | | | PNI | | |
|---|---|---|---|---|---|---|
| | NLR-low group (n = 42) | NLR-high group (n = 92) | p-value | PNI-high group (n = 102) | PNI-low group (n = 32) | p-value |
| Age [years] | 71.31 ±5.57 | 71.42 ±7.48 | 0.930 | 71.32 ±6.43 | 71.59 ±8.41 | 0.848 |
| Female, n (%) | 21 (50) | 31 (33.7) | 0.072 | 43 (42.2) | 9 (28.1) | 0.155 |
| BSA [m$^2$] | 1.54 ±0.18 | 1.59 ±0.15 | 0.153 | 1.57 ±0.17 | 1.57 ±0.14 | 0.991 |
| BMI [kg/m$^2$] | 22.28 (20.23, 23.38) | 22.04 (20.27, 24.15) | 0.694 | 22.35 (20.31, 24.22) | 21.73 (18.82, 23.13) | 0.186 |
| STS score | 1.90 (1.52, 3.23) | 2.50 (1.70, 4.03) | 0.032 | 2.12 (1.53, 3.25) | 3.57 (2.25, 5.65) | <0.001 |
| NYHA IV, n (%) | 6 (14.3,) | 25 (27.2,) | 0.101 | 16 (15.7,) | 15 (46.9,) | <0.001 |
| Hypertension, n (%) | 14 (33.3,) | 56 (60.9,) | 0.003 | 54 (52.9,) | 16 (50,) | 0.771 |
| Diabetes mellitus, n (%) | 1 (2.4,) | 16 (17.4,) | 0.015 | 13 (12.7,) | 4 (12.5,) | 0.971 |
| CHD, n (%) | 8 (19,) | 27 (29.3,) | 0.208 | 25 (24.5,) | 10 (31.3,) | 0.449 |
| Atrial fibrillation, n (%) | 4 (9.5,) | 15 (16.3,) | 0.297 | 14 (13.7,) | 5 (15.6,) | 0.788 |
| CVD, n (%) | 7 (16.7,) | 9 (9.8,) | 0.254 | 13 (12.7,) | 3 (9.4,) | 0.761 |
| COPD, n (%) | 1 (2.4,) | 13 (14.1,) | 0.064 | 8 (7.8,) | 6 (18.8,) | 0.099 |
| CKD, n (%) | 2 (4.8,) | 13 (14.1,) | 0.145 | 10 (9.8,) | 5 (15.6,) | 0.351 |
| Laboratory index | | | | | | |
| RBC [×10$^9$/L] | 4.07 ±0.55 | 4.12 ±0.55 | 0.621 | 4.17 ±0.54 | 3.92 ±0.53 | 0.027 |
| Hemoglobin [g/L] | 123.95 ±13.87 | 125.17 ±17.00 | 0.684 | 126.47 ±15.14 | 119.44 ±17.87 | 0.030 |
| Platelet count [×10$^9$/L] | 162.0 (135.5, 192.0) | 168.0 (131.3, 200.0) | 0.631 | 167.5 (135.5, 198) | 161 (118.25, 203) | 0.395 |
| NLR | 1.87 (1.53, 2.07) | 3.73 (2.83, 6.12) | <0.001 | 2.65 (1.96, 3.66) | 5.62 (3.2, 8.78) | <0.001 |
| PLR | 104.02 (71.09, 132.03) | 145.02 (109.07, 188.57) | <0.001 | 115.6 (88.87, 159.04) | 159.04 (126.53, 210.86) | 0.000 |
| MHR | 0.31 (0.24, 0.45) | 0.40 (0.29, 0.63) | 0.016 | 0.36 (0.27, 0.54) | 0.45 (0.32, 0.72) | 0.052 |
| Hematocrit [%] | 37.76 ±3.74 | 38.28 ±4.80 | 0.527 | 38.59 ±4.17 | 36.63 ±5.18 | 0.030 |
| RDW [%] | 12.95 (12.30, 13.63) | 13.70 (12.80, 14.48) | 0.002 | 13.2 (12.48, 13.93) | 14.05 (13.63, 15.53) | <0.001 |
| MPV [fL] | 10.95 (10.43, 11.60) | 11.10 (10.40, 11.90) | 0.494 | 11.05 (10.35, 11.83) | 11.05 (10.4, 11.85) | 0.909 |
| HDL-c [mmol/L] | 1.22 (1.03, 1.52) | 1.13 (0.95, 1.38) | 0.152 | 1.2 (1.04, 1.49) | 1.05 (0.84, 1.22) | 0.003 |
| LDL-c [mmol/L] | 2.46 (1.62, 3.05) | 2.23 (1.73, 3.10) | 0.842 | 2.37 (1.7, 3.1) | 2.18 (1.58, 2.94) | 0.149 |
| NHDL-c [mmol/L] | 3.07 (2.20, 3.77) | 2.97 (2.43, 3.10) | 0.558 | 3.04 (2.29, 3.94) | 3.01 (2.33, 3.49) | 0.357 |
| Lp (a) [mg/L] | 140.45 (69.90, 262.87) | 180.60 (79.83, 385.53) | 0.415 | 177.05 (78.08, 351.78) | 142.95 (67.08, 312.45) | 0.661 |
| PNI | 48.68 ±3.72 | 44.58 ±5.37 | <0.001 | 48.04 ±3.61 | 38.93 ±3.3 | <0.001 |
| BNP [pg/mL] | 387.57 (203.50, 789.01) | 806.73 (311.00, 2611.49) | 0.003 | 634.54 (240.25, 1428.84) | 2215.46 (360.41, 5000) | 0.002 |
| Creatinine [µmol/L] | 75.00 (66.49, 92.30) | 86.70 (74.29, 113.16) | 0.006 | 80.47 (69.25, 106.43) | 86.7 (72.11, 128.3) | 0.098 |
| Baseline echocardiographic parameters | | | | | | |
| Aortic regurgitation ≥moderate, n (%) | 12 (28.6) | 24 (26.1) | 0.763 | 28 (27.5) | 8 (25) | 0.785 |
| LVEDD [mm] | 51.00 (42.75, 58.25) | 52.00 (46.00, 59.00) | 0.226 | 52 (45.75, 57.25) | 52.5 (46, 63.75) | 0.255 |
| LVESD [mm] | 34.50 (27.00, 42.25) | 37.00 (31.00, 45.75) | 0.053 | 36 (29, 42) | 39 (30.25, 49.5) | 0.098 |
| LVEF [%] | 59.0 (51.0, 66.0) | 54.0 (42.0, 62.0) | 0.017 | 58 (45, 64) | 49 (30.25, 63.75) | 0.044 |
| Peak aortic jet velocity [m/s] | 4.74 (4.13, 5.36) | 4.33 (3.95, 4.88) | 0.081 | 4.44 (4.01, 5.14) | 4.32 (3.95, 4.72) | 0.287 |
| Baseline MDCT parameters | | | | | | |
| Annulus diameter [mm] | 24.60 ±2.83 | 25.08 ±2.57 | 0.335 | 24.75 ±2.62 | 25.48 ±2.74 | 0.175 |
| Annulus area [mm$^2$] | 465.98 ±110.26 | 483.44 ±98.52 | 0.361 | 473.39 ±101.42 | 492.56 ±105.13 | 0.357 |
| LVOT diameter [mm] | 24.95 (22.95, 28.30) | 26.30 (23.80, 29.20) | 0.131 | 25.65 (23.55, 28.73) | 25.85 (23.73, 29.2) | 0.699 |
| Ascending aorta diameter [mm] | 37.77 ±4.57 | 37.89 ±4.58 | 0.886 | 37.51 ±4.35 | 38.95±5.1 | 0.119 |
| Procedural details | | | | | | |
| Circulatory support, n (%) | 0 (0,) | 9 (9.8,) | 0.057 | 1 (1,) | 8 (25,) | <0.001 |
| Valve size >26 mm, n (%) | 13 (31.0,) | 37 (40.2,) | 0.304 | 39 (38.2,) | 11 (34.4,) | 0.694 |
| 2$^{nd}$ valve needed, n (%) | 9 (21.4,) | 25 (27.2,) | 0.478 | 25 (24.5,) | 9 (28.1,) | 0.682 |
| CEES, n (%) | 3 (7.1,) | 31 (33.7,) | 0.001 | 18 (17.6,) | 16 (50,) | <0.001 |

Values are presented as counts (percentages) or median (IQR). CEES – composite endpoints of early safety; BSA – body surface area; STS – Society of Thoracic Surgery Risk Score; NYHA – New York Heart Association; CHD – coronary heart disease; CVD – cerebrovascular disease; COPD – chronic obstructive pulmonary disease; CKD – chronic kidney disease; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; MHR – monocyte-to-high density lipoprotein cholesterol ratio; RDW – red blood cell distribution width; MPV – mean platelet volume; HDL-c – high-density lipoprotein cholesterol; LDL-c – low-density lipoprotein cholesterol; NHDL-c – non-high-density lipoprotein cholesterol; Lp(a) – lipoprotein(a); PNI – prognostic nutritional index; BNP – B-type natriuretic peptide; LVEDD – left ventricular end-diastolic dimension; LVESD – left ventricular end- systolic dimension; LVEF – left ventricular ejection fraction; MDCT – multidetector computed tomography; LVOT – left ventricular outflow tract.

Table 3. Univariate and multivariate logistic regression analysis of NLR and PNI to predict CEES

| Variable | | Unadjusted | | Adjusted | |
|---|---|---|---|---|---|
| | | OR (95% CI) | p-value | OR (95% CI) | p-value |
| NLR | low (<2.27) | 1 (reference) | – | 1 (reference) | – |
| | high (≥2.27) | 6.61 (1.89–23.09) | 0.003 | 5.55 (1.52–20.29) | 0.010 |
| PNI | high (>42.9) | 1 (reference) | – | 1 (reference) | – |
| | low (≤42.9) | 4.67 (1.98–11.23) | <0.001 | 4.43 (1.55–12.65) | 0.005 |
| Combined NLR + PNI | NLR-low + PNI-high | 1 (reference) | – | 1 (reference) | – |
| | NLR-high or PNI-low | 4.04 (1.09–15.00) | 0.037 | 4.07 (1.06–15.68) | 0.041 |
| | NLR-high + PNI-low | 13.51 (3.43–53.19) | <0.001 | 9.85 (2.24–43.37) | 0.003 |

NLR – neutrophil-to-lymphocyte ratio; PNI – prognostic nutritional index; CEES – composite endpoints of early safety; OR – odds ratio; 95% CI – 95% confidence interval.

high-risk (OR = 9.85 (95% CI: 2.24–43.37)) groups. These results also indicated that the combination of a high NLR and low PNI significantly heightened the risk of CEES occurrence compared to the presence of either variable alone.

## Ability to predict CEES

We further evaluated the prognostic abilities of NLR and PNI in predicting CEES using a ROC curve. The area under the ROC curve (AUC) for the NLR in predicting the occurrence of CEES was 0.691 (95% CI: 0.593–0.790), and the optimal cutoff value was 2.27, with 91% sensitivity and 39% specificity (Fig. 1A). The optimal cutoff value of PNI to predict freedom from CEES was 42.9, with a sensitivity of 84%, a specificity of 47% and an AUC of 0.660 (95% CI: 0.593–0.790, Fig. 1B). Furthermore, Kaplan–Meier survival curves were plotted based on the optimal cutoff values for NLR and PNI, indicating significant differences in the occurrence of outcome events within 30 days between the 2 groups divided by the optimal cutoff values of NLR and PNI (Fig. 2).

# Discussion

The impact of NLR and PNI on CEES following TAVR was retrospectively analyzed in this study. The primary study findings were as follows: 1) A high NLR or low PNI at baseline is associated with an increased incidence of CEES at 30 days following TAVR; 2) The presence of a high NLR or low PNI at baseline could serve as an independent risk factor for CEES; 3) Combining high NLR and low PNI may offer additional prognosis information for predicting the risk of CEES.

In previous studies, inflammatory biomarkers such as C-reactive protein (CRP) and interleukin 6 (IL-6) have

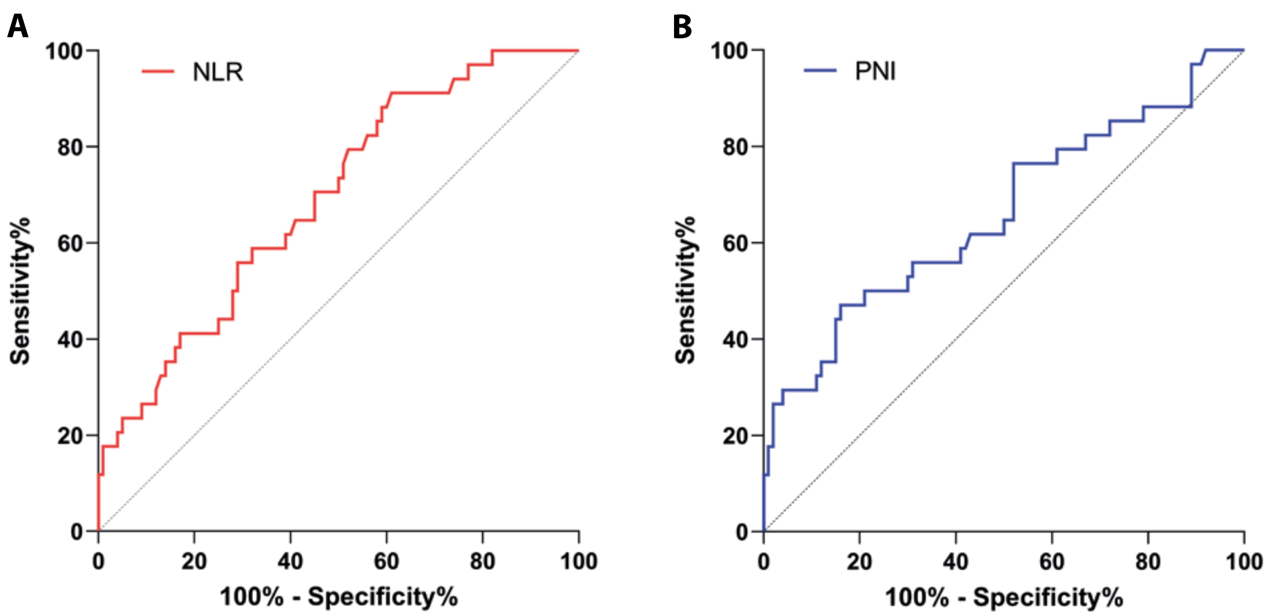


Fig. 1. ROC analysis of NLR and PNI in predicting CEES. A. ROC curve of NLR in predicting the occurrence of CEES; B. ROC curve of PNI in predicting freedom from CEES

ROC – receiver operating characteristic; NLR – neutrophil-to-lymphocyte ratio; PNI – prognostic nutritional index; CEES – composite endpoint of early safety.

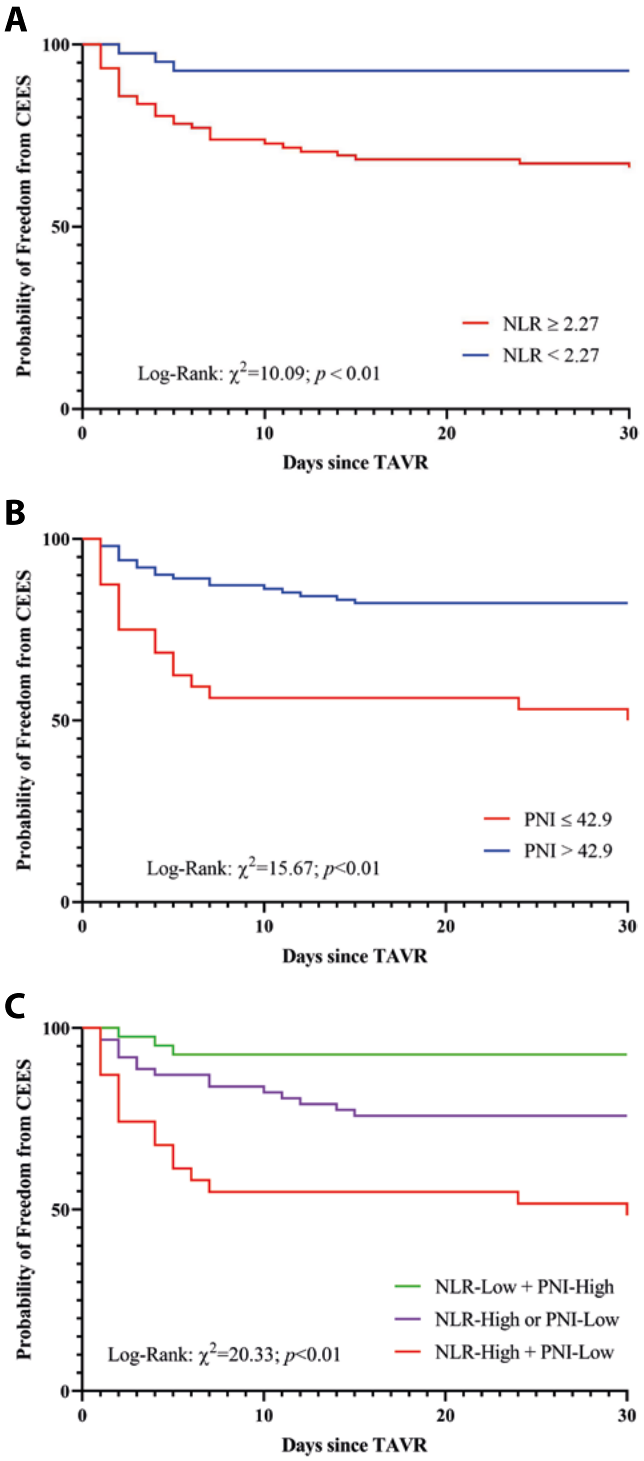


Fig. 2. Kaplan–Meier curves for CEES. A. Kaplan–Meier curves for CEES according to the cutoff value of NLR; B. Kaplan–Meier curves for CEES according to the cutoff value of PNI; C. Kaplan–Meier curves for CEES according to the combination of NLR and PNI

NLR – neutrophil-to-lymphocyte ratio; PNI – prognostic nutritional index; CEES – composite endpoint of early safety.

been utilized to predict the prognosis of patients who underwent TAVR and have shown promising results.[22–24] Although we recognize the importance of inflammation biomarkers in determining prognosis, these biomarkers are not routinely included in preoperative laboratory examinations for TAVR. Therefore, exploring inflammatory indicators in routine blood tests for risk stratification is of paramount importance. It should be noted thatNLR, PLR, MHR, and RDW are a class of inflammation biomarkers that can be easily obtained from routine blood tests and have demonstrated their predictive value for the long-term prognosis and complications following TAVR.[13,14,25] Previous studies have also confirmed significant correlations between inflammatory indicators, such as NLR and PLR, and early safety composite outcomes after TAVR.[26] However, thus far, the existing research on the risk factors associated with composite endpoints of early safety following TAVR has relied on the definition of composite endpoints outlined in VARC-2.[27] With the introduction of the latest VARC-3 definition for CEES, which includes new permanent pacemaker implantation due to procedure-related conduction abnormalities and moderate or severe aortic regurgitation, there is a lack of studies that investigate the risk factors for these updated composite endpoints. In this study, in addition to inflammatory markers, we also included the PNI, an indicator reflecting nutritional status. Similar to NLR and PLR, PNI can also be indirectly inferred from routine blood tests and offers similar advantages.

In our study, we observed significant differences in NLR and PNI between the CEES group and the non-CEES group. Therefore, we further analyzed these 2 indicators by dividing them into high- and low-level groups and comparing their baseline characteristics. We found that a high NLR was associated with an increased rate of CEES, which is consistent with prior studies that reported the correlation between NLR and CEES defined by VARC-2. Similarly, we obtained the same result for low PNI. In the multivariate analysis, we confirmed that a high NLR and low PNI were independent risk factors for an increased rate of CEES following TAVR. After adjusting for multiple potential confounders, patients with a NLR ≥2.27 had a 5.55 times higher risk of CEES following TAVR compared to patients with low NLR, while patients with a PNI ≤42.9 had a 4.43 times higher risk compared to patients with high PNIs. These results prove that NLR and PNI, which are routine blood parameters representing inflammation and nutritional levels, respectively, can provide valuable prognostic information for predicting the risk of CEES following TAVR. To further investigate whether their combination increases the risk of CEES, we stratified patients into low-, intermediate- and high-risk groups based on the NLR and PNI. The high-risk group (i.e., high NLR combined with low PNI) had a higher risk of CEES compared to patients with a high NLR or low PNI alone. This indicates a promising potential of combining NLR and PNI for the risk stratification of CEES following TAVR.

Neutrophil-to-lymphocyte ratio, as an inflammation marker, has previously been shown to be linked to various cardiovascular diseases.[28] A high NLR may reflect a systemic inflammatory state, which may be attributed to a significant elevation of neutrophils as a marker of ongoing inflammation and relatively diminished lymphocytes, which play an essential role in immune regulation and inhibition of inflammation.[29]

Recent studies have revealed a correlation between NLR and negative outcomes in patients undergoing TAVR. Our study provides additional evidence supporting a notable link between high NLR and early adverse clinical outcomes after TAVR. A previous study by Condado et al. demonstrated the correlation between high NLR and PLR with the occurrence of CEES 30 days after TAVR.[26] However, as TAVR experience advanced and large-scale clinical studies were conducted worldwide, the VARC-3 had updated the definitions of CEES, including additional specifications and improvements in the definition of postoperative bleeding and vascular complications. Notably, the VARC-3 also included new permanent pacemaker implantation due to procedure-related conduction abnormalities in the definition of CEES, necessitating further investigation into the correlation between NLR and this updated definition. In our study, we found a significant correlation between NLR and the latest definition, providing further support for the importance of NLR in predicting adverse prognosis after TAVR. However, other biomarkers such as PLR, MHR and RDW did not show a similar predictive ability compared to NLR in our study.

Another indicator studied in our research is PNI, which serves as an important marker reflecting nutritional status. Given the TAVR patient population is predominantly comprised of the elderly, where malnutrition is common in this population, it is crucial to evaluate the potential risks of malnourished patients undergoing TAVR. Recent studies reported that comorbidities such as weakness and malnutrition increase the risk of an adverse prognosis after TAVR.[15,30,31] Therefore, assessing the nutritional status of patients in a reasonable and appropriate way before the procedure is beneficial for early risk stratification of TAVR patients. However, there is currently no research demonstrating the correlation between nutritional status and the occurrence of early safety composite outcomes after TAVR.

Prognostic nutritional index combines albumin levels, reflecting nutritional status, and lymphocyte count, reflecting immune function, both having an adverse impact on mortality.[26,32] Previous research has demonstrated a notable association between low PNI and increased mortality following TAVR.[20,33] In our study, we confirmed that a low PNI increases the risk of CEES after TAVR, although the specific mechanism has yet to be determined. Magri et al. found that the logistic EuroSCORE was an important predictor of CEES, which is a useful tool in assessing comorbidities and weakness.[34] This may explain the association between PNI, an indicator reflecting weakness, and the occurrence of CEES. Additionally, a low PNI may itself be a potential intermediate factor for CEES. However, further research is needed to identify potential confounders and the detailed relationship between PNI and CEES.

Recently, Conners et al.[35] used the metabolic vulnerability index (MVX), a novel biomarker that reflects both systemic inflammation and metabolic malnutrition, to explore its prognostic value in patients with heart failure. The results showed that in the heart failure population, a higher MVX was associated with mortality independently of existing chronic heart failure scores and other biomarkers, and MVX had additional value in the stratification of death risk in patients with heart failure. These results suggest such indicators that reflect both inflammation and malnutrition may have special value in evaluating the prognosis of patients with cardiovascular disease. However, the complexity of obtaining MVX may impede its widespread adoption in clinical applications. Thus, the combination of NLR and PNI has certain advantages because of the easily accessible and inexpensive characteristics. This study has preliminarily confirmed the prognostic value of the combination of NLR and PNI in the occurrence of adverse events following TAVR. Future research can further explore its value in other cardiovascular diseases.

## Limitations

There are several limitations in our study. Firstly, this is a single-center, retrospective study, which restricts the generalizability of the findings to the entire TAVR patient population. Although we have proposed preliminary cutoff values for NLR and PNI in the TAVR population, these values need to be validated in larger cohorts due to the small sample size of this study. Secondly, certain potential confounding factors, such as some special inflammatory cytokines or other markers of nutritional status, were not included in this study. Moreover, the study population overall consisted primarily of low/moderate-risk individuals based on STS scores. However, 7% of patients required mechanical circulatory support, and 25% underwent 2$^{nd}$ valve implantation. It may be due to the prophylactic use of mechanical circulatory support in some high-risk patients to ensure procedural safety. Regarding the 2$^{nd}$ valve, besides the early lack of experience in our center, it may also be attributed to the enrollment of patients with pure aortic regurgitation in our study cohort. These patients typically have a higher risk of 2$^{nd}$ valve requirement due to anatomical factors. This also implies that caution should be exercised when extrapolating the results of this study to other populations. Lastly, due to the limited sample size of this study, subgroup analyses of various endpoints within the CEES were not performed, and larger patient populations will be required in the future to refine this study.

# Conclusions

This study investigated the impact of inflammation status and nutritional level on CEES at 30 days following TAVR. The results demonstrated that baseline high NLR and low PNI are important independent predictors of CEES. These routine and inexpensive indicators may provide valuable references in the early risk stratification of TAVR patients.

# Ethical approval

This study was approved by the Institutional Review Board of the Second Affiliated Hospital of Nanchang University (approval 2022.No.07).

# Data availability

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

# Consent for publication

Not applicable.


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