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Association between haematological parameters and outcomes following transcatheter aortic valve implantation at mid-term follow-up

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ABSTRACT

Background Patients undergoing transcatheter aortic valve implantation (TAVI) often have multiple comorbidities, such as anaemia and chronic inflammatory disorders. We sought to investigate the association between preoperative and postoperative haematological parameters and clinical outcomes in TAVI patients at mid-term follow-up.

Methods In the present study, consecutive patients (N=908) who underwent TAVI at the Cleveland Clinic between 2017 and 2019 with available complete blood counts were studied. Data were collected on preoperative and postoperative anaemia and elevations in neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Survival analysis was used to study the association of haematologic parameters with all-cause mortality and major adverse cardiac and cerebrovascular events (MACCE).

Results We found that preoperative anaemia and elevated NLR were significantly associated with a higher risk of all-cause mortality (aHR=1.6 (95% CI: 1.1 to 2.0) and 1.4 (95% CI: 1.1 to 1.6), respectively) and MACCE (aHR=1.9 (95% CI: 1.3 to 2.8) and 1.6 (95% CI: 1.1 to 2.4), respectively). While an elevated preoperative PLR was not associated with increased mortality risk, it had a significant association with MACCE risk (aHR: 1.6 (95% CI: 1.1 to 2.4)). Further, postoperative anaemia, elevated NLR and PLR were associated with increased risks of all-cause mortality and MACCE.

Conclusion Pathological alterations in haematological parameters were associated with higher risks of post-TAVI mortality and MACCE at mid-term follow-up. Our findings advocate for further incorporating haematological parameters in the preoperative evaluation of TAVI candidates.

INTRODUCTION

Since its introduction, transcatheter aortic valve implantation (TAVI) has changed the approach to the management of patients with severe aortic stenosis (AS).[1] Patients undergoing TAVI are generally of advanced age with multiple comorbidities, such as anaemia,

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Inflammation plays a role in the pathogenesis of calcific aortic valve disease and has been linked to worse outcomes after transcatheter aortic valve implantation (TAVI).

WHAT THIS STUDY ADDS

⇒ The study explores the relationship between pathological alterations in haematological parameters and poor TAVI outcomes at 4-year of follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study advocates for a larger role for haematological parameters in the preoperative evaluation of TAVI candidates.

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diabetes mellitus and chronic kidney disease. Several studies have been undertaken to understand the prognostic value of different comorbidities and biomarkers on TAVI outcomes.[2][3] For instance, former studies have shown that preoperative anaemia is associated with an increased risk of post-TAVI mortality and adverse clinical outcomes.[4][5]

As inflammation plays a pivotal role in the pathogenesis and outcomes of calcific aortic valve disease,[6–8] markers reflecting high inflammatory states have been studied in patients undergoing TAVI. Earlier studies have reported that proinflammatory markers as C-reactive protein and interleukin-16 as well as lower Th2 cell counts can predict the risk of mortality after TAVI. These markers, however, are not routinely measured in the preoperative evaluation and can be expensive to quantify.[9][10] Emerging markers of proinflammatory responses that can be calculated from routine preoperative tests such as the neutrophil-to-lymphocyte ratio (NLR) and

platelet-to-lymphocyte ratio (PLR) have been recently evaluated in TAVI patients.[11–13] Previous studies have suggested possible roles for neutrophils in the pathogenesis of AS. These include the release of elastase enzymes and neutrophil extracellular traps, promoting inflammation, calcification and apoptosis of endothelial cells.[14–17] In addition, platelets have long been considered as an acute phase reactant of inflammatory responses. Therefore, elevated neutrophils and platelet counts may contribute to or signify an underlying inflammatory process, supporting the rationale behind measuring those markers.

However, the prognostic role of these markers is not yet established, as the studies on their association with TAVI outcomes have shown inconsistent results.[18–20] Moreover, data on their prognostic utility beyond 1-year of follow-up are limited. The present study was conducted to assess the prognostic role of preoperative and postoperative haematological parameters, including anaemia, and elevated NLR and PLR, in patients undergoing TAVI at mid-term follow-up; figure 1.

METHODS

Study population

We analysed data of 908 consecutive patients who underwent TAVI at the Cleveland Clinic Foundation (Cleveland, Ohio) between 2017 and 2019. Data on the baseline variables, haematological parameters, mortality and clinical outcomes were collected through a comprehensive chart review. The methods and results of this study are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

Measurement of haematological parameters

We collected complete blood counts (CBC) with differential data from blood samples, withdrawn within the 72 hours before the procedure (preoperative) and at 48 hours immediately after the procedure (postoperative). The haematological parameters of interest included haemoglobin (Hb) (g/dL), platelet counts (cells/mL), neutrophil and lymphocyte cell counts (cells/mL) (measured using Coulter LH 750 Hematology Analyzer, Beckman Coulter, Brea, California, USA). We used the WHO definition for anaemia as Hb<12 g/dL in nonpregnant women and <13 g/dL in men. We used a cut-off of 150×10^9/L to define thrombocytopaenia. Regarding the cut-off for NLR and PLR, the median values for preoperative and postoperative data were used; patients were divided into two groups with values above and below the median NLR and PLR values.

Outcome definitions

The primary outcomes were all-cause mortality and major adverse cardiovascular and cerebrovascular events (MACCE). MACCE was defined as a composite of myocardial infarction, stroke (ischaemic or haemorrhagic) and heart failure rehospitalisation. The secondary outcomes included in-hospital and rehospitalisation for major/life-threatening bleeding (defined as overt bleeding that requires transfusion of ≥2 units of whole-blood/packaged red blood cells, associated with a Hb drop≥3 g/dL, causing severe hypotension, or requiring reintervention) and aortic valve reintervention. Four independent coauthors adjudicated the reported clinical outcomes, using the Valve Academic Research Consortium-3 endpoint definitions.[21] The follow-up of each patient was censored at the date of death or last follow-up in our medical records. The median follow-up period for the study patients was 2.5 years (IQR: 2–4 years).

Statistical analysis

All analysis undertaken in the present study was prespecified in our protocol. Patients with normal Hb and platelet counts served as the control group in each respective comparison. The associations of different haematologic parameters with the study outcomes were assessed through survival analyses with the Kaplan-Meier non-parametric method. In order to adjust for differences in baseline characteristics and calculate survival estimates, a multivariable Cox proportional hazard model was employed after confirming the proportional hazards assumption. The analysis was adjusted for age, gender, body mass index (BMI), comorbidities (hypertension, diabetes, coronary artery disease, congestive heart failure, atrial fibrillation), left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, serum creatinine and urgent status. All analyses were conducted with STATA V.13.0 (StataCorp, College Station, Texas, USA).

RESULTS

Anaemic versus non-anaemic patients

Preoperatively, 46% of the study cohort had anaemia. Anaemic patients were more likely (p<0.05) than nonanaemic patients to be older, females, have a lower BMI, lower LVEF, higher Society of Thoracic Surgeons (STS) risk scores, higher international normalized ratio (INR) and creatinine values and more frequent comorbidities (diabetes mellitus, atrial fibrillation and higher NYHA class). Out of 149 patients with available iron studies, 81 (54.4%) had iron deficiency anaemia.

Kaplan-Meier survival curves showed that over the follow-up period, having anaemia before or after TAVI was associated with higher risks of all-cause mortality and MACCE (p<0.001 for both); online supplemental figure 1. Regression analysis showed that preoperative and postoperative anaemia were significantly associated with all-cause mortality (aHR: 1.6, 95% CI: 1.1 to 2.0; p=0.01 and aHR: 1.5, 95% CI: 1.04 to 2.5; p=0.04, respectively) and MACCE (aHR: 1.9, 95% CI: 1.3 to 2.8; p=0.002 and aHR: 2.6, 95% CI: 1.4 to 4.9; p=0.003, respectively); table 1.

To quantify this association, we show that over the follow-up period, every reduction in Hb levels by 1 g/dL before TAVI was associated with an 11% increased risk of all-cause mortality (aHR: 1.11, 95% CI: 1.02 to 1.21;

CENTRAL ILLUSTRATION: The association between peri-operative hematological parameters and TAVI outcomes at 2-4 years of follow-up
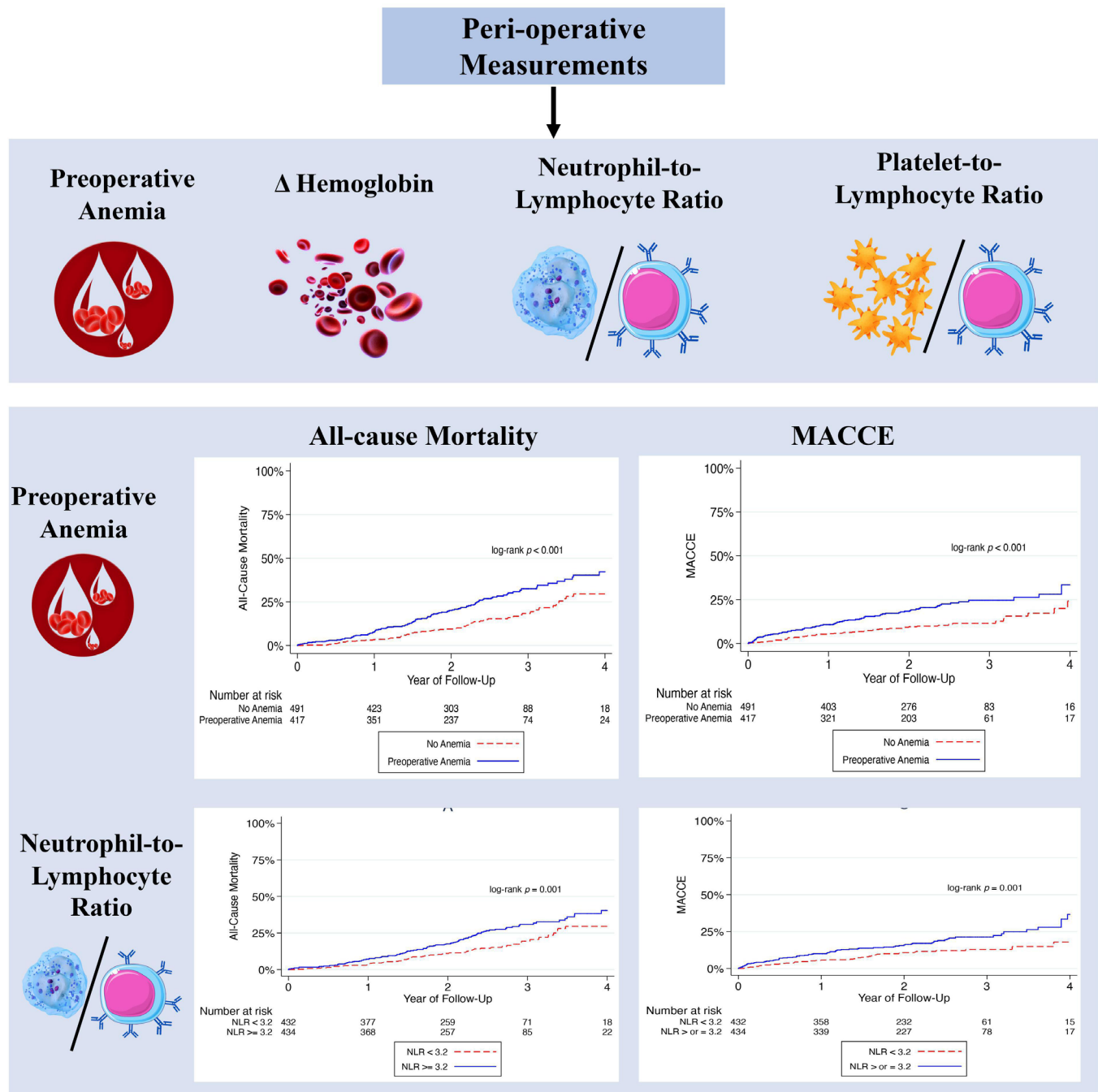

Figure 1 A central illustration of the main findings in the present study. MACCE, major adverse cardiovascular and cerebrovascular events; NLR, neutrophil-to-lymphocyte ratio.

p=0.01) and 10% increased risk of MACCE (aHR: 1.1, 95% CI: 1.05 to 1.2, p=0.002). Similarly, every reduction in Hb levels by 1 g/dL after TAVI was associated with 17% increased risk of all-cause mortality (aHR: 1.17, 95% CI: 1.06 to 1.29; p=0.002) and 20% increased risk of MACCE (aHR: 1.2, 95% CI: 1.1 to 1.3; p=0.003).

On the other hand, having preoperative or postoperative thrombocytopaenia were not associated with either outcome. For other outcomes, anaemic patients at baseline were more likely to have major bleeding (7% vs 3%, p=0.03) and aortic valve reintervention (1.5% vs 0.3%, p=0.02).

Patients with high versus low PLR
Kaplan-Meier survival curves showed that over the follow-up period, patients with higher PLR before or

Table 1 Results of multivariable Cox proportional hazard model testing the association between haematological parameters and clinical outcomes

	Unadjusted		Multivariable-adjusted model*	
	HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality				
Preoperative anaemia	1.8 (1.3 to 2.5)	<0.001	1.6 (1.1 to 2.0)	0.01
Postoperative anaemia	1.9 (1.3 to 3.0)	0.002	1.5 (1.04 to 2.5)	0.048
Preoperative haemoglobin†	1.1 (1.08 to 1.2)	<0.001	1.1 (1.02 to 1.2)	0.01
Postoperative haemoglobin	1.2 (1.1 to 1.3)	<0.001	1.2 (1.1 to 1.3)	0.002
Preoperative thrombocytopaenia	1.7 (1.2 to 2.3)	0.001	1.4 (1.01 to 2.0)	0.03
Postoperative thrombocytopaenia	1.3 (0.9 to 1.7)	0.12	1.1 (0.8 to 1.5)	0.56
Preoperative NLR>3.2	1.7 (1.2 to 2.3)	0.001	1.4 (1.01 to 2.0)	0.03
Postoperative NLR>5	1.8 (1.2 to 2.6)	0.002	1.6 (1.1 to 2.4)	0.01
Preoperative PLR>140	1.2 (0.9 to 1.6)	0.2	1.1 (0.8 to 1.5)	0.5
Postoperative PLR>137	1.7 (1.2 to 2.6)	0.002	1.6 (1.1 to 2.3)	0.01
MACCE				
Preoperative anaemia	2.1 (1.4 to 2.9)	<0.001	1.9 (1.3 to 2.8)	0.002
Postoperative anaemia	3.0 (1.7 to 5.4)	<0.001	2.6 (1.4 to 4.9)	0.003
Preoperative haemoglobin	1.2 (1.1 to 1.3)	<0.001	1.1 (1.05 to 1.2)	0.002
Postoperative haemoglobin	1.3 (1.1 to 1.4)	<0.001	1.2 (1.1 to 1.3)	0.003
Preoperative thrombocytopaenia	0.9 (0.6 to 1.6)	0.99	1.04 (0.6 to 1.7)	0.85
Postoperative thrombocytopaenia	0.7 (0.5 to 1.0)	0.08	0.7 (0.4 to 1.0)	0.07
Preoperative NLR>3.2	1.8 (1.2 to 2.6)	0.002	1.6 (1.1 to 2.4)	0.01
Postoperative NLR>5	1.7 (1.2 to 2.6)	0.005	1.7 (1.1 to 2.6)	0.01
Preoperative PLR>140	1.7 (1.1 to 2.4)	0.006	1.6 (1.1 to 2.4)	0.01
Postoperative PLR>137	2.2 (1.5 to 3.3)	<0.001	2.1 (1.3 to 3.2)	0.001

Anaemia is defined as haemoglobin <12 g/dL in females and <13 g/dL in males. Thrombocytopaenia is defined as platelet count <150 x 10^9/L.
*Adjusted for age, gender, body mass index, comorbidities (hypertension, diabetes, coronary artery disease, congestive heart failure, atrial fibrillation), left ventricular ejection fraction, New York Heart Association class, serum creatinine and urgent status.
†Per 1 unit decrease.
MACCE, major adverse cardiovascular and cerebrovascular events ; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

after TAVI were at higher risks of all-cause mortality and MACCE (p<0.001 for both). Regression analysis showed that preoperative PLR was not associated with a significant increase in all-cause mortality (aHR: 1.1, 95% CI 0.8 to 1.5; p=0.5), but it was associated with increased risk of MACCE (aHR: 1.6, 95% CI: 1.1 to 2.4; p=0.01). Postoperative PLR was significantly associated with all-cause mortality (aHR: 1.6, 95% CI: 1.1 to 2.3; p=0.01) and MACCE (aHR: 2.1, 95% CI: 1.3 to 3.2; p=0.001); table 1 (Online supplemental figure 2).

Patients with high versus low NLR
Kaplan-Meier survival curves showed that over the follow-up period, patients with higher NLR before or after TAVI were at higher risks of all-cause mortality and MACCE (p<0.001 for both). Regression analysis showed that preoperative and postoperative higher NLR were significantly associated with all-cause mortality (aHR: 1.4, 95% CI: 1.1 to 1.6; p=0.03 and aHR: 1.6, 95% CI: 1.1 to

2.4; p=0.01, respectively) and MACCE (aHR: 1.6, 95% CI: 1.1 to 2.4; p=0.01 and aHR: 1.7, 95% CI: 1.1 to 2.6; p=0.01, respectively); table 1 (Online supplemental figure 3).

DISCUSSION
In the present study, we analyzed the prognostic utility of haematological parameters in predicting all-cause mortality and clinical outcomes following TAVI, using a large contemporary cohort of patients from a tertiary medical centre. Our analysis shows that nearly half of patients undergoing TAVI had anaemia preoperatively, consistent with results from prior reports.[22–24] In line with former studies, iron deficiency was reported as the cause in more than half of anaemic patients, undergoing TAVI.[25 26] Other authors attributed anaemia in patients with severe AS to shear stress-dependent intravascular haemolysis.[27] Our study also showed that preoperative and postoperative anaemia were strongly associated with

all-cause mortality and MACCE in adjusted regression analyses.Whether the treatment of preoperative anaemia can improve TAVI outcomes remains under investigation. To date, two small studies investigated the efficacy of treatment strategies for anaemia before TAVI, showing mixed results. The Erythropoietin plus Iron Therapy for Anemic Patients Undergoing Aortic Valve Replacement (EPICURE) randomised trial failed to show a reduction in blood transfusion rates in TAVI patients, randomised to preoperative erythropoietin and iron therapy.[28] On the other hand, another observational study showed that anaemic patients who received preoperative iron and erythropoietin had significant reductions in blood transfusion rates.[26]

In line with previous studies, the number of anaemic patients increased significantly following TAVI. This is probably attributed to blood loss during the procedure, haemodilution with procedural fluids and acute stress during the TAVI procedure.[22 29] We attempted to identify the predictors of anaemia post-TAVI. Our analysis demonstrated that patients with urgent TAVI, higher STS risk score, creatinine and NT proBNB had an increased vulnerability to anaemia following TAVI. These associations make sense as they indicate a worse general condition; the higher creatinine for example may indicate an underlying renal dysfunction and inability to respond to bleeding during/after TAVI by increasing erythropoietin levels. These patients may require more attention by serial monitoring of Hb levels and adequate interventions to correct the predisposing factors for anaemia.

Another marker that was investigated in prior TAVI studies is NLR. A higher NLR is an established marker of subclinical inflammatory states and it reflects the dynamic relationship between the innate and adaptive immune responses. It has been shown to be a strong prognostic marker in several conditions as cancer, sepsis and atherosclerosis. Some even suggested that changes in NLR can precede the clinical condition and may serve as an early warning sign of clinical deterioration.[30 31] Our study adds to the accumulating evidence indicating that high NLR is a prognostic marker of poor outcomes after TAVI.[18 32] Most studies used a pathological cut-off of NLR around 3, which is similar to our preoperative cut-off value that is more specific to our population. The median value for postoperative NLR was quite higher and it might reflect a subclinical inflammatory response following the procedure. We confirm the available evidence on NLR in TAVI and show that elevations in both preoperative and postoperative NLR were associated with all-cause mortality and MACCE, further highlighting the importance of inflammation in predicting outcomes post-TAVI. What makes NLR a good biomarker is that how easy and cheap it is to measure neutrophil and lymphocyte counts using a complete blood count. However, PLR did not perform as good as NLR in predicting outcomes, as elevated preoperative PLR was not associated with increased risk of all-cause mortality. While most studies support a prognostic role for NLR after TAVI, the literature on PLR has been inconsistent. One study by Condado *et al* showed that elevated NLR and PLR were associated with worse 30-day outcomes, but only NLR was associated with 1-year readmission and survival.[18] A recent study by Navani *et al* showed that high PLR before TAVI was not associated with 30-day major adverse cardiovascular events,[19] while another study by Tabata *et al* showed that PLR was associated with worse TAVI outcomes in both patients with cancer and non-cancer.[20]

The most commonly used risk assessment scores in TAVI patients are the STS score and Euroscore II, which were both developed to predict outcomes after cardiac surgery.[33] The STS score does include measurements of Hb and platelet count in addition to a myriad of clinical characteristics, highlighting that these blood markers are important prognostic tools in the preoperative workup. Based on our findings, we believe that adding NLR to the current predictive scores can enhance their clinical use and prognostic utility.

Our study is not without limitations. First, our study is retrospective in nature and thus subject to the intrinsic limitations of selection bias and lack of causality. Despite its relatively large sample size, it remains a single-centre study and as such, generalisability of the results might be limited. Yet, our centre is a tertiary referral centre and treats a population of patients from all over the world. Second, while we adjusted for multiple factors in our analysis, it is difficult to account for all potential confounders. Third, the cut-offs for NLR and PLR dichotomous comparisons have been estimated differently in different studies due to the lack of a universal cut-off value. Future studies should work out standardised cut-off points for both values. In addition, the efficacy of normalising haematological parameters in improving long-term mortality, clinical and functional outcomes should be thoroughly investigated.

In conclusion, our analysis shows that preoperative and postoperative anaemia and NLR elevations are associated with adverse clinical outcomes after TAVI at mid-term follow-up. Future studies should assess the value of adding these parameters to the existing risk scores used in the preoperative evaluation of TAVI patients.

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