

Association of the hemoglobin-to-red cell distribution width ratio with clinical outcomes after transcatheter aortic valve implantation

Zeynep Kaplan¹, Mehmet Erdoğan¹, Hakan Süygün^{2,✉}, Serdal Baştuğ¹, Murat Akçay¹, Tahir Durmaz¹

1. Department of Cardiology, Faculty of Medicine, Ankara Yildirim Beyazıt University, Ankara Bilkent City Hospital, Ankara, Turkey; 2. Department of Cardiology, Faculty of Medicine, Karamanoğlu Mehmetbey University, Karaman Training and Research Hospital, Karaman, Turkey

✉ Correspondence to: hakansuygun@kmu.edu.tr

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ABSTRACT

BACKGROUND Risk stratification after transcatheter aortic valve implantation (TAVI) remains challenging, particularly in elderly patients with substantial frailty and comorbidity burden. The hemoglobin-to-red cell distribution width ratio (HRR) has recently emerged as an integrated biomarker reflecting anemia, systemic inflammation, and nutritional status. However, evidence regarding its prognostic value in patients undergoing TAVI remains limited.

METHODS This retrospective observational study included 584 consecutive patients who underwent TAVI for severe aortic stenosis between 2019 and 2023. Baseline HRR was calculated from preprocedural laboratory measurements. Patients were categorized into the low HRR group and the high HRR group according to a receiver operating characteristic-derived cut-off value (0.74). The primary endpoint was long-term all-cause mortality. Multivariable Cox regression analyses evaluated HRR as both a continuous and a categorical variable. Additional receiver operating characteristic, reclassification, and restricted cubic spline analyses were performed.

RESULTS Patients in the low HRR group experienced significantly higher in-hospital, 30-day, one-year, and long-term all-cause mortality compared with those in the high HRR group (all $P < 0.001$). Kaplan-Meier survival analysis demonstrated significantly reduced long-term survival in the low HRR group (log-rank $P < 0.001$). HRR showed moderate discriminatory ability for one-year (AUC = 0.73) and long-term all-cause mortality (AUC = 0.70). HRR outperformed hemoglobin alone and improved risk discrimination and reclassification beyond the STS (Society of Thoracic Surgeons) score. In multivariable Cox regression analyses, HRR remained independently associated with long-term mortality when assessed as a continuous variable (HR = 0.09, 95% CI: 0.03–0.25, $P < 0.001$) and as a categorical variable (HR = 0.34, 95% CI: 0.24–0.49, $P < 0.001$), after adjustment for age, sex, STS score, and malignancy.

CONCLUSIONS Preprocedural HRR is independently associated with long-term all-cause mortality after TAVI. HRR may provide complementary prognostic information when integrated into multiparametric risk assessment strategies for elderly patients undergoing TAVI.

Severe aortic stenosis (AS) is one of the most prevalent valvular heart diseases in the elderly population and is associated with substantial morbidity and mortality if left untreated.^[1,2] Transcatheter aortic valve implantation (TAVI) has evolved from a treatment modality reserved for patients at prohibitive or high surgical risk to a widely accepted therapeutic option across low-, intermediate-, and high-risk populations.^[3,4] Despite advances in device technol-

ogy and procedural techniques, patients undergoing TAVI remain predominantly elderly, frail, and burdened with multiple comorbidities, resulting in considerable heterogeneity in post-procedural outcomes. Therefore, improving risk stratification using simple and readily available biomarkers remains a clinical priority.^[5,6]

Increasing evidence suggests that systemic inflammation, oxidative stress, and impaired nutritional status play a critical

role in cardiovascular disease progression and adversely affect outcomes after structural heart intervention.^[9] Parameters derived from routine complete blood count have gained attention in this context due to their low cost and widespread availability. Red cell distribution width (RDW), a measure of erythrocyte size variability, has been consistently associated with adverse outcomes in various cardiovascular conditions, including heart failure, coronary artery disease, and valvular heart disease.^[7-9] Elevated RDW levels reflect underlying inflammation, oxidative stress, ineffective erythropoiesis, and malnutrition, all of which are common in elderly patients with severe AS.

Anemia and reduced hemoglobin levels are also highly prevalent among patients undergoing TAVI and have been linked to impaired functional capacity, increased peri-procedural complications, and worse long-term prognosis.^[10-12] However, hemoglobin and RDW evaluated separately may not fully capture the complex interplay between oxygen-carrying capacity, inflammatory burden, and nutritional status that characterizes this high-risk population. Because the hemoglobin-to-red cell distribution width ratio (HRR) integrates two complementary hematological parameters, hemoglobin and RDW, it may better reflect the combined effects of anemia, inflammation, and nutritional status compared with either parameter alone.

Recently, the HRR has emerged as a composite biomarker integrating both hemoglobin concentration and erythrocyte heterogeneity. HRR has been shown to provide incremental prognostic value over its individual components by reflecting inflammatory, oxidative, and nutritional status more comprehensively. Prior studies have demonstrated the prognostic significance of HRR in patients with heart failure, coronary artery disease, and sepsis.^[13-15] Nevertheless, despite the established associations of hemoglobin and RDW individually with outcomes after TAVI, data specifically evaluating the prognostic role of HRR in patients undergoing TAVI are currently lacking.

Accordingly, the present study aimed to investigate the association between preprocedural HRR levels and early as well as long-term clinical outcomes in patients undergoing TAVI. We hypothesized that lower HRR values would be associated with increased mortality and adverse clinical outcomes following TAVI, and that HRR could serve as a simple, practical, and clinically applicable prognostic biomarker in routine practice.

METHODS

Study Design and Population

This retrospective observational study included consecutive patients who underwent TAVI at Ankara Bilkent City Hospital between March 21, 2019 and December 29, 2023. Patients aged ≥ 18 years who underwent TAVI for severe, symptomatic AS were eligible for inclusion. Severe AS was defined according to current guideline-based echocardiographic criteria.

Patients with missing baseline laboratory data, active infection or inflammatory disease, hematologic malignancies, acute coronary syndrome, chronic inflammatory or autoimmune disorders, recent blood transfusion, or incomplete follow-up data were excluded. A total of 584 consecutive patients who fulfilled the inclusion criteria were included in the final analysis. The study protocol was approved by the Ankara Bilkent City Hospital No.2 Scientific and Ethical Evaluation Committee for Medical Research (No.TABED 2-24-179) and was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for written informed consent was waived.

Data Collection and HRR Calculation

Baseline demographic characteristics, comorbidities, cardiovascular risk factors, medication use, surgical risk scores [the Society of Thoracic Surgeons (STS) score and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II)], laboratory parameters, electrocardiographic findings, transthoracic echocardiographic measurements, and computed tomography angiography data were obtained from electronic medical records. Procedural characteristics, including access route, valve type and size, and peri-procedural complications, were also recorded.

Baseline laboratory parameters were obtained from venous blood samples collected prior to the TAVI procedure as part of routine clinical evaluation. Hemoglobin concentration and RDW were measured using standardized automated hematology analyzers (Mindray BC-6000, Mindray Bio-Medical Electronics Co., Shenzhen, China). HRR was calculated by dividing hemoglobin level (g/dL) by RDW (%). For categorical analyses, patients were classified into the low HRR group and the high HRR group according to the optimal cut-off value derived from receiver operating characteristic (ROC) curve analysis.



TAVI Procedure

All patients were evaluated by a multidisciplinary Heart Team comprising interventional cardiologists, cardiac surgeons, cardiac imaging specialists, and anesthesiologists. The indication for TAVI and the selection of valve type were determined based on contemporary guideline recommendations, anatomical suitability, and individual clinical characteristics.

Preprocedural evaluation included detailed transthoracic echocardiography to confirm the diagnosis and severity of AS and to assess left ventricular systolic function. Multidetector computed tomography was routinely performed for procedural planning, including annular sizing, assessment of aortic root anatomy, vascular access evaluation, and estimation of calcification burden. Coronary angiography was performed according to institutional protocol.

TAVI procedures were primarily performed via the transfemoral approach under conscious sedation, in line with the standard practice of our institution. Following vascular access, unfractionated heparin was administered to maintain an activated clotting time > 250 s. TAVI was carried out under fluoroscopic guidance using either balloon-expandable or self-expandable valves, as determined by anatomical characteristics and Heart Team consensus.

Clinical Outcomes and Follow-up

Clinical outcomes were defined and adjudicated in accordance with the Valve Academic Research Consortium 3 (VARC-3) criteria.^[6] The primary endpoint of the study was long-term all-cause mortality following TAVI. Secondary endpoints included early (30-day) and mid-term (one-year) all-cause mortality.

VARC-3-defined clinical events that were available in the dataset, including major bleeding, vascular complications, stroke, and myocardial infarction, were recorded when applicable. Follow-up data were obtained from outpatient clinic visits, hospital electronic medical records, and national health registry databases. Survival time was calculated from the date of the TAVI procedure to the date of death or the last available clinical follow-up.

Statistical Analysis

Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean $\pm$ SD, and non-normally distributed variables as medians (interquartile range). Categorical vari-

ables were presented as counts (percentages). Group comparisons were performed using the independent samples *t*-test or the Mann-Whitney *U* test for continuous variables and the Pearson's chi-squared test or the Fisher's exact test for categorical variables, as appropriate.

ROC curve analysis was performed to evaluate the discriminatory performance of HRR for all-cause mortality and to determine the optimal cut-off value using the Youden's index. The area under the curve (AUC) with 95% CI was calculated. The discriminatory performance of HRR was further compared with its individual components, hemoglobin and RDW, using ROC curve analyses. Differences between correlated ROC curves were assessed using the DeLong's test. Kaplan-Meier survival curves were constructed to evaluate long-term all-cause mortality according to the HRR groups. Differences between groups were assessed using the log-rank test. To explore the potential non-linear association between HRR and long-term all-cause mortality, restricted cubic spline analysis was performed within the Cox proportional hazards regression framework. The spline model was adjusted for the same covariates included in the multivariable analyses, and overall and non-linearity *P*-values were calculated. Figures were generated using the Python programming language with the Matplotlib libraries for visualization. To evaluate the incremental prognostic value of HRR beyond conventional surgical risk assessment, additional reclassification analyses were performed. A baseline model including STS score alone was compared with a model incorporating both STS score and HRR. Model discrimination was assessed using the AUC. Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to quantify the added predictive value of HRR.

To identify independent predictors of long-term all-cause mortality, Cox proportional hazards regression analyses were performed using two sequential models. Variables considered clinically relevant for long-term mortality after TAVI, as well as potential confounders, were initially evaluated. To minimize the risk of overfitting, the number of covariates entered into the multivariable models was limited according to the number of observed events ($n = 169$), following the event-per-variable principle. Candidate variables were selected from those associated with long-term mortality in univariable analyses ($P < 0.10$) and from variables with established prognostic importance in TAVI populations. Before model construction, multicollinearity was assessed, and highly correlated variables were not simultaneously included in the same model. Because



HRR is derived from hemoglobin and RDW, these parameters were not entered together with HRR. Likewise, STS score was selected as the representative surgical risk score, whereas EuroSCORE II was excluded to avoid collinearity between closely related risk indices. HRR was evaluated as a continuous variable in Model 1 and as a categorical variable based on the ROC-derived cut-off value in Model 2.

A two-sided P -value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 25.0 (SPSS Inc., IBM, Armonk, NY, USA). Additional ROC curve comparisons using the DeLong's test and reclassification analyses (NRI and IDI) were performed with R statistical software 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between March 2019 and December 2023, a total of 632 consecutive patients who underwent TAVI for severe AS were screened. After exclusion of 48 patients due to predefined exclusion criteria, the final study population consisted of 584 patients. The patient selection process is summarized in Figure 1. According to the ROC-derived HRR cut-off value (0.74), patients were categorized into the low HRR group (< 0.74 , $n = 226$) and the high HRR group (≥ 0.74 , $n = 358$).

Baseline demographic characteristics, comorbidities, and medication use of the low HRR group and the high HRR group are presented in Table 1. Patients in the low HRR group were significantly older and had higher STS score and Euro-

SCORE II values compared with those in the high HRR group (all $P < 0.001$). Atrial fibrillation (AF) and malignancy were more prevalent among patients with low HRR. In terms of medical therapy, diuretic and oral anticoagulant use were significantly more frequent in the low HRR group, whereas statin use was higher in the high HRR group.

Comparisons of laboratory parameters, imaging findings, and procedural characteristics between the low HRR group and the high HRR group are shown in Table 2. Patients with low HRR had significantly higher urea, creatinine, C-reactive protein, N-terminal pro-B-type natriuretic peptide, neutrophil, monocyte, and platelet counts, while albumin, lipid parameters, lymphocyte count, hemoglobin levels, mean corpuscular volume, and HRR values were significantly lower (all $P < 0.05$). Echocardiographic parameters including left ventricular ejection fraction, aortic valve area, mean gradient, and peak velocity were comparable between the low HRR group and the high HRR group. However, moderate-to-severe tricuspid regurgitation (TR) was more frequently observed in the low HRR group. Computed tomography-derived annular measurements, Agatston calcium score, access route, valve type, and balloon pre- or post-dilatation rates did not differ significantly between the low HRR group and the high HRR group.

ROC curve analyses were performed to assess the discriminatory ability of HRR for predicting one-year and long-term all-cause mortality (Figure 2A & 2B). HRR demonstrated good predictive performance for one-year mortality (AUC = 0.73, 95% CI: 0.68–0.79) and long-term mortality (AUC = 0.70,

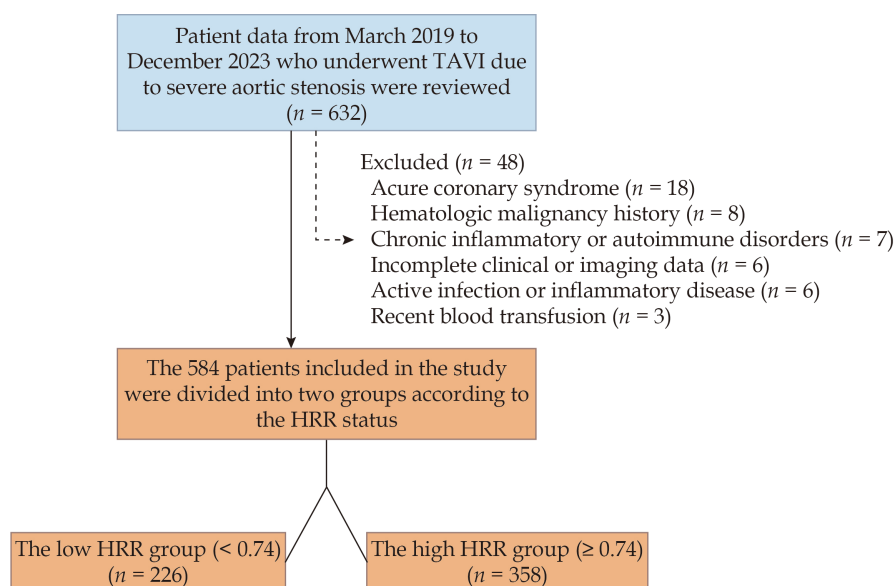


Figure 1 Flow chart of the study. HRR: hemoglobin-to-red cell distribution width ratio; TAVI: transcatheter aortic valve implantation.



Table 1 Baseline demographic, comorbidity and drug characteristics between the low HRR group and the high HRR group.

Variables	The low HRR group (< 0.74) (n = 226)	The high HRR group (≥ 0.74) (n = 358)	P-value
Demographics			
Age, yrs	78 ± 8	76 ± 8	0.001
Male	87 (38%)	163 (45%)	0.094
STS score	4.8 (3.4–6.8)*	3.2 (2.2–4.8)*	< 0.001
EuroSCORE II	7.1 (4.5–10.4)*	5.3 (3.5–8.3)*	< 0.001
Body mass index, kg/m ²	28 ± 6	29 ± 5	0.312
Comorbidities			
Diabetes mellitus	106 (47%)	143 (40%)	0.098
Hypertension	189 (84%)	290 (81%)	0.421
Chronic obstructive pulmonary disease	57 (25%)	80 (22%)	0.425
AF	61 (27%)	64 (18%)	0.009
Previous coronary artery bypass grafting	37 (16%)	64 (18%)	0.639
Previous sternotomy	47 (21%)	81 (23%)	0.603
Previous myocardial infarction	56 (25%)	89 (25%)	0.982
Heart failure	80 (35%)	104 (29%)	0.113
Stroke	16 (7%)	22 (6%)	0.656
Renal replacement therapy	7 (3%)	4 (1%)	0.086
Malignancy	31 (14%)	28 (8%)	0.021
Drugs			
Beta-blockers	164 (73%)	251 (70%)	0.524
Statins	80 (35%)	157 (44%)	0.043
Renin-angiotensin-aldosterone system blockers	141 (62%)	238 (66%)	0.313
Diuretics	101 (45%)	114 (32%)	0.002
Calcium channel blockers	66 (29%)	114 (32%)	0.501
Single antiplatelet therapy	104 (46%)	190 (53%)	0.097
Dual antiplatelet therap	25 (11%)	30 (8%)	0.280
Oral anticoagulants	71 (31%)	80 (22%)	0.015

Data are presented as means ± SD or n (%). *Presented as median (interquartile range). AF: atrial fibrillation; HRR: hemoglobin-to-red cell distribution width ratio; STS: the Society of Thoracic Surgeons.

95% CI: 0.66–0.75). The optimal HRR cut-off value of 0.74 yielded a sensitivity of 78% and specificity of 67% for one-year mortality, and a sensitivity of 65% and specificity of 72% for long-term mortality. Detailed ROC analysis results are provided in supplemental material, [Table 1S](#).

Additional ROC analyses were performed to compare the predictive performance of HRR with its individual components, hemoglobin and RDW. For one-year all-cause mortality, HRR demonstrated the highest discriminatory performance (AUC = 0.731), compared with hemoglobin (AUC = 0.694) and RDW (AUC = 0.694). The DeLong's analyses demonstrated that HRR significantly outperformed hemoglobin (Δ AUC

= 0.037, 95% CI: 0.003–0.071, P = 0.033) and RDW (Δ AUC = 0.037, 95% CI: 0.000–0.075, P = 0.050). For long-term all-cause mortality, the AUC values were 0.704 for HRR, 0.648 for hemoglobin, and 0.699 for RDW. HRR significantly outperformed hemoglobin (Δ AUC = 0.056, 95% CI: 0.031–0.081, P < 0.001), whereas its performance was comparable to RDW (Δ AUC = 0.005, 95% CI: –0.022–0.032, P = 0.713). Detailed results are provided in supplemental material, [Table 2S](#).

Procedural complications and clinical outcomes are summarized in [Table 3](#). In-hospital and 30-day mortality rates were significantly higher in the low HRR group. Patients with low HRR also required blood transfusion more frequently

Table 2 Comparison of laboratory and imaging measurements and procedural characteristics in patients with low and high HRR.

Variables	The low HRR group (< 0.74) (n = 226)	The high HRR group (≥ 0.74) (n = 358)	P-value
Laboratory parameters			
Urea, mg/dL	56 (41–73)*	45 (36–58)*	< 0.001
Creatinine, mg/dL	1.04 (0.83–1.41)*	0.95 (0.77–1.14)*	< 0.001
Aspartate aminotransferase, U/L	21 (16–29)*	22 (17–30)*	0.386
Albumin, g/L	3.8 ± 0.4	4.10 ± 0.4	< 0.001
Total cholesterol, mg/dL	148 (125–175)*	166 (139–196)*	< 0.001
Low-density lipoprotein cholesterol, mg/dL	84 (63–107)*	96 (73–118)*	< 0.001
High-density lipoprotein cholesterol, mg/dL	40 (33–49)*	44 (36–52)*	< 0.001
Triglyceride, mg/dL	106 (79–148)*	114 (91–166)*	0.005
Non-high-density lipoprotein cholesterol, mg/dL	107 (84–132)*	120 (96–148)*	< 0.001
Baseline N-terminal pro-B-type natriuretic peptide, pg/mL	5267 (1991–11,491)*	1979 (796–4446)*	< 0.001
Baseline troponin I, ng/L	28 (12–151)*	24 (10–89)*	0.097
Baseline C-reactive protein, mg/dL	10 (2–30)*	6 (0–12)*	< 0.001
White blood cell count, × 10 ⁹ /L	7.0 (5.7–8.9)*	6.9 (5.8–8.1)*	0.269
Neutrophil count, × 10 ⁹ /L	4.7 (3.6–6.3)*	4.4 (3.5–5.3)*	0.007
Lymphocyte count, × 10 ⁹ /L	1.3 (0.9–1.8)*	1.7 (1.3–2.1)*	< 0.001
Monocyte count, × 10 ⁹ /L	0.5 (0.4–0.6)*	0.4 (0.3–0.5)*	0.020
Haemoglobin, g/dL	10.3 ± 1.3	12.9 ± 1.3	< 0.001
Platelets, × 10 ⁹ /L	238 (188–312)*	221 (177–267)*	< 0.001
Red cell distribution width, %	17.2 ± 2.2	14.4 ± 1.0	< 0.001
Mean platelet volume, fL	8.7 ± 1.0	8.8 ± 1.0	0.217
Mean corpuscular volume, fL	84 ± 9	89 ± 5	< 0.001
Echocardiography			
Left ventricular ejection fraction, %	55 (42–60)*	55 (45–60)*	0.387
Aortic valve area, cm ²	0.7 (0.6–0.8)*	0.7 (0.6–0.8)*	0.083
Mean gradient, mmHg	45 (40–54)*	46 (40–54)*	0.176
Peak velocity, m/sn	4.3 ± 0.6	4.4 ± 0.6	0.568
Moderate to severe aortic regurgitation	73 (32%)	148 (41%)	0.028
Moderate to severe mitral regurgitation	135 (60%)	186 (52%)	0.057
Moderate to severe tricuspid regurgitation	126 (56%)	136 (38%)	< 0.001
Computed tomography			
Anulus perimeter, mm	77 ± 8	78 ± 9	0.478
Anulus area, mm ²	471 (415–522)*	469 (406–549)*	0.757
Agatston calcium score, HU	2611 (1715–3440)*	2534 (1584–3770)*	0.641
Procedural and bioprosthetic valve characteristics			
Transfemoral approach	221 (98%)	353 (99%)	0.459
Balloon predilatation	138 (61%)	223 (62%)	0.734
Balloon postdilatation	56 (24%)	102 (29%)	0.315
Valve type			0.278
Balloon expandable	70 (31%)	96 (27%)	
Self expanding	156 (69%)	262 (73%)	

Data are presented as means ± SD or n (%). *Presented as median (interquartile range). HRR: hemoglobin-to-red cell distribution width ratio.



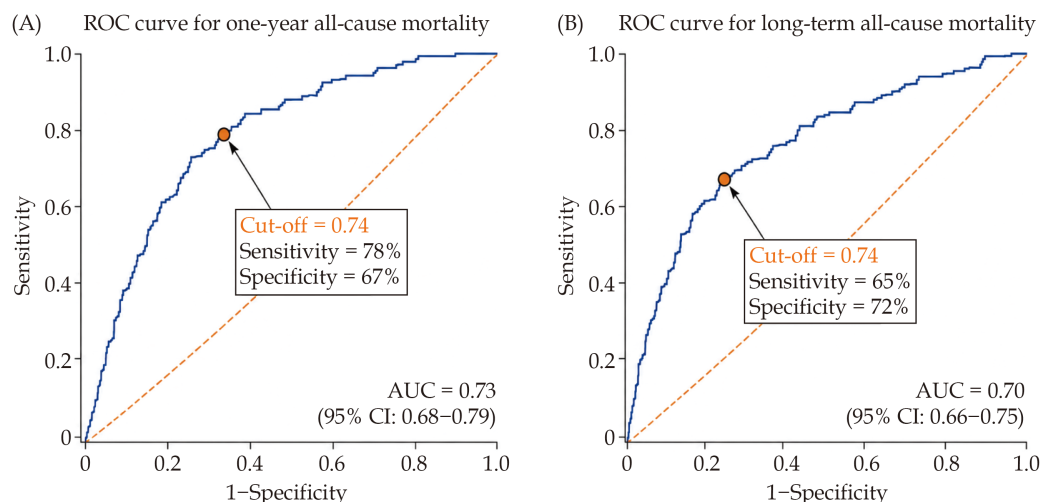


Figure 2 ROC curves of the HRR for prediction of mortality after transcatheter aortic valve implantation. (A) ROC curve for one-year all-cause mortality (AUC = 0.73, 95% CI: 0.68–0.79). The optimal HRR cut-off value was 0.74, yielding a sensitivity of 78% and a specificity of 67%; and (B) ROC curve for long-term all-cause mortality (AUC = 0.70, 95% CI: 0.66–0.75). The optimal HRR cut-off value was 0.74, yielding a sensitivity of 65% and a specificity of 72%. The orange dashed line represents the line of no discrimination (AUC = 0.50), and the highlighted points indicate the optimal cut-off values determined by the Youden's index. AUC: area under the curve; HRR: hemoglobin-to-red cell distribution width ratio; ROC: receiver operating characteristic.

Table 3 Procedural complications and clinical endpoints of the patients.

Variables	Overall (n = 584)	The low HRR group (< 0.74) (n = 226)	The high HRR group (≥ 0.74) (n = 358)	P-value
In-hospital mortality	11 (2%)	8 (3.5%)	3 (1%)	0.019
One-month mortality	16 (3%)	13 (6%)	3 (1%)	< 0.001
Major vascular complication	5 (1%)	5 (2%)	0	0.018
Minor vascular complication	37 (6%)	14 (6%)	23 (6%)	0.912
Stroke	17 (3%)	9 (4%)	8 (2%)	0.221
Myocardial infarction	0	0	0	
Need for blood transfusion	106 (18%)	64 (28%)	42 (12%)	< 0.001
Intensive care duration, days	2 (1–5)	3 (1–8)	2 (1–4)	< 0.001
One-year all-cause mortality	78 (13%)	61 (27%)	17 (5%)	< 0.001
All-cause mortality	169 (29%)	109 (48%)	60 (17%)	< 0.001

Data are presented as median (interquartile range) or n (%). HRR: hemoglobin-to-red cell distribution width ratio.

and had longer intensive care unit stays. During a median follow-up of 28 months (interquartile range: 19–41 months), with a mean follow-up duration of 31 ± 17 months, one-year all-cause mortality was significantly higher in the low HRR group compared with the high HRR group (27% vs. 5%, $P < 0.001$). During long-term follow-up, overall all-cause mortality remained markedly higher among patients with low HRR (48% vs. 17%, $P < 0.001$). Kaplan-Meier survival analysis demonstrated significantly reduced long-term survival in patients with low HRR compared with those with high HRR (Figure 3). The mean survival time was 40 months (interquartile range: 36–44

months) in the low HRR group and 60 months (interquartile range: 58–63 months) in the high HRR group, while the mean survival time for the overall study population was 53 months (interquartile range: 50–55 months). The cumulative survival curves diverged early after TAVI and continued to separate throughout follow-up (log-rank $P < 0.001$).

The results of univariable and multivariable Cox regression analyses for long-term all-cause mortality are shown in Table 4. In univariable analysis, HRR, age, sex, diabetes mellitus, STS score, malignancy, albumin levels, TR severity, and left ventricular ejection fraction were significantly associated with

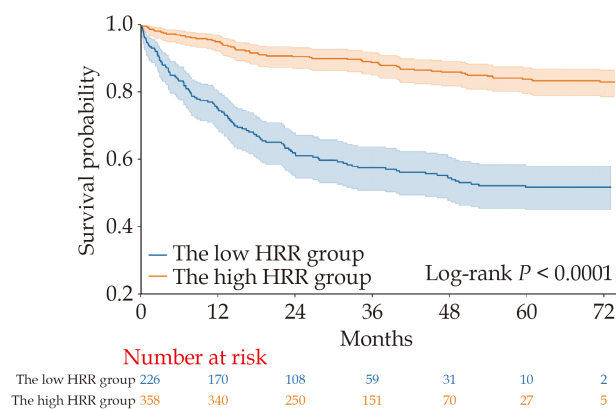


Figure 3 Kaplan-Meier survival plot showing survival curves among patients stratified by the HRR. HRR: hemoglobin-to-red cell distribution width ratio.

long-term all-cause mortality. In multivariable Model 1, HRR evaluated as a continuous variable remained an independent

predictor of long-term all-cause mortality (HR = 0.09, 95% CI: 0.03–0.25, $P < 0.001$), after adjustment for relevant clinical covariates. In Model 2, HRR evaluated as a categorical variable (low HRR vs. high HRR) was also independently associated with long-term all-cause mortality (HR = 0.34, 95% CI: 0.24–0.49, $P < 0.001$). As shown in Table 4, advanced age, male sex, higher STS score, and non-hematological malignancy remained independently associated with long-term all-cause mortality in both multivariable models, together with HRR. The incremental prognostic value of HRR beyond the STS score was further evaluated using reclassification analyses. Compared with the model including STS score alone, addition of HRR improved discrimination for long-term all-cause mortality, increasing the AUC from 0.661 to 0.721 ($\Delta\text{AUC} = 0.061$, $P = 0.002$). Moreover, incorporation of HRR significantly improved risk reclassification, with a continuous NRI of 0.587 ($P < 0.001$) and

Table 4 Estimation of all-cause mortality rates using time-dependent multivariate Cox proportional hazards regression analysis.

Variables	Univariate Model		Multivariate Model 1		Multivariate Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.04 (1.02–1.06)	< 0.001	1.02 (1.00–1.05)	0.048	1.03 (1.01–1.05)	0.021
Male	1.51 (1.12–2.05)	0.007	1.91 (1.37–2.66)	< 0.001	1.86 (1.34–2.58)	< 0.001
Diabetes mellitus	1.38 (1.02–1.87)	0.035	1.46 (1.05–2.04)	0.025	1.37 (0.98–1.92)	0.062
Hypertension	1.45 (0.96–2.21)	0.080	1.48 (0.96–2.29)	0.076	1.38 (0.90–2.13)	0.140
STS score	1.12 (1.08–1.16)	< 0.001	1.06 (1.01–1.10)	0.017	1.05 (1.01–1.10)	0.025
Body mass index	1.00 (0.96–1.05)	0.996				
Previous myocardial infarction	1.44 (1.04–2.00)	0.029	1.16 (0.81–1.68)	0.417	1.25 (0.87–1.80)	0.229
AF	1.18 (0.84–1.64)	0.339				
Malignancy	2.01 (1.32–3.06)	0.001	1.58 (1.01–2.48)	0.045	1.75 (1.12–2.73)	0.014
Creatinine	1.01 (0.98–1.04)	0.561				
Low-density lipoprotein cholesterol	0.99 (0.99–1.01)	0.706				
Albumin	0.41 (0.29–0.57)	< 0.001	0.69 (0.47–1.01)	0.051	0.74 (0.51–1.08)	0.120
Aortic valve area	0.63 (0.25–1.58)	0.327				
Moderate to severe aortic regurgitation	0.78 (0.56–1.08)	0.136				
Moderate to severe mitral regurgitation	1.07 (0.79–1.45)	0.646				
Moderate to severe tricuspid regurgitation	1.51 (1.11–2.05)	0.008	1.13 (0.80–1.59)	0.499	1.16 (0.82–1.63)	0.409
Left ventricular ejection fraction	0.99 (0.98–1.00)	0.048	0.99 (0.98–1.01)	0.353	0.99 (0.98–1.01)	0.327
Anulus area	1.00 (0.99–1.01)	0.797				
Calcium score	1.00 (1.00–1.00)	0.204				
Valve type (self vs. balloon)	1.25 (0.91–1.74)	0.160				
Balloon postdilatation	0.85 (0.59–1.22)	0.371				
HRR _{continuous}	0.05 (0.02–0.11)	< 0.001	0.09 (0.03–0.25)	< 0.001		
HRR _{categorical}	0.27 (0.20–0.37)	< 0.001			0.34 (0.24–0.49)	< 0.001

The log-likelihood value of multivariate Model 1 is 1836, the chi-square value is 111, and the P -value is < 0.001. The log-likelihood value of multivariate Model 2 is 1821, the chi-square value is 128, and the P -value is < 0.001. AF: atrial fibrillation; HRR: hemoglobin-to-red cell distribution width ratio; STS: the Society of Thoracic Surgeons.



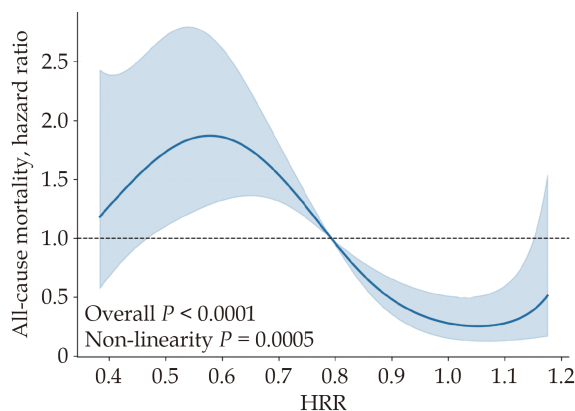


Figure 4 Restricted cubic spline analysis illustrating the association between HRR and long-term all-cause mortality. The solid line represents the adjusted hazard ratio, and the shaded area indicates the 95% CI. The dashed horizontal line denotes a hazard ratio of 1.0. Overall and non-linearity P -values are shown. HRR: hemoglobin-to-red cell distribution width ratio.

an IDI of 0.055 ($P=0.003$) (supplemental material, Table 3S). Restricted cubic spline analysis demonstrated a significant non-linear association between HRR and long-term all-cause mortality, with increasing hazard observed at lower HRR values (overall $P<0.0001$, non-linearity $P=0.0005$) (Figure 4).

DISCUSSION

The main finding of the present study is that preprocedural HRR is independently associated with long-term all-cause mortality in patients undergoing TAVI. To the best of our knowledge, this study represents one of the first comprehensive evaluations of HRR as a prognostic biomarker in the TAVI population. HRR remained a significant predictor of mortality when evaluated both as a continuous and a categorical variable across two multivariable Cox regression models, supporting its prognostic value in a contemporary, real-world TAVI cohort.

Patients with low HRR exhibited a higher burden of adverse clinical characteristics, including advanced age, higher surgical risk scores, AF, malignancy, impaired renal function, and laboratory profiles consistent with systemic inflammation and nutritional impairment. These findings are in line with previous studies demonstrating that anemia and RDW, the individual components of HRR, are associated with worse outcomes following TAVI. Baseline anemia has consistently been linked to increased mortality and rehospitalization after TAVI^[10,11,17] while elevated RDW has been shown to reflect chronic inflammation, oxidative stress, and ineffective erythropoiesis, all of which are prevalent in elderly patients with

severe AS.^[12,18,19] In this context, HRR may serve as an integrative biomarker by simultaneously capturing anemia-related reductions in oxygen-carrying capacity and RDW-related inflammatory and nutritional disturbances. Supporting this concept, recent studies have demonstrated the prognostic significance of HRR in patients with heart failure, coronary artery disease, and sepsis, often outperforming hemoglobin or RDW alone.^[13-15,20] Taken together, these observations suggest that composite hematological indices such as HRR may better reflect the complex interplay between inflammation, erythropoietic dysfunction, and nutritional status than single laboratory parameters. Importantly, additional analyses demonstrated that HRR provided greater discriminatory performance than hemoglobin alone for both one-year and long-term mortality prediction. Although the predictive performance of HRR and RDW was comparable for long-term mortality, HRR demonstrated superior discrimination for one-year mortality. These findings support the concept that combining hemoglobin and RDW into a single composite biomarker may capture prognostic information that is not fully reflected by hemoglobin alone.

Notably, patients in the low HRR group exhibited a substantially higher burden of adverse baseline characteristics, including advanced age, higher STS and EuroSCORE II values, and a greater prevalence of AF and malignancy. These findings raise the possibility that HRR could simply reflect overall disease severity or comorbidity burden. However, HRR remained independently associated with long-term mortality after adjustment for established clinical predictors, including age, sex, STS score, and malignancy. Although surgical risk scores are routinely used to guide patient selection and estimate procedural risk, they may not adequately capture biological vulnerability, inflammatory burden, or nutritional status. The persistence of HRR as an independent predictor suggests that HRR captures aspects of systemic disease and frailty that are not fully represented by conventional risk stratification tools, supporting its role as a complementary rather than redundant prognostic biomarker. Furthermore, HRR provided incremental prognostic value beyond the STS score, significantly improving both discrimination and risk reclassification metrics. These findings further support the notion that HRR captures biological vulnerability, inflammatory burden, and nutritional impairment that are not fully reflected by conventional surgical risk scores. Although the optimal HRR cut-off value was derived from ROC analysis in the present cohort, HRR remained independently associated with mortality when analyzed

as a continuous variable, suggesting that the observed association is not solely dependent on a single threshold.

Although moderate-to-severe mitral regurgitation (MR) and TR have been associated with adverse outcomes after TAVI in several previous studies,^[21-24] neither parameter remained independently associated with long-term mortality in our multivariable models. This finding may be explained by the complex interplay between functional atrioventricular valve regurgitation, ventricular remodeling, and systemic disease burden in patients with severe AS. Functional MR and TR often reflect advanced myocardial remodeling, right ventricular dysfunction, and elevated filling pressures rather than acting as independent drivers of mortality. After adjustment for global clinical risk, comorbidity burden, and laboratory markers reflecting inflammation and nutritional status, the prognostic impact of moderate-to-severe MR and TR may therefore be attenuated. Similar observations have been reported in prior TAVI cohorts, in which the prognostic significance of atrioventricular valve regurgitation diminished after multivariable adjustment or when competing risk factors were considered.^[25-27]

Although serum albumin was significantly associated with long-term mortality in univariable analysis, it did not retain independent prognostic significance after multivariable adjustment. This finding should be interpreted in the context of previous large-scale TAVI studies, particularly the OCEAN-TAVI registry, which demonstrated that the prognostic impact of hypoalbuminemia was most pronounced in patients with markedly reduced albumin levels (≤ 3.5 g/dL).^[28] In our cohort, baseline albumin levels were relatively preserved, with only modest differences between groups, suggesting the absence of severe malnutrition or cachexia in the majority of patients. Under such conditions, albumin may lose its discriminatory power as a standalone prognostic marker. In contrast, HRR integrates hemoglobin-related oxygen-carrying capacity with RDW-related inflammatory and erythropoietic dysregulation, potentially capturing subtler biological vulnerability that is not reflected by albumin levels alone. These findings suggest that while severe hypoalbuminemia identifies a distinctly high-risk subgroup, composite hematological indices such as HRR may provide superior prognostic resolution in contemporary TAVI populations with relatively preserved nutritional status.

From a clinical perspective, HRR represents an inexpensive, widely available, and easily calculable biomarker derived from routine blood tests. In the present study, HRR demonstra-

ted a moderate discriminatory ability for long-term all-cause mortality, as reflected by the ROC analyses. Although these AUC values indicate that HRR should not be considered a standalone prognostic tool, they support its role as a complementary marker within a broader, multiparametric risk assessment framework. In this context, HRR may add incremental prognostic information when interpreted alongside established clinical risk scores, comorbid conditions, and procedural characteristics. In this regard, HRR may help identify patients with increased biological vulnerability who could benefit from individualized follow-up and optimization strategies before and after TAVI. Importantly, identification of patients with low HRR may help clinicians recognize a particularly vulnerable subgroup who could benefit from closer clinical surveillance, optimization of nutritional status, and more meticulous peri-procedural and post-procedural management. Given its simplicity and low cost, HRR could be readily incorporated into preprocedural evaluation or integrated into composite risk models. Future studies should explore whether combining HRR with existing clinical and echocardiographic parameters can further improve risk stratification and decision-making in patients undergoing TAVI. Such an approach may be particularly relevant in contemporary TAVI populations, in whom traditional risk scores may not fully capture biological vulnerability and frailty. The non-linear relationship observed in spline analysis further supports the notion that the prognostic impact of HRR is most pronounced at lower values, consistent with a threshold effect rather than a purely linear association.

LIMITATIONS

Several limitations should be acknowledged. Firstly, the retrospective and single-center design may limit the generalizability of our findings. Secondly, although multivariable adjustment was performed, residual confounding cannot be excluded. Thirdly, HRR was assessed at a single preprocedural time point, and longitudinal changes in HRR were not evaluated. Fourthly, competing risk analysis was not performed, which may have affected the differentiation between cardiovascular and non-cardiovascular causes of death. Last but not least, cause-specific mortality data were not available, and only all-cause mortality could be analyzed.

CONCLUSIONS

In conclusion, HRR is independently associated with long-



term all-cause mortality after TAVI and may serve as a simple and practical prognostic biomarker in this high-risk population. Prospective, multicenter studies are warranted to validate these findings and to explore whether incorporation of HRR into existing risk models can improve prognostic accuracy and clinical decision-making.

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