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ORIGINAL RESEARCH

Neutrophil-to-Lymphocyte Ratios in Patients Undergoing Aortic Valve Replacement: The PARTNER Trials and Registries

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BACKGROUND: The neutrophil-to-lymphocyte ratio (NLR) as a marker of systemic inflammation has been associated with worse prognosis in several chronic disease states, including heart failure. However, few data exist on the prognostic impact of elevated baseline NLR or change in NLR levels during follow-up in patients undergoing transcatheter or surgical aortic valve replacement (TAVR or SAVR) for aortic stenosis.

METHODS AND RESULTS: NLR was available in 5881 patients with severe aortic stenosis receiving TAVR or SAVR in PARTNER (Placement of Aortic Transcatheter Valves) I, II, and S3 trials/registries (median [Q1, Q3] NLR, 3.30 [2.40, 4.90]); mean NLR, 4.10; range, 0.5–24.9) and was evaluated as continuous variable and categorical tertiles (low: NLR ≤2.70, n=1963; intermediate: NLR 2.70–4.20, n=1958; high: NLR ≥4.20, n=1960). No patients had known baseline infection. High baseline NLR was associated with increased risk of death or rehospitalization at 3 years (58.4% versus 41.0%; adjusted hazard ratio [aHR], 1.39; 95% CI, 1.18–1.63; *P*<0.0001) compared with those with low NLR, irrespective of treatment modality. In both patients treated with TAVR and patients treated with SAVR, NLR decreased between baseline and 2 years. A 1-unit observed decrease in NLR between baseline and 1 year was associated with lower risk of death or rehospitalization between 1 year and 3 years (aHR, 0.86; 95% CI, 0.82–0.89; *P*<0.0001).

CONCLUSIONS: Elevated baseline NLR was independently associated with increased subsequent mortality and rehospitalization after TAVR or SAVR. The observed decrease in NLR after TAVR or SAVR was associated with improved outcomes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00530894, NCT0134313, NCT02184442, NCT03225001, NCT0322141.

Key Words: aortic stenosis ■ neutrophil-to-lymphocyte ratio ■ NLR ■ surgical aortic valve replacement ■ transcatheter aortic valve replacement

Systemic inflammation and heart failure (HF) are believed to be strongly interconnected and potentially synergistic to each other.[1] While inflammatory mediators from peripheral tissues can influence the development and progression of HF, mechanical overload and shear stress in HF may cause the release of proinflammatory cytokines from the myocardium, which in addition to having direct local effects, may

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CLINICAL PERSPECTIVE

What Is New?

- In the PARTNER (Placement of Aortic Transcatheter Valves) I, II, and S3 trials or registries of 5881 patients treated with transcatheter aortic valve replacement or surgical aortic valve replacement, elevated preprocedure neutrophil-to-lymphocyte ratio was associated with increased risk of mortality and rehospitalization.
- Decrease in neutrophil-to-lymphocyte ratio during follow-up was associated with lower risk of subsequent events in both patients treated with surgical aortic valve replacement and patients treated with transcatheter aortic valve replacement.

What Are the Clinical Implications?

- Future studies are needed to determine whether changes in neutrophil-to-lymphocyte ratio after transcatheter aortic valve replacement or surgical aortic valve replacement may help inform prognosis and symptom relief and whether strategies targeting the pathobiology underlying elevated neutrophil-to-lymphocyte ratio will improve patient outcomes.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
AVR	aortic valve replacement
NLR	neutrophil-to-lymphocyte ratio
NYHA	New York Heart Association
PARTNER	Placement of Aortic Transcatheter Valves
RASTAVI	Renin-Angiotensin System Blockade Benefits in Clinical Evolution and Ventricular Remodeling After Transcatheter Aortic Valve Implantation
SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement

cause remodeling in organs distal from the heart as HF progresses.[2] Systemic inflammation also appears to contribute to frailty, which might explain why the prevalence of frailty is high in patients with HF.[3]

The neutrophil-to-lymphocyte ratio (NLR) is an index of the innate (ie, neutrophils) and adaptive (ie, lymphocytes) immune pathways that has been proposed to be a better marker of systemic inflammation compared with total white blood count or the individual components of the white blood count.[4–6] Elevated NLR has been associated with worse outcomes in patients with cancer and cardiovascular diseases, including acute and chronic HF.[7]

Although an association has been observed for NLR and prognosis among patients with HF, few data exist on the prognostic implications of NLR for patients with severe aortic stenosis (AS) undergoing aortic valve replacement (AVR). Accordingly, we examined whether NLR was associated with clinical and functional outcomes following transcatheter AVR (TAVR) or surgical AVR (SAVR) for severe AS; if treatment with SAVR or TAVR differentially affects NLR levels at follow-up; and whether change in NLR after AVR is associated with clinical and functional outcomes in a large, individual patient-level, pooled database of the PARTNER (Placement of Aortic Transcatheter Valves) trials and registries.

METHODS

Study Design and Patient Population

We conducted a cohort study of all patients included in the PARTNER trials and registries. The designs of these trials and registries have been previously reported.[8–11] Specifically, the patient study population included patients from PARTNER IA (operable high-risk randomized cohort and continued access registries; NCT00530894); PARTNER IB (inoperable high-risk randomized cohort, randomized continued access, and nonrandomized continued access registries; NCT00530894); PARTNER IIA (operable intermediate-risk randomized cohort; NCT01314313), PARTNER IIB (inoperable randomized SAPIEN XT cohort and nested registries of inoperable transapical, transaortic, 29-mm transfemoral, continued access registries and valve-in-valve registries; NCT02184442, NCT03225001) and PARTNER II (SAPIEN 3 high-risk/inoperable observational cohort; NCT03222141). The pooled patient populations included in the study are itemized by trials and registries in Figure S1. Patients randomized to medical therapy in PARTNER IB were excluded. The population was analyzed in an as-treated fashion with respect to TAVR and SAVR. In all cohorts, patients had severe AS, defined as an aortic valve area <0.8 cm^2 (or indexed aortic valve area <0.5 cm^2/m^2) and either resting or inducible mean gradient >40 mm Hg or peak jet velocity >4 m/s. All patients were symptomatic from their AS with New York Heart Association (NYHA) functional class II or higher symptoms. Key exclusion criteria for all cohorts included baseline active infection, serum creatinine >3 mg/dL or renal replacement therapy, acute myocardial infarction, a congenitally bicuspid aortic valve, severe aortic regurgitation, left ventricular ejection fraction (LVEF) <20%, and estimated life expectancy of <2 years. The study was conducted

according to the Declaration of Helsinki. Informed consent was required before trial and registry enrollment, and the study was approved by individual site institutional review boards. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Clinical Data and End Points

Clinical data and transthoracic echocardiograms were obtained at baseline, hospital discharge, 30 days, 1 year, and 2 years. NLR was measured at baseline (preprocedure), discharge, 30 days, and 1-year and 2-year follow-up. All echocardiograms were interpreted by independent core laboratories. The primary end point of this analysis was death or rehospitalization. Rehospitalization was defined as the need for repeat hospitalization because of aortic stenosis (ie, heart failure, angina, or syncope) or for complications related to the valve procedure (ie, infection, stroke, renal failure, vascular complication). Outcomes were adjudicated by an independent clinical events committee in each individual trial. NLR was calculated as the ratio of neutrophil count to lymphocyte count. NLR was evaluated both as a continuous log-transformed variable and tertiles (low <2.70), intermediate (2.70–4.20), or high (≥4.20) since there is no universal cutoff for NLR as an inflammatory marker.

Statistical Analysis

Patients were grouped according to NLR tertiles (T1-T3) to compare demographic, clinical, echocardiographic, and procedural characteristics. Baseline characteristics were summarized as means and SDs or medians and interquartile ranges for continuous measures and proportions for categorical variables. Continuous variables are presented as means and SDs and compared using analysis of variance. Categorical variables are shown as counts and frequencies and compared using the chi-square or Fisher's exact test. For time-to-first-event analyses, event rates were estimated by the Kaplan-Meier method and compared with Cox regression. Multivariable Cox proportional hazards models were adjusted for the following predefined clinically pertinent covariates and baseline characteristics that were significantly different between the NLR tertile groups: age, sex, diabetes, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, previous stroke or transient ischemic attack, major arrhythmia, NYHA class III or IV, LVEF, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), coronary artery disease, peripheral arterial disease, LVEF, left ventricular mass index, left ventricular end diastolic diameter, moderate to severe mitral regurgitation, B-type natriuretic peptide, randomized treatment, and study cohort. Data on tricuspid regurgitation and frailty were uniformly available only in the P2 cohort, in which a sensitivity analysis was performed adjusting for moderate to severe tricuspid regurgitation and frailty as reflected by gait speed (15-foot walk test), in addition to the above-mentioned covariates. Because the presence of cancer and immunosuppressive treatment might affect NLR, a second sensitivity analysis was performed that excluded patients with current cancer or previous or current immunosuppressive treatment. These patients were infrequent (n=106 with current cancer and n=149 with previous or current immunosuppressive therapy) and were included in the primary analysis given that the distribution of NLR in these patients was similar to that of the overall population (Figure S2A through S2C). All multivariable models were stratified by study.

Interaction terms were included to assess whether the impact of NLR differed in SAVR versus TAVR, in patients with and without coronary artery disease, and without diabetes, with obesity (body mass index ≥30 versus <30) and at high versus intermediate or low surgical risk. Nonlinear relationships between NLR and the risk of clinical outcomes were explored using penalized splines with 2 degrees of freedom.[12] NLRs were right skewed and normalized with a logarithmic transformation when analyzed as a continuous variable. The change in NLR levels over time was normally distributed.

ANCOVA was performed in the randomized cohorts to compare mean changes in NLR from baseline to follow-up between TAVR and SAVR, adjusted for baseline NLR values. Changes in NLR over time in the overall cohort were analyzed using a linear mixed-effects model, adjusting for study using a random effect. The association of change in NLR at several time points (baseline, 30 days, and 1 year) with clinical outcomes at 2 years was analyzed using a landmark approach. The landmark analysis refers to designating a time point occurring during the follow-up period known as the landmark time, which in the present analysis was the change in NLR levels between baseline and each follow-up time point and excluding events occurring before the landmark time.[13]

Associations between change in NLR levels from baseline to follow-up time points (follow-up value–baseline value) with changes in the Kansas City Cardiomyopathy Questionnaire, 6-minute walk distance, left ventricular function (LVEF), and mean aortic gradients were assessed by ANCOVA regression models, adjusting for the baseline values of those variables with the assumption of equal variance.

All P values are 2-tailed, and $P<0.05$ was considered significant for all analyses. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Study Population and Baseline Characteristics

Out of a total of 8530 patients, baseline NLR was available in 5881 patients (68.9%), of whom 2446 were from the PARTNER I trial, 3022 were from the PARTNER 2 Sapien XT, and 413 were from Partner II Sapien 3 cohorts (Figure S1). Most patients underwent TAVR (n=4 840, 82.3%) as opposed to SAVR (n=1041, 17.7%). The distribution of NLR was nonnormal and right-skewed (Figure S2A) with a median [Q1, Q3] of 3.30 [2.40, 4.90], ranging from 0.5 to 24.9. Table 1 shows various baseline clinical and echocardiographic characteristics of patients stratified by NLR tertiles (high [≥4.20], intermediate [2.70–4.20], and low [≤2.70]). Higher NLR was associated with male sex, more comorbidities, higher Society of Thoracic Surgeons risk score, and worse left ventricular function. Patients with higher NLR were more often treated with diuretics, antiarrhythmics, and anticoagulants (Table S1). Higher NLR was also associated with longer hospital stay, larger prosthesis size (TAVR arm), and longer aortic cross-clamp time (SAVR arm) (Table S2).

Clinical Outcomes

The median [Q1, Q3] duration of follow-up for the entire cohort was 34 [18, 50] months. Outcomes by NLR tertiles are shown in Figure 1, Table S3, and Table 2. Compared with patients in the lowest NLR tertile, patients in the highest tertile had higher rates of the 3-year composite end point of death or rehospitalization (58.4% versus 41.0%, adjusted hazard ratio [aHR], 1.39; 95% CI, 1.18–1.63; $P<0.0001$) as well as the individual end points of death and rehospitalization, separately. The association of NLR with the risk of adverse outcomes remained similar in sensitivity analysis, excluding patients with current cancer or previous or current immunosuppressive therapy (Table S4) or when adjusting for moderate to severe tricuspid regurgitation and gait speed (Table S5). The association between NLR and the risk of adverse outcomes remained significant when NLR was modeled as a continuous log-linear variable (Figure 2 and Table S6). In spline analysis (Figure 2), the nonlinearity P value of 0.23 was consistent with the linear relationship between NLR and the 3-year risk of the composite of death or rehospitalization. There were no significant interactions between NLR and treatment modality (TAVR versus SAVR), Society of Thoracic Surgeons risk score >8 versus ≤8, presence of diabetes, coronary artery disease, or obesity with the risk of adverse outcomes at 3 years (Table S7). The association between NLR and the risk of adverse outcomes within each cohort was overall similar to that of the pooled study population (Figure S3). When neutrophils and lymphocytes were analyzed individually as continuous variables, increase in neutrophils and decrease in lymphocytes were independently associated with the risk of adverse outcomes (Table S8).

Change in NLR After TAVR or SAVR and Clinical Outcomes

NLR increased more immediately following SAVR compared with TAVR (Figure S4) but at 30 days, 1 year, and 2 years, NLR levels decreased to similar levels between TAVR and SAVR. To compare change in NLR between treatments, only the 1726 patients enrolled in either of the randomized cohorts were considered (PARTNER 1A and PARTNER 2A). A total of 950 of 1726 patients (55.0%) in the TAVR arm and 776 of 1726 patients (45.0%) in the SAVR arm had paired measurements of NLR values available and were included in this analysis. The least squares mean change in NLR from baseline to 30 days was 0.2±2.6 in patients treated with TAVR and 0.9±2.6 in patients treated with SAVR (difference between groups −0.5 [−0.7 to −0.3; $P<0.0001$]). After adjustment including baseline NLR values, an increase of 1 unit in NLR between baseline and 30 days was associated with an increased risk of death or rehospitalization between 30 days and 3 years (Table 3).

Change in NLR in the Overall Population and Clinical Outcomes

When compared with baseline, mean NLR decreased significantly in the overall cohort at both 1 year (0.92, 95% CI, 0.90–0.99; $P<0.0001$) and 2 years (0.87; 95% CI, 0.84–0.90; $P<0.0001$). In landmark analysis including adjustment for baseline NLR values, a 1-unit decrease in NLR between baseline and 1 year was associated with lower risk of death or rehospitalization between 1 year and 3 years (aHR, 0.80; 95% CI, 0.76–0.85; $P<0.0001$) (Table 3).

Associations Between Change in NLR and Post-AVR Echocardiographic Indices

Increase in NLR between baseline and 30 days and baseline and 1 year was independently associated with increased risk of moderate or severe paravalvular leak at 30 days and 1 year (Table S9), and a decrease in LVEF at 1 year (Table S10). There was no significant association between change in NLR at follow-up and mean aortic gradient (Table S11).

Associations Between Change in NLR and Post-AVR Quality of Life and Functional Outcomes

Increase in NLR between baseline and 30 days and baseline and 1 year was independently associated with worse NYHA class and lower Kansas City

Table 1. Baseline Clinical and Echocardiographic Characteristics of Patients by Tertiles of NLR

	NLR Tertile			
	Low (≤2.7) n=1963	Intermediate (2.7–4.2) n=1958	High (≥4.2) n=1960	Overall *P* value
Clinical characteristics				
Age, y	83.1 (7.7)	83.1 (7.8)	82.8 (7.5)	0.43
Male sex	48.0 (942/1963)	57.9 (1134/1958)	61.0 (1196/1960)	<0.0001
Race				
White	92.1 (1770/1922)	94.6 (1819/1922)	95.5 (1840/1927)	<0.0001
Black or African American	3.8 (73/1922)	1.8 (35/1922)	1.1 (22/1927)	<0.0001
Body mass index, kg/m^2	27.7 (6.3)	27.6 (6.2)	27.5 (6.5)	0.55
Diabetes	34.5 (677/1961)	36.7 (718/1958)	36.9 (723/1960)	0.23
Insulin dependent	16.8 (329/1957)	18.1 (353/1953)	20.3 (396/1954)	0.02
Non–insulin dependent	17.6 (344/1957)	18.4 (360/1953)	16.4 (321/1954)	0.25
Previous or current smoker	46.5 (911/1961)	51.2 (1002/1958)	53.4 (1047/1960)	<0.0001
Previous smoker	44.9 (550/1225)	51.1 (587/1149)	52.7 (559/1061)	0.0004
Current smoker	2.6 (32/1225)	2.6 (30/1149)	2.3 (24/1061)	0.83
Renal insufficiency (SCr ≥2 mg/dL)	8.3 (162/1961)	11.5 (224/1956)	16.2 (317/1960)	<0.0001
Liver disease	2.4 (48/1961)	2.9 (56/1957)	3.1 (61/1957)	0.44
Previous or current immunosuppressive therapy	4.5 (36/800)	6.7 (47/703)	12.0 (66/551)	<0.0001
Previous cancer	26.9 (330/1225)	31.2 (358/1149)	32.0 (339/1061)	0.02
Current cancer	2.1 (26/1225)	2.9 (33/1149)	4.4 (47/1061)	0.006
Anemia	19.1 (234/1225)	22.0 (253/1149)	27.0 (286/1061)	<0.0001
Thrombocytopenia	5.1 (62/1225)	4.3 (49/1149)	6.4 (68/1061)	0.07
Coagulopathy	2.0 (39/1960)	1.5 (29/1955)	2.2 (43/1958)	0.24
Previous or current bleeding	11.2 (89/795)	11.6 (81/697)	13.3 (73/548)	0.48
STS-PROM score	8.5 (4.1)	9.2 (4.5)	10.1 (4.8)	<0.0001
<4	7.6 (150/1962)	4.7 (92/1957)	4.3 (84/1960)	<0.0001
4–8	40.1 (787/1962)	36.6 (717/1957)	28.9 (567/1960)	<0.0001
>8	52.2 (1025/1962)	58.7 (1148/1957)	66.8 (1309/1960)	<0.0001
EuroSCORE I	15.0 (14.0)	17.1 (15.6)	19.0 (16.3)	<0.0001
NYHA functional class				
I	0.0 (0/1963)	0.0 (0/1958)	0.2 (3/1960)	0.05
II	13.2 (260/1963)	10.6 (208/1958)	7.4 (145/1960)	<0.0001
III	55.0 (1079/1963)	55.2 (1080/1958)	52.8 (1035/1960)	0.26
IV	31.8 (624/1963)	34.2 (670/1958)	39.6 (777/1960)	<0.0001
Congestive heart failure	90.2 (1770/1962)	91.2 (1783/1955)	92.7 (1816/1959)	0.02
Hypertension	93.1 (1825/1961)	92.8 (1818/1958)	92.3 (1809/1959)	0.67
Dyslipidemia	81.8 (1604/1961)	83.9 (1642/1958)	82.4 (1615/1960)	0.21
Coronary artery disease	76.5 (1500/1960)	76.9 (1506/1958)	79.4 (1557/1960)	0.060
Peripheral arterial disease	34.6 (679/1961)	38.7 (757/1958)	38.4 (752/1959)	0.01
Prior stroke or transient ischemic attack	17.7 (346/1959)	18.0 (352/1956)	17.4 (340/1958)	0.87
Prior endocarditis	0.7 (14/1961)	0.9 (18/1955)	0.7 (14/1957)	0.70
History of atrial fibrillation or flutter	33.1 (406/1225)	39.9 (459/1149)	45.8 (486/1061)	<0.0001
Katz activities of daily living index	5.5 (1.1)	5.4 (1.1)	5.2 (1.3)	<0.0001
Grip strength average grasp	20.0 (9.8)	21.0 (10.2)	20.6 (9.5)	0.06
15-foot walk, sec	8.4 (4.8)	8.6 (4.9)	10.2 (26.2)	0.009
Serum albumin <3.5 mg/dL	17.0 (229/1348)	19.9 (250/1258)	28.7 (335/1168)	<0.0001
B-type natriuretic peptide	827.0 (2331.0)	985.9 (2148.8)	1328.9 (2822.5)	<0.0001

(*Continued*)

Table 1. (Continued)

	NLR Tertile			
	Low (≤2.7) n=1963	Intermediate (2.7–4.2) n=1958	High (≥4.2) n=1960	Overall *P* value
Echocardiographic characteristics				
AV mean area (cm^2)	0.69 (0.22)	0.68 (0.20)	0.67 (0.21)	0.08
AV area index, cm^2/m^2	0.38 (0.11)	0.37 (0.11)	0.36 (0.11)	0.001
AV peak velocity, cm/s	426.0 (63.7)	425.1 (65.6)	422.6 (65.9)	0.25
AV mean gradient, mm Hg	43.6 (13.6)	43.6 (14.0)	43.3 (14.0)	0.70
AV peak gradient, mm Hg	74.2 (22.1)	74.0 (23.0)	73.2 (22.7)	0.34
LV end diastolic diameter, cm	4.52 (0.76)	4.64 (0.79)	4.67 (0.79)	<0.0001
LV end systolic diameter, cm	3.21 (0.90)	3.35 (0.94)	3.43 (0.95)	<0.0001
LV ejection fraction*	54.4 (12.4)	53.0 (12.7)	51.3 (13.5)	<0.0001
LV mass, g	233.6 (73.0)	243.1 (75.4)	250.9 (77.2)	<0.0001
LV stroke volume*, mL	57.4 (19.2)	59.3 (20.0)	59.7 (20.4)	0.007
LV stroke volume index, mL/m^2	31.7 (9.8)	32.3 (9.9)	32.4 (10.3)	0.19
E/A ratio	1.15 (0.72)	1.46 (1.02)	1.31 (0.77)	0.03
E/E′ ratio (lateral)	15.1 (8.3)	15.3 (8.2)	15.5 (8.8)	0.67
Left atrial volume index, mL/m^2	41.9 (13.8)	43.2 (15.6)	46.2 (17.2)	<0.0001
Aortic regurgitation (moderate/severe)	12.6 (239/1892)	13.4 (256/1904)	13.9 (264/1894)	0.49
Mitral regurgitation (moderate/severe)	20.1 (366/1825)	22.6 (419/1852)	24.3 (449/1850)	0.008
Tricuspid regurgitation (moderate/severe)	15.4 (165/1070)	21.4 (216/1011)	22.0 (204/926)	0.0002
Right ventricular systolic pressure, mm Hg	36.5 (12.6)	39.2 (13.3)	41.1 (14.7)	<0.0001

Values are mean (SD) or % (n/N). AV indicates aortic valve; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LV, left ventricular; NLR, neutrophil-to-lymphocyte ratio; NYHA, New York Heart Association; SCr, serum creatinine; and STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

*Visual or Simpson.

†Assessed by Doppler.

Cardiomyopathy Questionnaire and 6-minute walk test at follow-up (Table S12 through S14).

DISCUSSION

There were 5 major findings of the present large-scale analysis of serial NLR in the PARTNER I and II trials and registries of patients with severe AS undergoing TAVR or SAVR: (1) Elevated baseline NLR was independently associated with higher subsequent death and rehospitalization rates regardless of treatment modality; (2) NLR increased more immediately following SAVR compared with TAVR but at 30 days, 1 year, and 2 years NLR decreased to similar levels between TAVR and SAVR; (3) an increase in NLR between baseline and 30 days was associated with increased risk of adverse clinical outcomes and worsened quality of life and functional capacity; (4) from baseline to 1 year, NLR decreased significantly in the overall cohort; and (5) in adjusted landmark analysis, a 1-unit decrease in NLR from baseline to 1 year was associated with a 15% lower risk of death and 12% lower risk of rehospitalization between 1 year and 3 years.

To the best of our knowledge, the current study is the largest study to date examining the prognostic impact of elevated baseline NLR on clinical outcomes of patients with severe symptomatic AS who undergo AVR. It is also the largest study to compare the change in NLR after TAVR versus SAVR, and to assess the association of this change in NLR with clinical, echocardiographic, and functional outcomes. Only 4 prior studies have investigated the relationship between NLR and clinical outcomes of patients with AS (Table S15) and found a significant association between baseline NLR and increased risk of subsequent events. However, these prior studies[14–17] included small sample sizes (N=119, 234, 298, and 520), reported single-center experiences, lacked longitudinal measurements, and did not adjust for important baseline differences between patients with high versus low NLR. In addition, since there is no universal cutoff for NLR that determines a health outcome as “normal” or “adverse,” these prior studies used their own study population to inform arbitrary cutoffs. In the present study, a strong continuous risk relationship was observed between NLR and clinical outcomes.

These findings suggest that NLR may have a role in risk stratification of patients who are more likely to

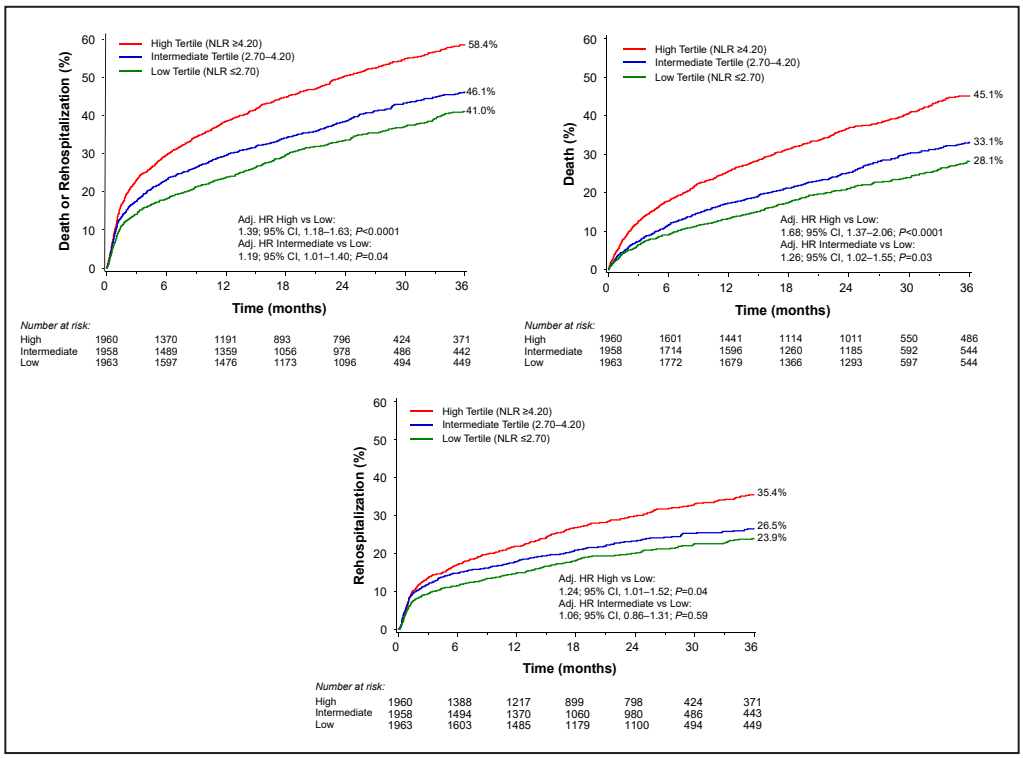

Figure 1. Kaplan–Meier time-to-first-event analyses by tertiles of neutrophil-to-lymphocyte ratio in patients undergoing transcatheter aortic valve replacement or surgical aortic valve replacement.
(**A**) Death or rehospitalization; (**B**) death; (**C**) rehospitalization. HR indicates hazard ratio; and NLR, neutrophil-to-lymphocyte ratio.

benefit from AVR based on a particular immunologic profile or inflammatory response, which is not currently part of the decision-making process because of a lack of an easily obtainable or validated biomarker. Changes in NLR over time could serve as a useful tool to identify patients who are at increased risk of worse outcomes following AVR, which may imply a more aggressive follow-up strategy in these patients.

Several risk factors and conditions associated with increased mortality were more likely present in patients with elevated NLR. It remains to be studied whether elevated NLR has an etiological role in the increased risk of adverse events after AVR or if it is merely a by-product of the conditions that lead to increased mortality. Several findings of the present analysis suggest that NLR at least reflects the presence of systemic inflammation. First, adjustment for patient characteristics, comorbidities, NYHA class, and Society of Thoracic Surgeons risk score did not alter the association of NLR with subsequent events. Second, although the cohorts included in the pooled analysis differed in surgical risk, the association of NLR with subsequent events remained significant when studying each cohort separately. Third, the inclusion of longitudinal NLR measurements allowed us to assess the natural history and changes over time in NLR.

It was interesting to observe that in the present study, mechanical unloading of the heart by AVR was associated with reduced NLR over time. Although controversies exist, a few prior studies of patients with HF have observed a similar association between improvement in cardiac function after cardiac synchronization therapy and a reduction in some inflammatory mediators.[18] However, AVR may not completely reverse the manifestations and pathophysiology of HF, yielding substantial residual risk related to ongoing HF.[19] Emerging data suggest a potential benefit of renin-angiotensin system inhibition after TAVR on left ventricular remodeling,[20,21] and this hypothesis is being tested in the ongoing RASTAVI (Renin-Angiotensin System Blockade Benefits in Clinical Evolution and Ventricular Remodeling After Transcatheter Aortic Valve Implantation) trial.[22] Whether aggressive medical therapy such as renin-angiotensin system inhibition after AVR would benefit those with residual HF and the extent to which improvements in HF symptoms would be accompanied by reduced systemic inflammation in these patients should be studied. Furthermore, reducing procedural complications such as moderate/severe paravalvular leak that is associated with more residual HF[23] might also have an impact on systemic inflammation.

Table 2. Association Between Baseline NLR and 3-Year Adverse Outcomes

	Unadjusted HR (95% CI)	*P* value	Model 1a adjusted HR (95% CI)	*P* value	Model 1b adjusted HR (95% CI)	*P* value
Death or rehospitalization						
High (NLR ≥4.2) vs low (NLR ≤2.7)	1.47 (1.35–1.59)	<0.0001	1.39 (1.18–1.63)	<0.0001	1.42 (1.20–1.69)	<0.0001
Intermediate (NLR 2.7–4.2) vs low (≤2.7)	0.92 (0.85–1.00)	0.06	1.19 (1.01–1.40)	0.04	1.28 (1.07–1.52)	0.006
All-cause death						
High (NLR ≥4.2) vs low (NLR ≤2.7)	1.60 (1.46–1.76)	<0.0001	1.68 (1.37–2.06)	<0.0001	1.69 (1.36–2.11)	<0.0001
Intermediate (NLR 2.7–4.2) vs Low (≤2.7)	0.88 (0.79–0.97)	0.012	1.26 (1.02–1.55)	0.03	1.36 (1.09–1.69)	0.007
Cardiovascular death						
High (NLR ≥4.2) vs low (NLR ≤2.7)	1.55 (1.37–1.75)	<0.0001	1.54 (1.19–1.99)	<0.0001	1.57 (1.18–2.07)	0.002
Intermediate (NLR 2.7–4.2) vs low (NLR ≤2.7)	0.90 (0.79–1.03)	0.12	1.23 (0.94–1.61)	0.12	1.31 (0.99–1.74)	0.06
Rehospitalization						
High (NLR ≥4.2) vs low (NLR ≤2.7)	1.37 (1.23–1.53)	<0.0001	1.24 (1.01–1.52)	0.04	1.30 (1.04–1.62)	0.02
Intermediate (NLR 2.7–4.2) vs low (≤2.7)	0.96 (0.85–1.08)	0.46	1.06 (0.86–1.31)	0.59	1.12 (0.89–1.40)	0.34

The following covariates were included in the adjusted model 1a: age, sex, diabetes, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, serum albumin, previous stroke or transient ischemic attack, atrial fibrillation/flutter, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, New York Heart Association class III or IV, Society of Thoracic Surgeons risk score, access (transfemoral vs transthoracic), randomized treatment, and study cohort. Model 1b was, in addition to the covariates included in model 1a, also adjusted for baseline B-type natriuretic peptide. HR indicates hazard ratio; and NLR, neutrophil-to-lymphocyte ratio.

It is also likely that there are other drivers of the association between elevated NLR and worse prognosis after AVR for patients with severe AS than HF or frailty, since adjusting for B-type natriuretic peptide, NYHA class, and gait speed (as a measure of frailty) did not attenuate the observed association between NLR and the risk of subsequent events. It remains to be studied whether drugs that reduce systemic inflammation might have a role as adjunctive therapy after AVR. Furthermore, it is possible that NLR is a marker of successful pre-AVR treatment of comorbidities, which would reduce baseline NLR and impact post-AVR outcomes. Additionally, improvements of AVR technique to decrease the inflammatory response might result in better long-term outcomes. The early postprocedure increase in NLR, which was greater after SAVR than TAVR, is likely associated with surgical injury and cardiopulmonary bypass. However, this temporary

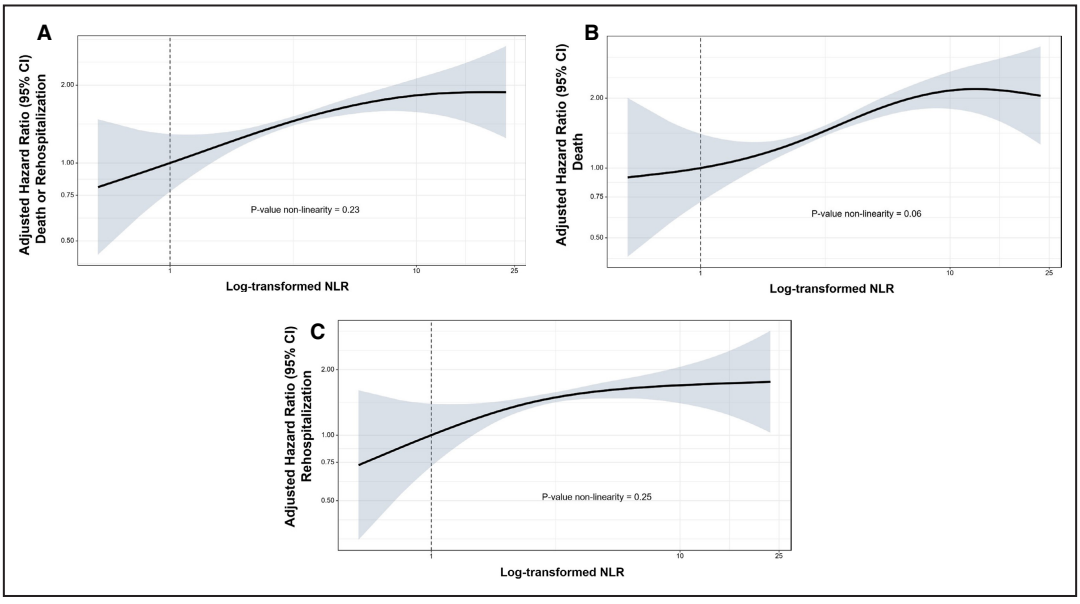

Figure 2. Kaplan-Meier time-to-first-event analyses by tertiles of neutrophil-to-lymphocyte ratio in patients undergoing transcatheter aortic valve replacement or surgical aortic valve replacement.
(**A**) Death or rehospitalization; (**B**) death; (**C**) rehospitalization. HR indicates hazard ratio; and NLR, neutrophil-to-lymphocyte ratio.

Table 3. Landmark Analysis for the Risks of Adverse Outcomes 3 Years After Aortic Valve Replacement by Change in NLR at Various Time Points

	Adjusted HR (95% CI)	*P* value
Association of change in NLR between baseline and 30 d per 1-unit increase and outcomes between 30 d and 3 y		
Death or rehospitalization	1.17 (1.12–1.22)	<0.0001
All-cause death	1.17 (1.11–1.23)	<0.0001
Cardiovascular death	1.21 (1.13–1.29)	<0.0001
Rehospitalization	1.16 (1.08–1.24)	<0.0001
Association of change in NLR between baseline and 1 y per 1-unit decrease and outcomes between 1 y and 3 y		
Death or rehospitalization	0.80 (0.76–0.85)	<0.0001
All-cause death	0.79 (0.73–0.85)	<0.0001
Cardiovascular death	0.77 (0.70–0.85)	<0.0001
Rehospitalization	0.83 (0.77–0.91)	<0.0001

Multivariable models were adjusted for: baseline neutrophil-to-lymphocyte ratio (NLR), age, sex, diabetes, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, serum albumin, previous stroke or transient ischemic attack, atrial fibrillation/flutter, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, New York Heart Association class III or IV, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), randomized treatment, and study cohort. HR indicates hazard ratio; and NLR, neutrophil-to-lymphocyte ratio.

inflammatory period normalized to similar levels as post-TAVR already at 30 days and NLR decreased similarly in TAVR and SAVR patients. Finally, there was no interaction between NLR and treatment modality (TAVR or SAVR) with regard to the risk of adverse outcomes, suggesting that NLR levels did not influence the choice of treatment.

Limitations

The present study is a post hoc analysis and should be considered hypothesis generating. The patients chosen for this study met the inclusion criteria for the PARTNER trial and therefore were at least intermediate surgical risk. Therefore, the patients in this analysis were elderly with numerous medical comorbidities and may be not representative of the general population of patients who are considered for TAVR or SAVR. Local laboratories were used for NLR measurement, which may have resulted in some imprecision. Although our findings regarding the association of NLR with clinical and functional outcomes remained statistically significant after multivariable adjustment, we cannot rule out the possibility that the analysis is confounded by other unmeasured factors that are correlated with NLR. Additionally, survival bias could have influenced our analyses such as why we did not observe an association between NLR and paravalvular leak at 2 years. Furthermore, data on CRP was not available to compare the prognostic value of NLR in relation to CRP.

CONCLUSIONS

In the present study, elevated baseline NLR was associated with worse clinical outcomes in patients with severe AS undergoing TAVR or SAVR. The decrease in NLR after AVR was associated with lower risk of subsequent events in both SAVR and TAVR.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S15
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Medications at Baseline by Tertiles of Neutrophil-to-Lymphocyte Ratio.

	Neutrophil-to-Lymphocyte Ratio (NLR) Tertile			
	Low (≤2.7)	Intermediate (2.7 <NLR <4.2)	High (≥4.2)	Overall p Value
Angiotensin-converting enzyme inhibitor	27.9% (544/1952)	28.3% (552/1952)	27.9% (543/1948)	0.95
Angiotension II receptor blocker	17.3% (338/1952)	15.5% (303/1952)	13.8% (269/1948)	0.01
Alpha-1 receptor blocker	1.5% (29/1952)	2.2% (43/1952)	2.0% (39/1948)	0.24
Antiarrhythmic	7.5% (147/1952)	10.6% (206/1952)	12.0% (234/1948)	<0.0001
Digoxin	8.6% (168/1952)	11.9% (232/1952)	14.8% (288/1948)	<0.0001
Statin	65.5% (1279/1952)	68.0% (1327/1952)	64.8% (1262/1948)	0.09
Anticholesterol	6.5% (126/1952)	5.1% (100/1952)	4.4% (86/1948)	0.016
Anticoagulant	21.0% (410/1952)	24.1% (471/1952)	26.4% (514/1948)	0.0004
Aspirin or other antiplatelet therapy	76.9% (1501/1952)	75.9% (1481/1952)	73.4% (1429/1948)	0.03
Beta blocker	62.4% (1219/1952)	63.0% (1230/1952)	59.8% (1165/1948)	0.09
Calcium channel blocker	27.5% (537/1952)	27.0% (527/1952)	25.2% (491/1948)	0.23
Diuretic	59.7% (1166/1952)	66.1% (1291/1952)	72.1% (1404/1948)	<0.0001
Nitrate/vasodilator	18.4% (359/1952)	16.8% (328/1952)	16.9% (330/1948)	0.35

Values are % (n/N). NLR – neutrophil-to-lymphocyte ratio.

Table S2. Procedural Characteristics by Tertiles of Neutrophil-to-Lymphocyte Ratio

	Neutrophil-to-Lymphocyte Ratio (NLR) Tertile			
	Low (≤2.7)	Intermediate (2.7 <NLR <4.2)	High (≥4.2)	Overall p value
Index hospitalization stay, days	7.9 (5.6)	7.7 (5.9)	8.4 (6.6)	0.002
Intensive care unit stay, days	3.7 (4.6)	3.6 (4.3)	3.8 (5.3)	0.43
Procedure to discharge, days	6.3 (5.0)	6.1 (5.3)	6.6 (5.6)	0.07
Transcatheter aortic valve replacement				0.08
Transcatheter heart valve size				—
20 mm	0.0% (0/1260)	0.0% (0/1264)	0.0% (0/1343)	—
23 mm	46.9% (591/1260)	42.1% (532/1264)	42.5% (571/1343)	0.03
26 mm	38.9% (490/1260)	41.0% (518/1264)	41.7% (560/1343)	0.32
29 mm	14.2% (179/1260)	16.9% (214/1264)	15.8% (212/1343)	0.17
20/23 mm	46.9% (591/1260)	42.1% (532/1264)	42.5% (571/1343)	0.03
26/29 mm	53.1% (669/1260)	57.9% (732/1264)	57.5% (772/1343)	0.03
Intra-aortic balloon pump	2.8% (43/1547)	2.7% (43/1598)	3.2% (54/1676)	0.62
Need for cardiopulmonary bypass	1.8% (29/1621)	1.4% (23/1685)	1.5% (27/1773)	0.61
Pre-dilatation	99.2% (779/785)	98.8% (839/849)	99.2% (926/933)	0.57
Post-dilatation	14.4% (221/1539)	15.3% (243/1586)	14.3% (238/1666)	0.65
Surgical aortic valve replacement				
Surgical valve size				
17 mm	0.2% (1/406)	0.0% (0/354)	0.0% (0/275)	0.46
19 mm	12.3% (50/406)	13.6% (48/354)	11.6% (32/275)	0.76
21 mm	37.4% (152/406)	31.4% (111/354)	29.8% (82/275)	0.07
22 mm	0.2% (1/406)	0.0% (0/354)	0.0% (0/275)	0.46
23 mm	34.2% (139/406)	34.7% (123/354)	39.3% (108/275)	0.36
25 mm	13.1% (53/406)	17.2% (61/354)	15.3% (42/275)	0.27
27 mm	2.0% (8/406)	2.5% (9/354)	3.3% (9/275)	0.57
29 mm	0.5% (2/406)	0.6% (2/354)	0.7% (2/275)	0.92
Aortic cross clamp time, mins	73.1 (30.4)	73.4 (28.8)	78.8 (30.3)	0.03
Pump time, mins	101.6 (40.0)	104.8 (46.4)	110.6 (50.9)	0.04

Data presented as % (n/N) or mean (SD). NLR = neutrophil-to-lymphocyte ratio.

Table S3. Thirty-Day and 3-Year Clinical Outcomes by Tertiles of Baseline Neutrophil-to-Lymphocyte Ratio

	Neutrophil-to-Lymphocyte Ratio (NLR) Tertile			
	Low (≤2.7)	Intermediate (2.7 <NLR <4.2)	High (≥4.2)	Overall p Value
30 Days				
Death or rehospitalization	8.4% (165)	10.9% (212)	12.4% (242)	0.0003
Death				
All-cause	3.0% (59)	3.8% (75)	5.6% (110)	0.0002
Cardiovascular	2.4% (47)	2.9% (57)	3.9% (77)	0.02
Non-cardiovascular	0.6% (12)	0.9% (18)	1.7% (33)	0.003
Rehospitalization	5.6% (108)	7.3% (140)	7.3% (137)	0.056
Stroke or transient ischemic attack	4.5% (87)	4.1% (79)	4.5% (88)	0.75
Myocardial Infarction	1.3% (26)	1.1% (22)	0.9% (17)	0.40
Vascular complications	11.8% (231)	10.4% (202)	11.4% (221)	0.35
Bleeding	36.4% (714)	33.2% (648)	34.3% (670)	0.10
Acute kidney injury (stage III)	1.6% (31)	2.4% (44)	3.6% (66)	0.0009
Aortic valve reintervention	1.1% (21)	1.5% (30)	0.9% (18)	0.18
3 Years				
Death or rehospitalization	41.0% (686)	46.1% (783)	58.4% (1019)	<0.0001
Death				
All-cause	28.1% (443)	33.1% (529)	45.1% (758)	<0.0001
Cardiovascular	18.5% (277)	22.7% (337)	30.7% (462)	<0.0001
Non-cardiovascular	11.8% (166)	13.4% (192)	20.9% (296)	<0.0001
Rehospitalization	23.9% (377)	26.5% (422)	35.4% (522)	<0.0001
Stroke or TIA	11.8% (186)	10.5% (171)	11.5% (174)	0.80
Myocardial infarction	3.9% (60)	4.0% (57)	3.7% (49)	0.84
Vascular complications	13.1% (253)	11.3% (215)	12.7% (241)	0.19
Bleeding	43.8% (829)	42.9% (792)	45.3% (824)	0.51
Acute kidney injury (stage III)	3.6% (61)	5.5% (87)	6.9% (114)	<0.0001
Aortic valve reintervention	1.9% (35)	2.8% (46)	2.5% (41)	0.41

Values are % (n). NLR = neutrophil-to-lymphocyte ratio; TIA = transient ischemic attack.

Table S4. Sensitivity Model for the Association Between Neutrophil-to-Lymphocyte Ratio and 3-Year Adverse Outcomes Excluding Patients With Current or Previous Immunosuppressive Therapy

	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Death or rehospitalization				
High (NLR ≥4.2) vs. Low (NLR ≤2.7)	1.49 (1.38, 1.62)	<0.0001	1.36 (1.16, 1.61)	0.0003
Intermediate (2.7 <NLR <4.2) vs. Low (≤2.7)	0.91 (0.84, 1.00)	0.038	1.18 (1.00, 1.40)	0.048
All-cause death				
High (NLR ≥4.2) vs. Low (NLR ≤2.7)	1.59 (1.45, 1.76)	<0.0001	1.58 (1.28, 1.95)	<0.0001
Intermediate (2.7 <NLR <4.2) vs. Low (≤2.7)	0.88 (0.79, 0.98)	0.015	1.21 (0.98, 1.51)	0.08
Cardiovascular death				
High (NLR ≥4.2) vs. Low (NLR ≤2.7)	1.53 (1.35, 1.73)	<0.0001	1.44 (1.10, 1.89)	0.007
Intermediate (2.7 <NLR <4.2) vs. Low (≤2.7)	0.91 (0.80, 1.03)	0.14	1.17 (0.89, 1.54)	0.27
Rehospitalization				
High (NLR ≥4.2) vs. Low (NLR ≤2.7)	1.41 (1.26, 1.58)	<0.0001	1.28 (1.03, 1.58)	0.03
Intermediate (2.7 <NLR <4.2) vs. Low (≤2.7)	0.95 (0.84, 1.07)	0.37	1.09 (0.88, 1.36)	0.42

The following covariates were included in the adjusted model: Age, sex, diabetes mellitus, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, serum albumin, atrial fibrillation/flutter previous stroke or transient ischemic attack, major arrythmia, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, New York Heart Association class III or IV, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), randomized treatment, and study cohort. Patients with current cancer or previous or current immunosuppressive therapy were excluded from this model. CI = confidence interval; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio.

Table S5. Sensitivity Model for the Association Between Neutrophil-to-Lymphocyte Ratio and 3-Year Adverse Outcomes Adjusting for Tricuspid Regurgitation and Frailty

	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Death or rehospitalization				
High (NLR ≥4.2) vs. Low (NLR ≤2.7)	1.40 (1.25, 1.57)	<0.0001	1.36 (1.14, 1.63)	0.0007
Intermediate (2.7 <NLR <4.2) vs. Low (≤2.7)	0.99 (0.87, 1.11)	0.038	1.20 (1.00, 1.44)	0.046
All-cause death				
High (NLR ≥4.2) vs. Low (NLR ≤2.7)	1.54 (1.33, 1.78)	<0.0001	1.55 (1.24, 1.94)	0.0001
Intermediate (2.7 <NLR <4.2) vs. Low (≤2.7)	0.95 (0.82, 1.11)	0.53	1.21 (0.96, 1.53)	0.10
Cardiovascular death				
High (NLR ≥4.2) vs. Low (NLR ≤2.7)	1.52 (1.26, 1.83)	<0.0001	1.37 (1.03, 1.82)	0.03
Intermediate (2.7 <NLR <4.2) vs. Low (≤2.7)	0.92 (0.76, 1.13)	0.43	1.13 (0.84, 1.52)	0.42
Rehospitalization				
High (NLR ≥4.2) vs. Low (NLR ≤2.7)	1.39 (1.20, 1.61)	<0.0001	1.25 (0.99, 1.57)	0.057
Intermediate (2.7 <NLR <4.2) vs. Low (≤2.7)	0.94 (0.81, 1.11)	0.48	1.08 (0.85, 1.36)	0.54

The following covariates were included in the adjusted model: Age, sex, diabetes mellitus, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), B-type natriuretic peptide, previous or current cancer, baseline hemoglobin, serum albumin, atrial fibrillation/flutter, previous stroke or transient ischemic attack, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, New York Heart Association class III or IV, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), randomized treatment, study cohort, moderate to severe tricuspid regurgitation, and frailty by gait speed (15-foot walk). CI = confidence interval; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio.

Table S6. Associations Between Neutrophil to Lymphocyte Ratio (NLR) at Baseline As a Continuous Log-transformed Variable And The Risks of Adverse Outcomes at 3 Years

	Unadjusted HR (95% CI) Per 5-Unit Increase in Log-Transformed NLR	p Value	Model 1a Adjusted HR (95% CI) Per 5-Unit Increase in Log-Transformed NLR	p Value	Model 1b Adjusted HR (95% CI) Per 5-unit increase in log-transformed NLR	p Value
Death or rehospitalization	1.27 (1.22, 1.34)	<0.0001	1.19 (1.10, 1.28)	<0.0001	1.19 (1.10, 1.30)	<0.0001
All-cause death	1.35 (1.28, 1.43)	<0.0001	1.28 (1.16, 1.41)	<0.0001	1.27 (1.14, 1.40)	<0.0001
Cardiovascular death	1.32 (1.22, 1.41)	<0.0001	1.22 (1.08, 1.38)	0.002	1.22 (1.06, 1.39)	0.004
Rehospitalization	1.21 (1.14, 1.30)	<0.0001	1.14 (1.03, 1.26)	0.01	1.15 (1.03, 1.28)	0.01

The following covariates were included in the adjusted model 1a: Age, sex, diabetes mellitus, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, previous stroke or transient ischemic attack, major arrythmia, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, New York Heart Association class III or IV, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), randomized treatment, and study cohort. CI = confidence interval; HR = hazard ratio; NLR = neutrophil to lymphocyte ratio.

Table S7. The Impact of a 5-Unit Increase in Log-Transformed Baseline Neutrophil-to-Lymphocyte Ratio on the Adjusted Risk of Adverse Outcomes at 3 Years According to Treatment Modality, Society of Thoracic Surgeons Risk Score, Presence of Diabetes, or Coronary Artery Disease

	TAVR (n = 1138)	SAVR (n = 1041)	adjP$_{int}$	STS >8 (n = 3482)	STS ≤8 (n = 2397)	adjP$_{int}$	DM (n = 814)	No DM (n = 1365)	adjP$_{int}$	CAD (n = 1608)	No CAD (n = 571)	adjP$_{int}$	BMI ≥30	BMI<30	adjP$_{int}$
	adHR [95% CI]	adjHR [95% CI]		adjHR [95% CI]	adjHR [95% CI]		adjHR [95% CI]	adjHR [95% CI]		adjHR [95% CI]	adjHR [95% CI]		adjHR [95% CI]	adjHR [95% CI]	
Death or rehospitalization	1.30 (1.09, 1.55)	1.32 (1.10, 1.59)	0.92	1.13 (0.85, 1.51)	1.28 (1.10, 1.50)	0.45	1.31 (1.11, 1.56)	1.25 (1.10, 1.42)	0.63	1.35 (1.16, 1.56)	1.19 (0.91, 1.57)	0.44	1.47 (0.79, 2.72)	1.72 (1.20, 2.46)	0.66
All-cause death	1.46 (1.16, 1.84)	1.36 (1.08, 1.71)	0.65	1.07 (0.73, 1.57)	1.41 (1.15, 1.73)	0.21	1.42 (1.15, 1.76)	1.34 (1.15, 1.58)	0.68	1.47 (1.22, 1.77)	1.23 (0.87, 1.72)	0.36	2.88 (1.26, 6.59)	1.69 (1.06, 2.68)	0.27
Cardiovascular death	1.25 (0.93, 1.68)	1.17 (0.87, 1.59)	0.77	0.84 (0.50, 1.43)	1.19 (0.91, 1.56)	0.25	1.34 (1.02, 1.75)	1.27 (1.02, 1.56)	0.75	1.26 (0.99, 1.60)	1.06 (0.67, 1.67)	0.51	2.04 (0.72, 5.77)	1.12 (0.60, 2.09)	0.33
Non-cardiovascular death	1.89 (1.30, 2.74)	1.70 (1.19, 2.45)	0.70	1.51 (0.85, 2.67)	1.83 (1.33, 2.52)	0.56	1.61 (1.13, 2.30)	1.46 (1.14, 1.87)	0.65	1.89 (1.40, 2.55)	1.52 (0.90, 2.55)	0.47	6.14 (1.49, 25.33)	3.08 (1.52, 6.24)	0.39
Rehospitalization	1.20 (0.95, 1.51)	1.15 (0.87, 1.51)	0.80	1.22 (0.85, 1.75)	1.17 (0.95, 1.45)	0.85	1.16 (0.91, 1.47)	1.22 (1.02, 1.46)	0.72	1.19 (0.98, 1.45)	1.11 (0.75, 1.65)	0.76	0.90 (0.41, 1.96)	1.93 (1.18, 3.13)	0.10

Adj = adjusted; BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

Table S8. Risks of Adverse Outcomes at 3 Years Per 5-Unit Increase or Decrease in Baseline Neutrophils and Lymphocytes

	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Increase per 1-unit in neutrophils				
Death or rehospitalization	1.09 (1.07, 1.11)	<0.0001	1.04 (1.00, 1.07)	0.03
All-cause death	1.11 (1.08, 1.14)	<0.0001	1.07 (1.02, 1.11)	0.003
Cardiovascular death	1.10 (1.07, 1.14)	<0.0001	1.06 (1.00, 1.11)	0.045
Rehospitalization	1.07 (1.04, 1.10)	<0.0001	1.01 (0.97, 1.06)	0.65
Decrease per 1-unit in lymphocytes				
Death or rehospitalization	1.14 (1.11, 1.17)	<0.0001	1.22 (1.09, 1.37)	0.0005
All-cause death	1.18 (1.14, 1.22)	<0.0001	1.31 (1.13, 1.52)	0.0003
Cardiovascular death	1.17 (1.12, 1.22)	<0.0001	1.24 (1.03, 1.49)	0.023
Rehospitalization	1.12 (1.08, 1.16)	<0.0001	1.23 (1.06, 1.42)	0.006

The following covariates were included in the adjusted model: Age, sex, diabetes mellitus, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, serum albumin, atrial fibrillation/flutter, previous stroke or transient ischemic attack, major arrythmia, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, New York Heart Association class III or IV, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), randomized treatment, and study cohort. CI = confidence interval; HR = hazard ratio.

Table S9. Adjusted Association Between 1-Unit Change in Neutrophil-to-Lymphocyte Ratio From Baseline to Discharge, 30 Days, 1 Year, and 2 Years with the Risk of Moderate/Severe Paravalvular Leak

	OR (95% CI)	p Value
PVL moderate/severe at discharge	1.01 (0.93, 1.09)	0.89
PVL moderate/severe at 30 days	1.09 (1.03, 1.15)	0.002
PVL moderate/severe at 1 year	1.08 (1.02, 1.15)	0.006
PVL moderate/severe at 2 years	0.96 (0.85, 1.10)	0.56

The following covariates were included in the adjusted model: Baseline neutrophil-to-lymphocyte ratio, age, sex, diabetes mellitus, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, previous stroke or transient ischemic attack, major arrythmia, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, New York Heart Association class III or IV, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), randomized treatment, and study cohort. CI = confidence interval;OR = odds ratio; PVL = paravalvular leak.

Table S10. Adjusted Association Between 1-Unit Change in Neutrophil-to-Lymphocyte Ratio From Baseline to Discharge, 30 Days, 1 Year, and 2 Years and Change in Left Ventricular Ejection Fraction

	Estimate (95% CI)*	p Value
LVEF at baseline	-0.08 (-0.20, 0.04)	0.18
LVEF change from baseline at discharge	0.02 (-0.11, 0.15)	0.76
LVEF change from baseline at 30 days	-0.07 (-0.17, 0.04)	0.22
LVEF change from baseline at 1 year	-0.34 (-0.50, -0.19)	<0.0001
LVEF change from baseline at 2 years	-0.33 (-0.68, 0.02)	0.06

*Analysis of covariance models were used to model the change in left ventricular ejection fraction (LVEF) to adjust for baseline values of LVEF and neutrophil-to-lymphocyte ratio. The following additional covariates were included in the adjusted model: Age, sex, diabetes mellitus, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, previous stroke or transient ischemic attack, major arrythmia, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, New York Heart Association class III or IV, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), randomized treatment, and study cohort. CI = confidence interval; LVEF = left ventricular ejection fraction.

Table S11. Adjusted Association Between 1-Unit Change in Neutrophil-to-Lymphocyte Ratio From Baseline to Discharge, 30 Days, 1 Year, and 2 Years and Change in Mean Aortic Gradient

	Estimate (95% CI)*	p Value
Mean gradient at baseline	0.15 (0.02, 0.28)	0.03
Change in mean aortic gradient baseline to discharge	-0.02 (-0.11, 0.07)	0.66
Change in mean aortic gradient baseline to 30 days	0.03 (-0.03, 0.09)	0.27
Change in mean aortic gradient baseline to 1 year	0.00 (-0.09, 0.10)	0.94
Change in mean aortic gradient baseline to 2 year	-0.10 (-0.30, 0.09)	0.30

*Analysis of covariance models were used to model the change in mean aortic gradient to adjust for baseline values of mean aortic gradient and NLR. The following additional covariates were included in the adjusted model: Age, sex, diabetes mellitus, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, previous stroke or transient ischemic attack, major arrythmia, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, New York Heart Association class III or IV, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), randomized treatment, and study cohort. CI = confidence interval; NLR = neutrophil-to-lymphocyte ratio.

Table S12. Adjusted Association Between 1-Unit Change in Neutrophil-to-Lymphocyte Ratio From Baseline to Discharge, 30 Days, 1 Year, and 2 Years and New York Heart Association Class III/IV

	OR (95% CI)	p Value
NYHA III/IV at baseline	1.15 (1.10, 1.21)	<0.0001
NYHA III/IV at discharge	1.04 (1.00, 1.09)	0.07
NYHA III/IV at 30 days	1.31 (1.26, 1.37)	<0.0001
NYHA III/IV at 1 year	1.11 (1.05, 1.17)	0.0002
NYHA III/IV at 2 years	1.08 (0.95, 1.23)	0.26

The following covariates were included in the adjusted model: Baseline neutrophil-to-lymphocyte ratio, age, sex, diabetes mellitus, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, previous stroke or transient ischemic attack, major arrythmia, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), randomized treatment, and study cohort. CI = confidence interval; NYHA = New York Heart Association; OR = odds ratio.

Table S13. Adjusted Association Between 1-Unit Change in Neutrophil-to-Lymphocyte Ratio from Baseline to Discharge, 30 Days, 1 Year, and 2 Years and Change in Kansas City Cardiomyopathy Questionnaire

	Estimate (95% CI)*	p Value
KCCQ at baseline	-0.70 (-0.92, -0.49)	<0.0001
KCCQ change from baseline at 30 days	-1.27 (-1.59, -0.96)	<0.0001
KCCQ change from baseline at 1 year	-0.76 (-1.06, -0.47)	<0.0001
KCCQ change from baseline at 2 years	-1.19 (-1.80, -0.57)	0.0002

*Analysis of covariance models were used to model the change in Kansas City Cardiomyopathy Questionnaire (KCCQ) to adjust for baseline values of neutrophil-to-lymphocyte ratio and KCCQ. The following additional covariates were included in the adjusted model: Age, sex, diabetes mellitus, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, previous stroke or transient ischemic attack, major arrythmia, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), randomized treatment, and study cohort. CI = confidence interval; KCCQ = Kansas City Cardiomyopathy Questionnaire.

Table S14. Adjusted Association Between 1-Unit Change in Neutrophil-to-Lymphocyte Ratio From Baseline to Discharge, 30 Days, 1 Year, and 2 Years and Change in 6-Minute Walk Test

	Estimate (95% CI)*	p Value
6MWT at baseline	-3.14 (-4.32, -1.96)	<0.0001
6MWT change from baseline at 30 days	-6.51 (-8.96, -4.06)	<0.0001
6MWT change from baseline at 1 year	-4.42 (-6.61, -2.23)	<0.0001
6MWT change from baseline at 2 years	-6.50 (-10.47, -2.52)	0.001

*Analysis of covariance models were used to model the change in 6-minute walk test (6MWT) to adjust for baseline values of neutrophil-to-lymphocyte ratio and 6MWT. The following additional covariates were included in the adjusted model: Age, sex, diabetes mellitus, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, previous stroke or transient ischemic attack, major arrythmia, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), randomized treatment, and study cohort. CI = confidence interval; 6MWT = 6-minute walk test.

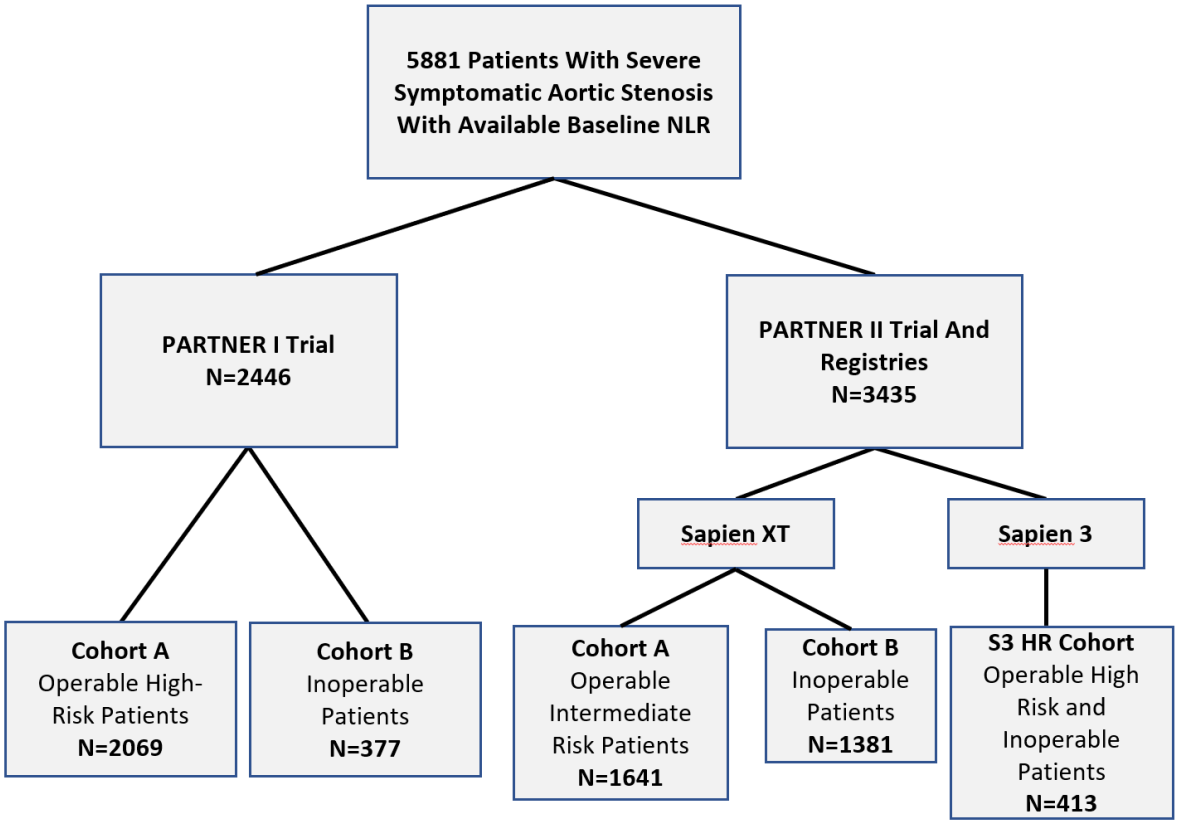
Table S15. Summary of Previous Studies Examining the Role of Neutrophil-to-Lymphocyte Ratio in Patients With Aortic Stenosis

Study	Patient Population	Neutrophil-to-Lymphocyte Ratio Cutoff	Outcome
Condado et al. [17]	Retrospective study of 520 patients with severe undergoing TAVR	Quartiles (Q1 <2.12, Q2 2.12-3.1, Q3 3.14-4.29, Q4 4.33-32)	No association between NLR and 1-year mortality or readmission in un-adjusted models or when models were adjusted for STS PROM, valve type, and transfemoral access; however, an increase of 1 SD=3.67 in NLR was associated with the composite of mortality or readmission (HR 1.22, 95% CI 1.03-1.43, p=0.02) after adjusting for STS PROM, valve type, and transfemoral access. NLR cut-offs 3.2 and 3.7 were associated with STS PROM 8 and 15, respectively.
Khalil et al. [16]	Prospective registry of 298 patients with symptomatic severe AS with a median STS score of 9.0 undergoing TAVR	ROC analysis identified a cutoff value of NLR = 4.0 with a sensitivity of 68% and specificity of 68% (AUC 0.65, 95% CI 0.51–0.79, p=0.03) for MACE (mortality, reinfarction, or stroke) and sensitivity of 60% and specificity of 57% (AUC 0.61, 95% CI 0.53–0.69, p=0.01) for HF hospitalization.	In unadjusted analysis, patients with NLR ≥4.0 before TAVR were significantly more likely to experience MACE after TAVR (68.4% vs. 31.6%, p=0.02). Patients with NLR ≥4.0 before TAVR had significantly worse survival from HF readmissions when adjusted for age (HR 1.9, 95% CI 1.02–3.39, p=0.04).
Cho et al. [14]	119 Patients with severe AS and mean EUROSCORE of 8.5 retrospectively enrolled after undergoing TAVR	Cutoffs were derived, and NLR was categorized as low risk if NLR ≤2, intermediate risk if 2 <NLR ≤9, and high risk if NLR >9.	Survival free from MACE (death, cardiovascular death, or myocardial infarction) at 5 years was 84.6% for the low-risk group, 67.7% for the intermediate-risk group, and 42.6% for the high-risk group.
Küçükseymen et al. [24]	A single-center study of 220 AS patients (mild/moderate group: n=110; severe group: n=110) and 157 healthy controls. The groups were similar with respect to age, sex, LVEF, GFR, hsCRP and fibrinogen levels.	Median NLR was 1.77 (1.48-2.03) in controls compared with 2.68 (2.13-2.68) in mild/moderate AS and 4.62 (3.50-5.76) in severe AS.	An ROC curve analysis yielded a strong predictive ability of NLR for the presence of AS (AUC 0.930, 95% CI 0.898–0.96, p<0.001). A cut-off of 2.310 for NLR had a sensitivity and specificity of 80.4% and 92.4%, respectively, for the presence of AS.
Habib et al. [15]	A retrospective single-center study of 234 patients with severe AS undergoing SAVR	NLR was dichotomized into NLR ≥3 and <3 by testing all possible cutoffs that would discriminate between mortality by Cox proportional analyses.	Patients with NLR ≥3 had a significantly higher prevalence of symptoms of HF (44.34% vs. 59.38%, p=0.03), lower ejection fraction (51.08±10.28 vs. 45.47±12.13, p=0.0001), presence of atrial fibrillation (16.04% vs. 28.13%, p=0.03), and higher serum creatinine levels (1.12±1.18 vs. 1.38±1.38, p=0.0012) when compared with those with lower NLR. NLR ≥3 was associated with the risk of mortality at 3 years after adjustment for LVEF, hypertension, history of cerebrovascular accident, previous coronary artery bypass grafting, serum creatinine, blood glucose symptoms of HF, and angina.
Avci et al. [25]	Retrospective single-center study of 96 patients divided into 3	Mean NLR was 2.05±0.64 in those with mild/moderate AS, 2.69±1.00 in severe AS with	The distribution of the age, sex, diabetes, hypertension, and hyperlipidemia was similar across the AS groups. There was a statistically significant correlation between NLR and both transaortic mean pressure gradient and

	groups as mild/moderate AS, severe AS with normal LVEF, and severe AS with reduced LVEF. AS was based on transaortic mean pressure gradient	normal LVEF, and 3.94±0.88 in those with severe AS and reduced LVEF.	aortic valve peak velocity in patients with mild-to-severe AS with normal LVEF (n=81; r=0.369, p<0.001; r=0.290, p=0.004, respectively).

Citation number reflects reference number in manuscript. AS = aortic stenosis; AUC = area under the curve; CI = confidence interval; GFR = glomerular filtration rate; HF = heart failure; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac events; NLR = neutrophil-to-lymphocyte ratio; PROM = predicted risk of mortality; ROC = receiver operating characteristics; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

Figure S1. Study Flow Chart.

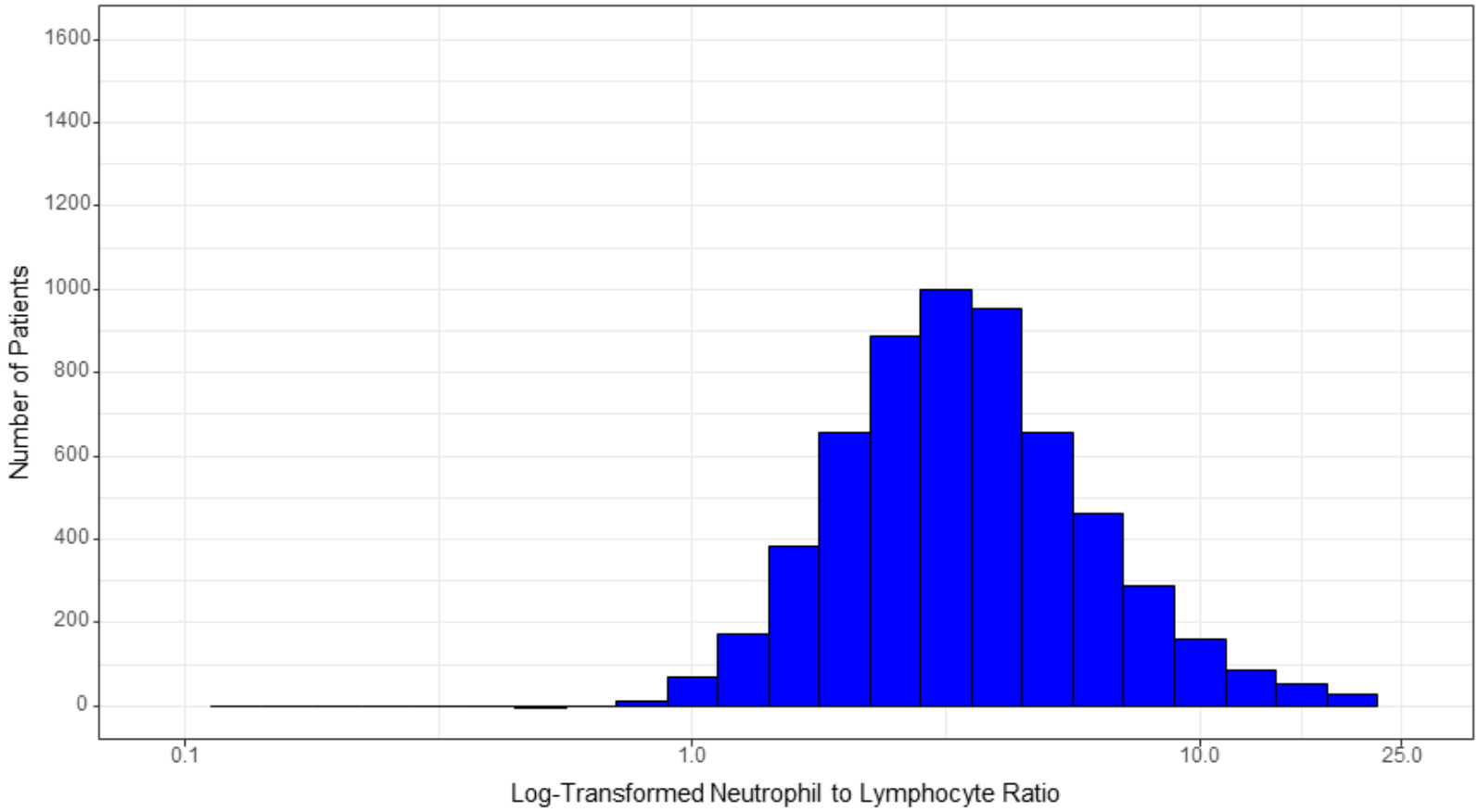


NLR = neutrophil-to-lymphocyte ratio.

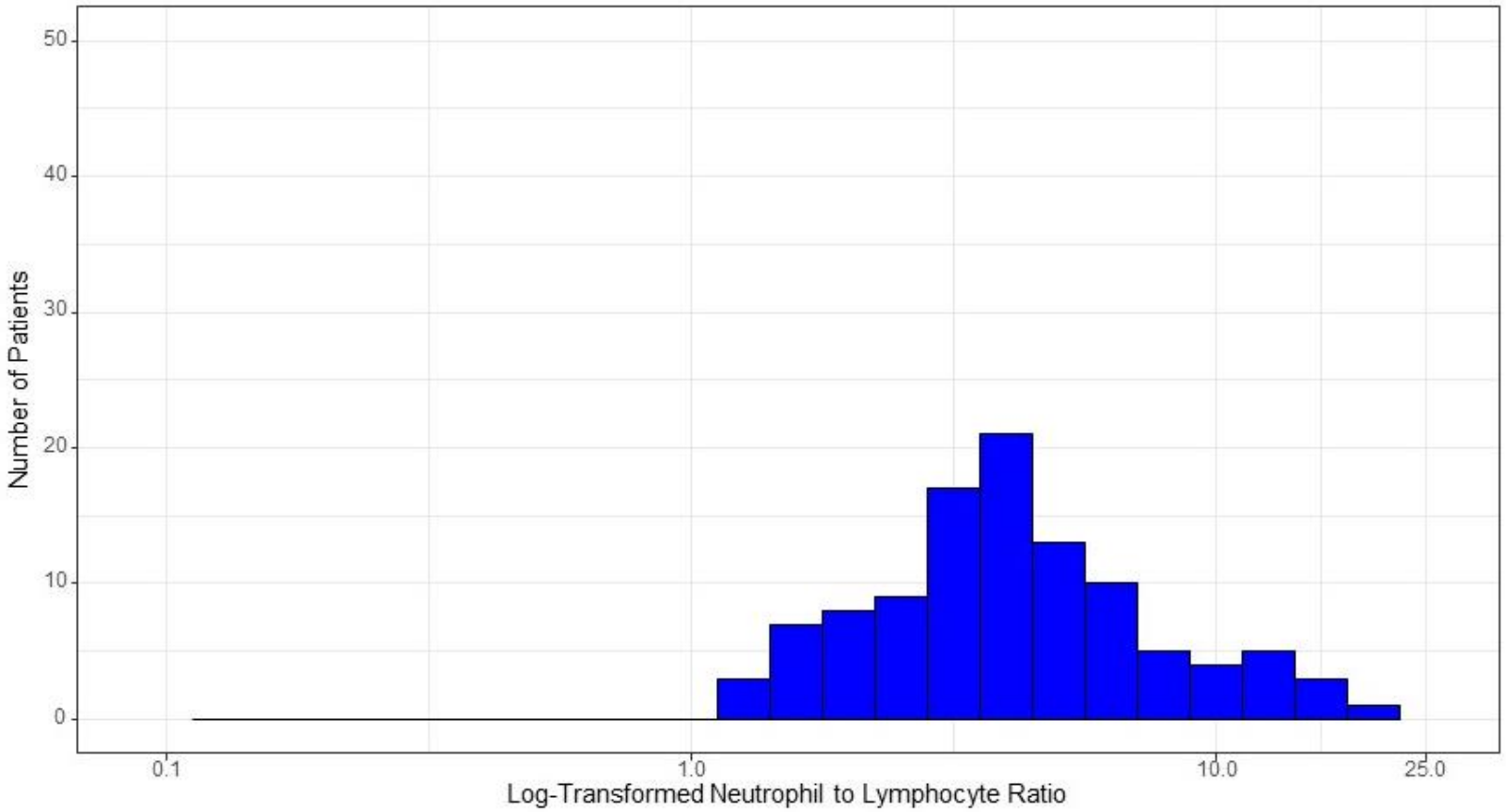
Figure S2. Distribution of Neutrophil-to-Lymphocyte Ratio.

(A) Overall population; (B) patients with current cancer; (C) patients with previous or current immunosuppressive therapy.

A



B


50
40
30
20
10
0
Number of Patients
0.1
1.0
10.0
25.0
Log-Transformed Neutrophil to Lymphocyte Ratio

C

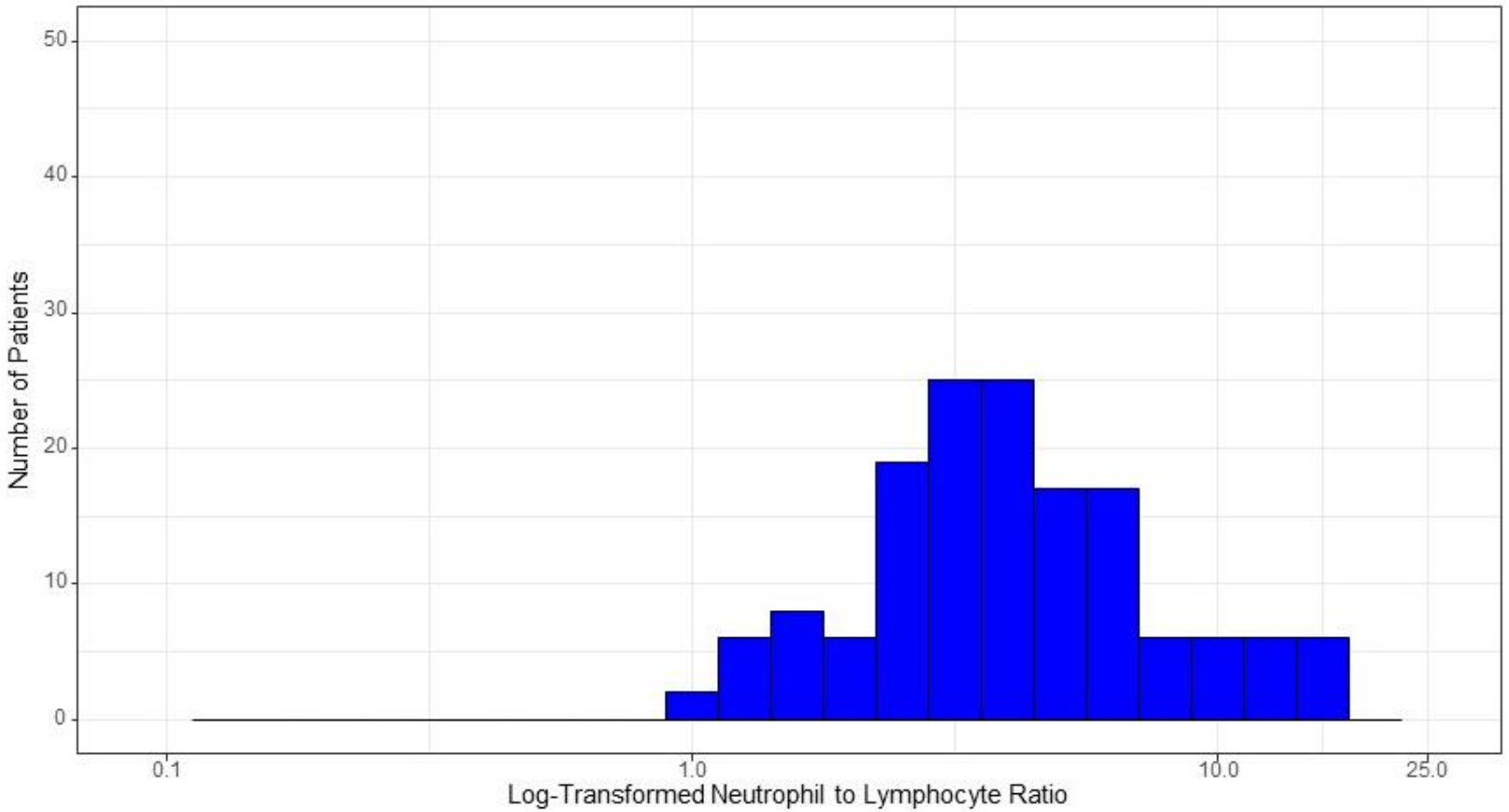
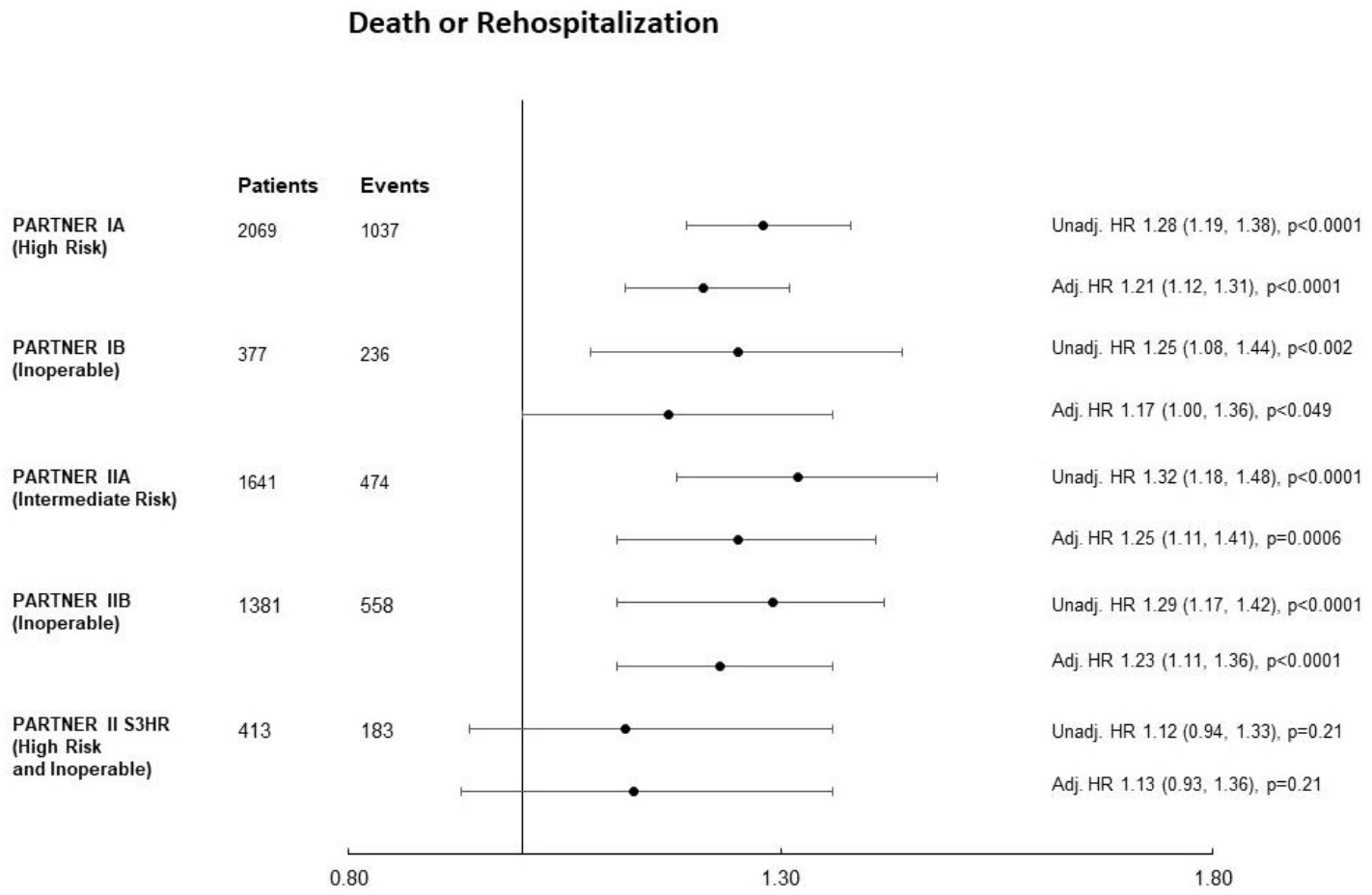
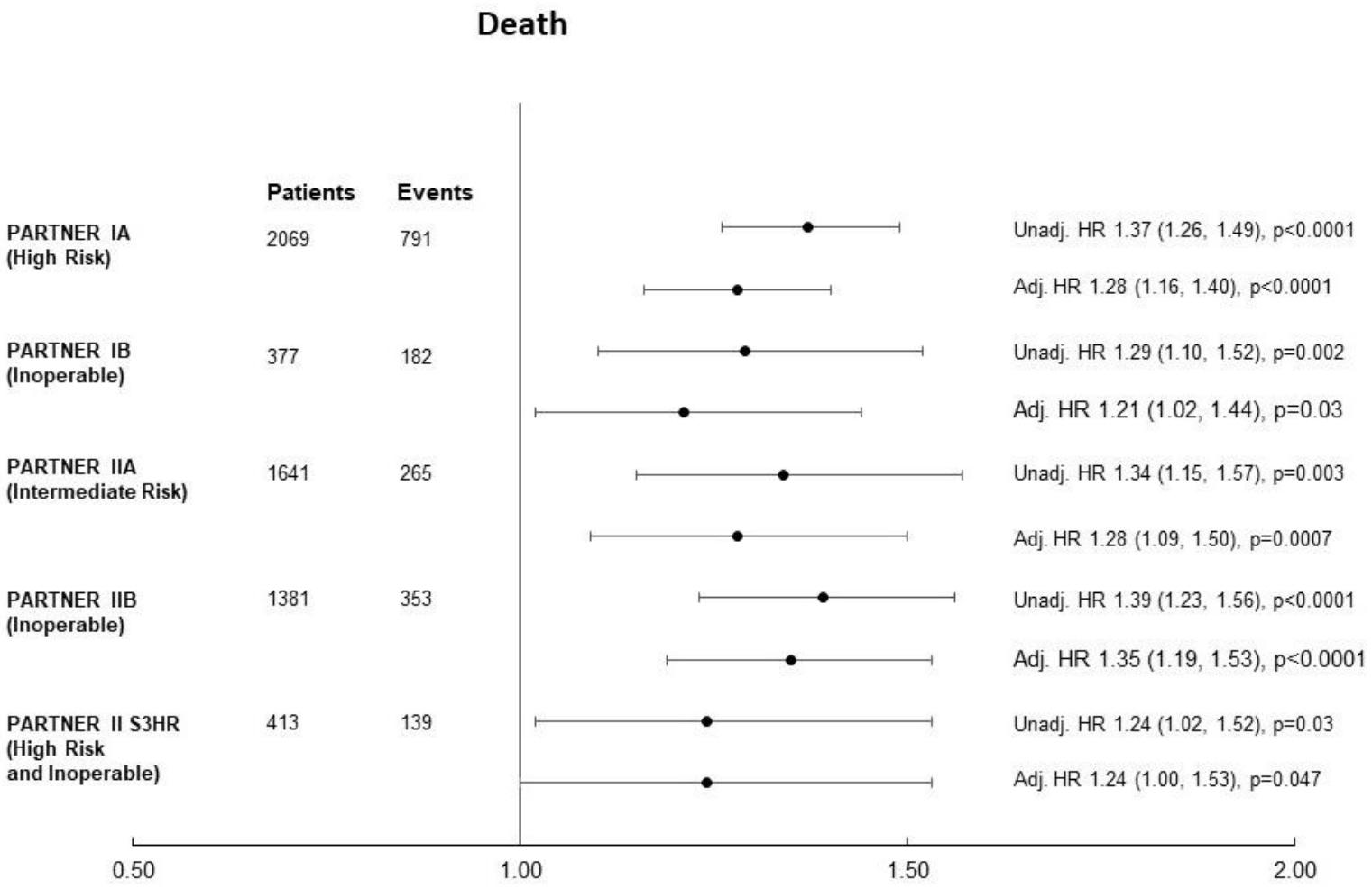

50
40
30
20
10
0
Number of Patients
0.1
1.0
10.0
25.0
Log-Transformed Neutrophil to Lymphocyte Ratio

Figure S3. Adjusted Association Between Baseline Neutrophil-to-Lymphocyte Ratio as a Continuous Log-Transformed Variable and the Relative Hazard of 3-Year Adverse Outcomes Within Each Cohort.

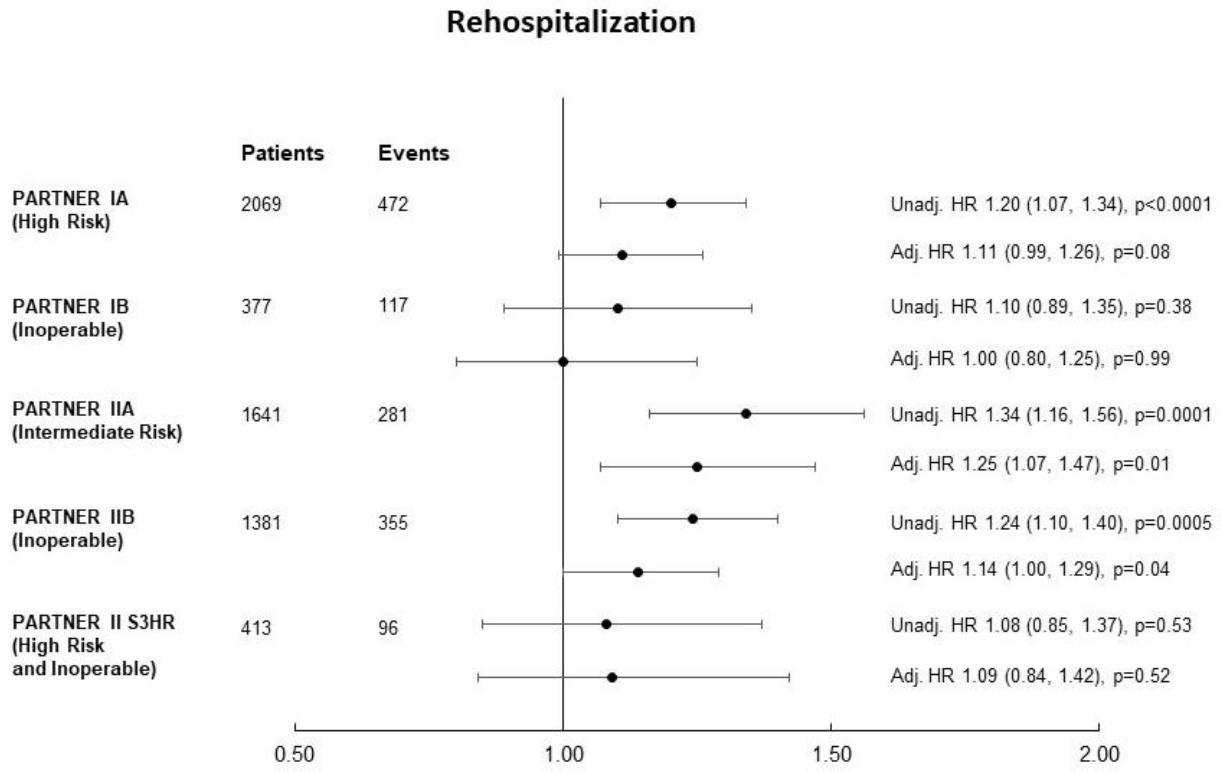
A.



B

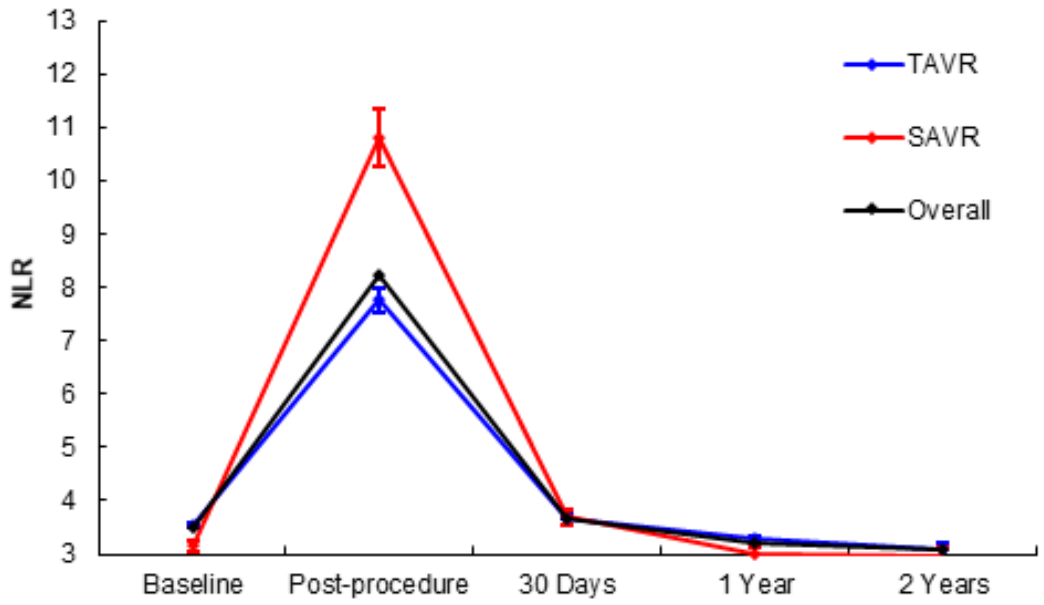

Death
Patients
Events
PARTNER IA (High Risk)
2069
791
Unadj. HR 1.37 (1.26, 1.49), p<0.0001
Adj. HR 1.28 (1.16, 1.40), p<0.0001
PARTNER IB (Inoperable)
377
182
Unadj. HR 1.29 (1.10, 1.52), p=0.002
Adj. HR 1.21 (1.02, 1.44), p=0.03
PARTNER IIA (Intermediate Risk)
1641
265
Unadj. HR 1.34 (1.15, 1.57), p=0.003
Adj. HR 1.28 (1.09, 1.50), p=0.0007
PARTNER IIB (Inoperable)
1381
353
Unadj. HR 1.39 (1.23, 1.56), p<0.0001
Adj. HR 1.35 (1.19, 1.53), p<0.0001
PARTNER II S3HR (High Risk and Inoperable)
413
139
Unadj. HR 1.24 (1.02, 1.52), p=0.03
Adj. HR 1.24 (1.00, 1.53), p=0.047
0.50
1.00
1.50
2.00

C



(A) Death or rehospitalization in all patients; (B) death; (C) rehospitalization. The following covariates were included in the adjusted model: Age, sex, diabetes mellitus, body mass index, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine ≥2 mg/dL), previous or current cancer, baseline hemoglobin, previous stroke or transient ischemic attack, major arrythmia, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass, moderate to severe mitral regurgitation, coronary artery disease, peripheral artery disease, New York Heart Association class III or IV, Society of Thoracic Surgeons risk score, access (transfemoral versus transthoracic), and randomized treatment. HR = hazard ratio.

Figure S4. Mean Values of Log-Transformed Neutrophil-to-Lymphocyte Ratio Levels During 3-Year Follow-up in Patients Undergoing Transcatheter Aortic Valve Replacement or Surgical Aortic Valve Replacement. Error bars represent the 95% Confidence Intervals.



NLR = neutrophil-to-lymphocyte ratio; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.