Original Article

Value of neutrophil to lymphocyte ratio as a predictor of mortality in patients undergoing aortic valve replacement

Mirette Habib[1], Mohammad Thawabi[2], Amer Hawatmeh[2], Habib Habib[1], Walid ElKhalili[1], Fayez Shamoon[1], Medhat Zaher[1]

[1]Department of Cardiology, New York Medical College, Saint Joseph Regional Medical Center, Paterson, NJ, USA; [2]Department of Cardiology, Newark Beth Israel Medical Center, Newark, NJ, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study material or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Amer Hawatmeh, MD. Department of Cardiology, Newark Beth Israel Medical Center, 201 Lyons Ave, Newark, NJ 07112, USA. Email: amer_hawatmeh@hotmail.com.

Background: Neutrophil to lymphocyte ratio (NLR) has been studied as a measure of inflammation and as a prognosticating factor in various medical conditions including neoplastic, inflammatory and cardiovascular. The prognostic role of NLR in predicting mortality in patients with aortic stenosis undergoing surgical aortic valve replacement (AVR) has not been studied. The aim of our study is to explore the utility of NLR as a predictor of both, short and long-term mortality, in patients undergoing surgical AVR.

Methods: Consecutive patients with aortic stenosis admitted for AVR to our institution were evaluated for study inclusion. Of the 335 patients admitted from January 2007 to September 2011, 234 met study inclusion criteria. Patients were divided into two groups depending on their initial preoperative NLR level with a cutoff value of 3. Three-year vital status was accessed with electronic medical records and Social Security Death Index. Survival analysis, stratified by NLR, was used to evaluate the predictive value of preoperative NLR levels.

Results: Patients with NLR ≥3, when compared to those with NLR <3, had a significantly higher short-term (9.40% *vs.* 0, P=0.0006), 6-month (19.54% *vs.* 0.95%, P<0.0001), and 3-year mortality (27.35% *vs.* 3.78%, P<0.0001). After adjustment for baseline characteristics, co-morbidities, symptomatology, echocardiographic findings, and blood tests, NLR level remained a significant independent predictor of 3-year mortality; Hazard ratios (HRs) increased by a factor of 1.18 (1.05–1.33, P=0.0068) and patients with a NLR ≥3 had 4.77 fold increase in 3-year mortality (1.48–15.32, P=0.0090).

Conclusions: NLR is an independent predictor of short-term and long-term mortality in patients with aortic stenosis undergoing AVR surgery, especially those with NLR ≥3. We strongly suggest the use of NLR as a tool to risk stratify patients with aortic stenosis undergoing AVR surgery.

Keywords: Neutrophil to lymphocyte ratio (NLR); aortic valve stenosis; surgical aortic valve replacement (surgical AVR); mortality

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Introduction

Calcific aortic valve stenosis is the most common valvular heart disease in the western world (1). Surgical aortic valve replacement (AVR) represents the gold standard of treatment, when indicated, with around 67,500 procedures done annually in the United States (2).

Calcific aortic valve disease is an indolent disease with a spectrum that ranges from mild valve thickening, aortic sclerosis, to severe calcification and impaired leaflet motion, aortic stenosis. This process was thought to be degenerative and a consequence of time-dependent leaflet damage and calcium deposition (3). Clinical aortic stenosis doesn't uniformly affect the elderly, with an estimated prevalence of only 3% to 5% in patients aged 75 or more (4,5). This suggests that other factors, besides age-related degeneration, play a major role in the disease pathogenesis. Evidence of chronic inflammation has been found, by immunohistochemical studies, in aortic valve leaflets; with the presence of macrophages and T lymphocytes, which release inflammatory cytokines. These inflammatory cells and cytokines help stimulate fibrotic and calcific processes, which in turn increase valve stiffness (3). Presence of chronic inflammation is also supported by studies demonstrating increased systemic C-reactive protein in patients with aortic stenosis (6), increased temperature in stenotic aortic valve cusps (7), and increased ^{18}F-sodium fluoride (^{18}F-NaF) uptake with the use of positron emission tomography, with progressive rise in activity with increasing valve severity (8).

Several studies showed that elevated neutrophil to lymphocyte ratio (NLR) is a significant predictor of adverse outcomes for patients with cardiovascular disease including stable coronary artery disease, acute coronary syndrome, heart failure and aortic stenosis. Additionally, a relationship between NLR and the severity of calcific aortic stenosis has been found (9-13).

Our objective in this study is to examine the utility of NLR as a predictor of short- and long-term mortality in patients with calcific aortic stenosis undergoing surgical AVR.

Methods

This longitudinal retrospective observational study examined the usefulness of NLR value as a predictor of survival in 335 patients who underwent AVR between January 2007 and September 2011. Patients undergoing non-emergent, AVR, secondary to aortic valve stenosis, were evaluated for study inclusion. Study exclusion criteria included age >85 years, clinical evidence of infective endocarditis or any other active infection, cancer, hematopoietic disease, autoimmune or inflammatory diseases, current steroid or chemotherapy use, emergent valve replacement, acute coronary syndrome on admission, and incomplete medical records. Two hundred and thirty-four patients out of the 335 were eligible for the study inclusion (*Figure 1*). All-cause short-term (30 days), 6-month, and 3-year mortality were obtained from electronic medical records and Social Security Death Index. This study was approved by the institutional review board of Saint Joseph Regional Medical Center.

White blood cell (WBC) counts and differentials were obtained from the first, pre-operative blood tests on index admissions. Differential leukocyte counts were obtained using automated blood cell counter. Electronic medical records were reviewed, independently, by two physicians for baseline characteristics, presenting symptoms, preoperative, in-hospital laboratory values, preoperative echocardiographic findings, and AVR surgical reports (*Table 1*). Aortic valve area, mean aortic flow gradient, presence of aortic insufficiency and other valvular pathologies were obtained from preoperative transthoracic and/or transesophageal echocardiograms. Smoking history included any current or previous smoking.

The patients were dichotomized based on their NLR, NLR ≥3 and <3. The cutoff value for NLR was calculated by testing all possible cutoffs that would discriminate between mortality by Cox proportional analyses. The cutoff value was then rounded to a clinically convenient value. Variables were assessed for the normality of distribution using D'Agostino-Pearson test. Continuous variables were presented as means ± SDs and categorical variables were presented as frequencies and percentages. Group comparisons used chi-square analysis for categorical variables. Continuous variables were compared using analysis of variance or Mann-Whitney U-test, depending on the probability distribution of the variable. All probabilities were 2-sided and P values <0.05 were considered statistically significant.

Univariate Cox proportional hazard models were used to examine the association of NLR and all other variables with long-term mortality. Then, a multivariate Cox proportional hazard model, adjusted for all predictors of long-term mortality of the univariate analysis and significant baseline characteristics was done. We confirmed that the

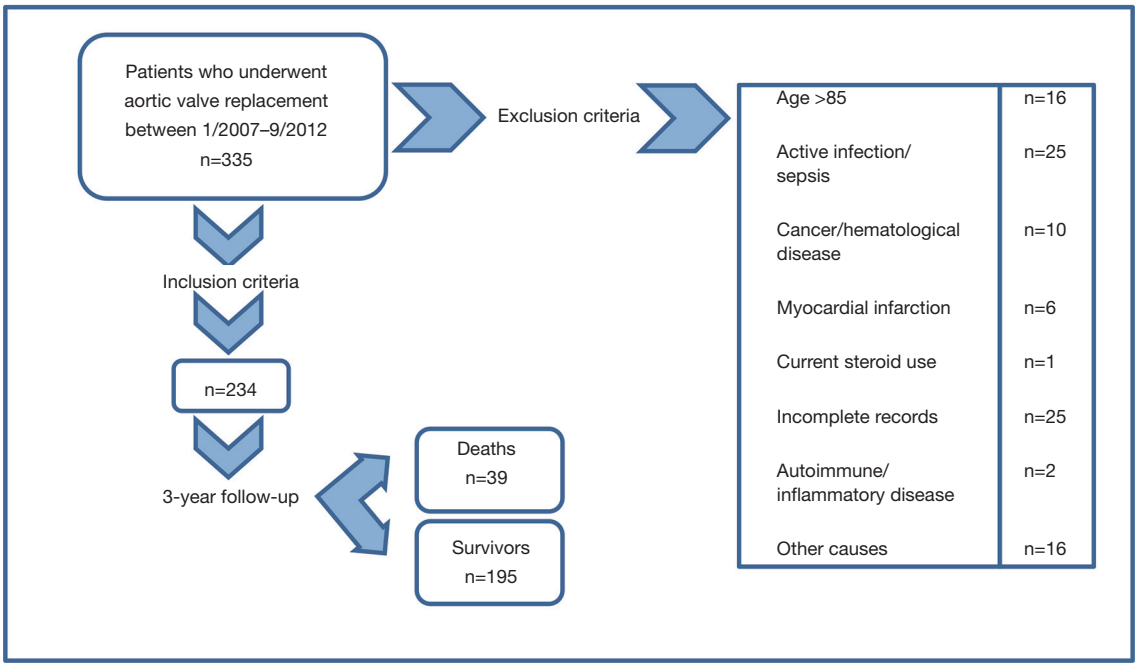

Figure 1 Schematic illustration of study design and patients' vital status.

proportionality of hazards assumption was met. Kaplan-Meier curves were used to illustrate the difference in 3-year survival function between the two groups.

Leukocytes and platelets parameters were investigated for superiority of mortality prediction in two ways. First, each leukocyte parameter was compared between survivor and mortality groups using Kruskal-Wallis test or analysis of variance, depending on normality of data distribution. Second, multivariate Cox proportional hazard model using leukocyte and platelets parameters was done.

All data were analyzed using MedCalc version 15.2.2 (MedCalc Software bvba, Belgium) and SPSS 22 (IBM Corp., USA).

Results

The primary outcome was all-cause 3-year mortality. Thirty-nine deaths occurred in the 234 patients (16.7%). *Figure 2* illustrates significant higher short-term (9.40% *vs.* 0, P=0.0006), 6-month (19.54% *vs.* 0.95%, P<0.0001), and 3-year mortality (27.35% *vs.* 3.78%, P<0.0001) in patients with NLR ≥3, when compared to those with NLR <3. Three-year Kaplan-Meier curves shows that patients with NLR ≥3 had significantly worse short, 6-month, and 3-year mortalities than patients with NLR <3 (Mantel-Cox Chi-square 10.4, 20.17, 23.40 respectively, P<0.001; *Figure 3*).

In the high NLR group, there was a significantly higher prevalence of symptoms of heart failure (44.34% *vs.* 59.38%, P=0.03), lower ejection fraction (51.08±10.28 *vs.* 45.47±12.13, P=0.0001), preoperative 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 to those with lower NLR. However, angina was significantly higher in the lower NLR group (53.77% *vs.* 39.84%, P=0.04).

Leukocyte parameters, including neutrophils and lymphocytes, total WBC, and NLR significantly differed by patients' vital status (P=0.02452, P=0.00015, P=0.03460, P<0.0001, respectively; *Table 2*). Of all, NLR was the best predictor of mortality (Kruskal-Wallis Chi-square 22.03, P<0.0001). Leukocyte parameters, WBC, and NLR adjusted mortality hazards also indicated that NLR significantly predict long term mortality [hazard ratio (HR) =1.27, 95% CI, 1.17–1.39], whereas the rest failed to demonstrate a significant mortality hazard.

In the univariate Cox regression analysis, patients with an NLR ≥3 had an 8.39 fold increase risk of 3-year mortality (HR =8.39; 95% CI, 3.00–23.48, P=0.0001). Univariate analysis also identified end-stage renal disease, hypertension, history of cerebrovascular accident, preoperative ejection

Table 1 Variables of patients undergoing AVR according to neutrophil/lymphocyte ratio dichotomization

Baseline characteristics	NLR <3 (n=106)	NLR ≥3 (n=128)	P value
Age (years)	69.43±12.04	71.59±10.71	0.17
Male gender	61 (57.55%)	75 (58.59%)	0.89
Hypertension	88 (83.02%)	98 (76.56%)	0.26
Diabetes millets	36 (33.96%)	48 (37.50%)	0.59
Hyperlipidemia	73 (68.87%)	74 (57.81%)	0.10
End-stage renal disease	2 (1.89%)	10 (7.81%)	0.07
History of myocardial infarction	11 (10.38%)	11 (8.59%)	0.66
History of smoking	20 (18.87%)	27 (21.09%)	0.74
History of cerebrovascular event	10 (9.43%)	7 (5.47%)	0.31
Previous coronary artery bypass surgery	8 (7.55%)	15 (11.72%)	0.38
Previous coronary angioplasty	14 (13.21%)	21 (16.41%)	0.58
Previous valve surgery	3 (2.83%)	2 (1.56%)	0.66
Presentation			
Syncope	8 (7.55%)	8 (6.25%)	0.80
Angina	57 (53.77%)	51 (39.84%)	0.04
Symptoms of heart failure	47 (44.34%)	76 (59.38%)	0.03
Preoperative atrial fibrillation	17 (16.04%)	36 (28.13%)	0.03
Preoperative aortic valve area (cm^2)	0.77±0.22	0.72±0.18	0.11
Preoperative aortic valve mean gradient (mmHg)	49.05±14.35	50.6±20.53	0.92
Preoperative aortic insufficiency	52 (49.06%)	51 (39.84%)	0.19
Preoperative ejection fraction (%)	51.08±10.28	45.47±12.13	0.0001
Surgical variables			
Concomitant CABG	45 (42.45%)	56 (43.75%)	0.69
Prosthetic valve size (mm)	22.19±2.03	22.19±2.05	0.89
Mean cardiopulmonary bypass time (minute)	57.9±6.62	57.6±5.05	0.64
Preoperative in-hospital laboratory data			
Serum creatinine (mg/dL)	1.12±1.18	1.38±1.38	0.0012
Fasting blood sugar (mg/dL)	111.41±38.51	118.63±41.53	0.12
High-density lipoprotein (mg/dL)	40.94±16.56	37.34±12.86	0.35
Low-density lipoprotein (mg/dL)	102.72±42.19	94.95±51.83	0.13
First white blood cell count (×10^3 cells/μL)	6.83±1.6	7.95±2.07	<0.0001
First lymphocyte count (×10^3 cells/μL)	2.05±0.69	1.46±1.70	<0.0001
First neutrophil count (×10^3 cells/μL)	4±1.12	6.23±5.48	<0.0001
First platelet count (×10^3 cells/μL)	213.86±62.60	215.70±87.83	0.49
Neutrophil/lymphocyte ratio	2.07±0.58	4.76±2.28	<0.0001

AVR, aortic valve replacement; NLR, neutrophil to lymphocyte ratio; CABG, coronary artery bypass graft.

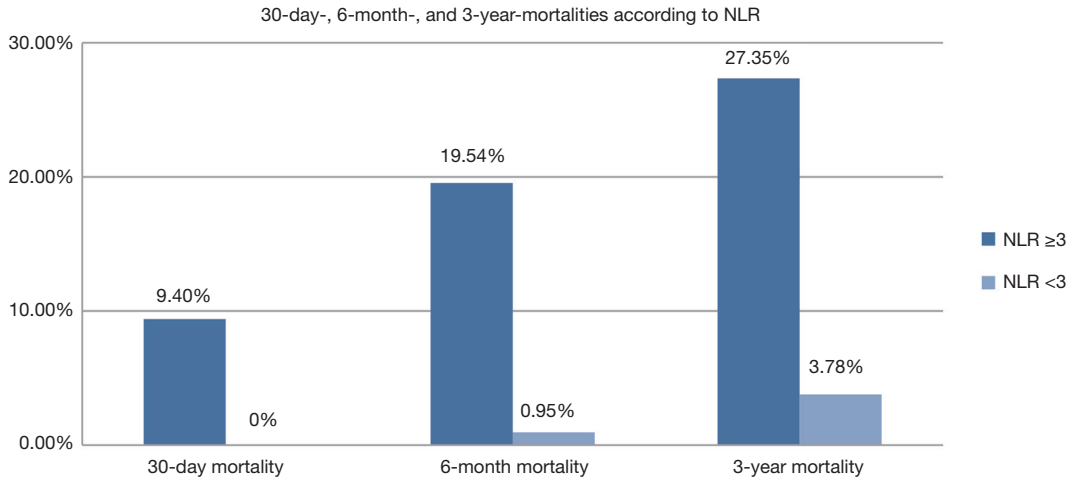

Figure 2 Thirty-day, 6-month, and 3-year all-cause mortality rates in patients between different NLR groups. NLR, neutrophil to lymphocyte ratio.

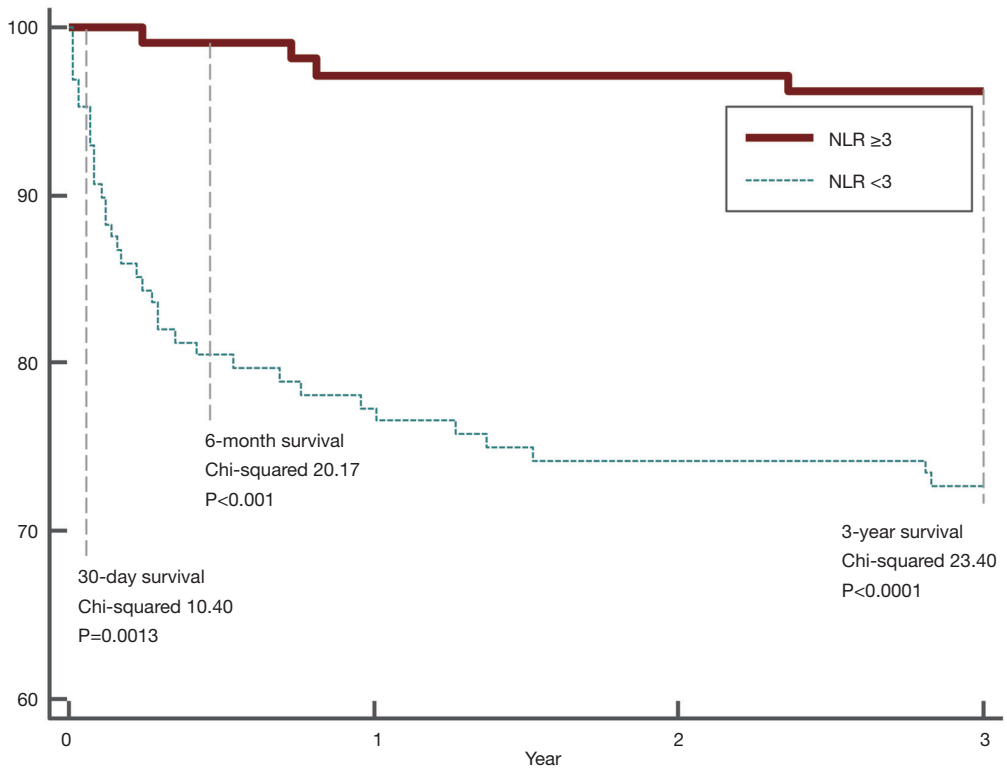

Figure 3 Kaplan-Meier curve showing 3-year all-cause mortality according to NLR dichotomization; NLR <3 (solid line) and NLR ≥3 (dashed line). NLR, neutrophil to lymphocyte ratio.

Table 2 Comparison of different leukocyte parameters, total WBC, and platelets in survivors and mortality groups

Leukocyte parameter	Median according to vital status				Kruskal-Wallis/ANOVA	
	1-month mortality	6-month mortality	3-year mortality	Alive	Chi-square or F	P value
NLR	4.23	3.96	3.77	2.90	22.03	<0.0001
WBC	8.75	6.90	7.80	7.10	8.63	0.03460
Neutrophils	5.95	4.85	4.90	4.60	9.38	0.02452
Lymphocytes	1.35	1.10	1.40	1.70	20.17	0.00015
Platelet	214	169	195	206.5	3.25	0.35404

WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; ANOVA, analysis of variance.

Table 3 Univariate and multivariate Cox proportional hazards models of the association between clinical and laboratory parameters and 3-year mortality

Clinical and laboratory parameters	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
NLR ≥3	8.39 (3.00–23.48)	0.0001	4.77 (1.48–15.32)	0.0090
NLR (continuous variable)	1.27 (1.17–1.39)	<0.0001	1.18 (1.05–1.33)	0.0068
ESRD	6.60 (3.03–14.36)	<0.0001	3.39 (1.06–10.89)	0.0413
History of CVA	3.32 (1.47–7.51)	0.0040	3.58 (1.42–9.07)	0.0074
Preoperative EF	0.95 (0.93–0.97)	<0.0001	0.98 (0.95–1.00)	0.1310
Fasting blood sugar	1.01 (1.00–1.01)	0.0127	1.01 (1.00–1.01)	0.0586
Hypertension	5.22 (1.27–21.50)	0.0229	5.01 (1.08–23.26)	0.0409
Previous bypass surgery	2.49 (1.15–5.39)	0.0217	2.19 (0.89–5.39)	0.0901
Serum creatinine	1.24 (1.08–1.41)	0.0016	1.17 (0.92–1.48)	0.2142
Preoperative A-fib	1.06 (0.51–2.23)	0.8764	0.99 (0.45–2.16)	0.9776
Symptoms of HF	0.67 (0.35–1.27)	0.2180	0.72 (0.32–1.60)	0.4286
Symptoms of angina	0.64 (0.34–1.23)	0.1849	0.77 (0.38–1.55)	0.4723

NLR, neutrophil to lymphocyte ratio; CVA, cerebrovascular accident; EF, ejection fraction; HR, hazard ratio; HF, heart failure.

fraction, history of bypass surgery, and serum creatinine as prognosticators of mortality (*Table 3*). The rest of variables failed to show any statistical significance.

In a multivariate Cox regression analysis NLR was independently associated with a higher 3-year mortality with a HR increase by a factor of 1.3 (HR =1.3, 95% CI, 1.18–1.44; P<0.0001) and a NLR ≥3 was associated with 4.77-fold increase in 3-year mortality. The multivariate analysis was adjusted for the independent predictors of outcome: history of end stage renal disease, cerebrovascular event, hypertension, and bypass surgery; symptoms of heart failure, angina and A-fib; and ejection fraction, fasting blood sugar, and serum creatinine as continuous variables. Additionally, previous cerebrovascular accident and end-stage renal disease were also found to be independent prognosticators of 3-year mortality (*Table 3*).

Discussion

The pathophysiology of calcific aortic valve disease is characterized by three primary processes: lipid accumulation, inflammation, and calcification (14). This disease process shares similar risk factors with atherosclerosis such as smoking, advanced age, male gender, metabolic syndrome, elevated lipoprotein (a) level, increased serum creatinine level, hypertension, diabetes mellitus, high low density lipoprotein-cholesterol and low level of high density lipoprotein-cholesterol (4,15-20).

The calcification of the aortic valve leaflets in AS are usually located on the aortic side of the leaflets, at the cusps coaptation lines and at the cusps attachment sites to the aortic wall and extend to the cusps. This pattern suggests that calcifications develop at sites of maximal mechanical stress. This was postulated to be the initiating factor in the disease process, in a similar manner to that of atherosclerosis, by causing endothelial injury (3). Histological studies have shown similarities between AS valvular lesions and atherosclerosis lesions. Inflammation manifests with T lymphocytes and macrophages which infiltrate the endothelium and release cytokines. These cytokines promote cellular proliferation and extracellular matrix remodeling by acting on valvular fibroblasts (3,21). Despite that, prospective randomized trials have failed to show a reduction in aortic valve calcific stenosis progression with anti-inflammatory, statin therapy (22,23). This might be a result of late initiation of statin therapy in the disease process, after reaching irreversible stages.

NLR was studied as a prognostic marker in atherosclerotic heart disease and cancer. Many authors reported that higher NLR values were associated with worse outcomes in patients with acute coronary syndrome, stable coronary artery disease, ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction and in patients undergoing percutaneous coronary interventions (12,24,25). Calcific aortic valve stenosis is a progressive disease, where the underlying pathophysiology of inflammation parallels that of atherosclerosis. Our study is the first study, to our knowledge, to examine the use of NLR value as a risk predictor for short and long-term mortality in patients diagnosed with severe AS undergoing AVR surgery.

NLR is a nonspecific marker of systemic inflammation. It represents a ratio between two different subtypes of leukocytes; neutrophils, which are part of the non-specific, innate immune system, and lymphocytes, which are part of the specific, regulatory pathway of the immune system. One major difficulty in using NLR value as a prognosticator in disease processes is determining an appropriate cut-off value around which disease outcomes differ. The appropriate NLR cut-off value is likely to change with the stage of illness, laboratory techniques employed, concomitant infection and patient demographic characteristics (26). In our study, a statistically significant difference in all-cause mortality was found between patients using the cutoff value of 3.

Despite the normal range of the index white blood cell counts in both of our NLR groups, the high NLR group had statistically significant higher normal white blood cell count values. In addition, the high NLR group had lower lymphocyte counts, as well as higher neutrophil counts, leading to the statistically significant higher NLR values. It is clear that NLR carries more information than its constituent elements especially when the absolute counts of these elements are in the normal range.

In our study, there was a higher prevalence of certain co-morbid conditions in the high NLR group (NLR ≥3). Those co-morbid conditions are symptomatic heart failure, lower ejection fraction (EF), preoperative atrial fibrillation, and elevated serum creatinine level. This is consistent with prior studies that showed an elevated NLR in these conditions (27-30). There was a higher prevalence of end-stage renal disease (ESRD) in the high NLR group; however, this was not statistically significant in our sample. The prevalence of angina was higher in the low NLR group; this is consistent with the fact that angina is associated with the longest median survival (approximately 5 years) in patients with severe AS when compared to heart failure and syncope (31).

Prior studies have demonstrated that risk factors such as tobacco use, diabetes mellitus, dyslipidemia, hypertension and coronary artery disease, have significant correlations (positive or negative) with NLR (32-35), however, both NLR groups in our study did not statistically differ in the prevalence of these conditions.

In our study, pre-operative NLR was demonstrated to predict short- and long-term mortality after AVR surgery in patients diagnosed with severe AS. It is not clear whether high NLR is related to the pathogenic process of AS or it is a component or marker of one or many unrelated deleterious systemic pathologic conditions that continue unabated after AVR increasing mortality rates in the high NLR group. It is also unclear whether high NLR has an etiological role in the increased mortality rates or it is just a marker of the etiological condition(s) of increased mortality. Assuming that high NLR is related to the pathogenesis of AS, the fact that higher mortality rates continue to occur after having a new prosthetic aortic valve in place, in the high NLR group, suggests that the disease process of AS is systemic and not confined to the aortic valve. Another possibility is that high NLR is a component or marker of a systemic abnormality that has many manifestations, with AS being one manifestation, but other manifestations continue to evolve over time after AVR leading to increased mortality.

The main limitation of our study is the non-randomized, retrospective, single-center, observational design. Our

study included a small number of patients which may have led to selection bias. A large multicenter prospective study that uses a clinically relevant NLR cut-off value is needed to establish NLR as a true prognostic factor in patients diagnosed with severe AS undergoing AVR surgery.

Conclusions

NLR is an independent predictor of short- and long-term mortality in patients with aortic stenosis undergoing AVR surgery. Patients with a NLR ≥3 had a statically significant mortality. We strongly suggest the use of NLR as a tool to risk stratify patients with aortic stenosis undergoing AVR surgery.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the institutional review board of Saint Joseph Regional Medical Center.

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