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A novel predictor in patients undergoing heart valve surgery: systemic inflammation response index: a single center cross-sectional study

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Abstract. – OBJECTIVE: Inflammation plays a pivotal role in heart valve disease (HVD). This study aimed at evaluating the prognostic value of systemic inflammation response index (SIRI) after valve replacement surgery.

SUBJECTS AND METHODS: The study enrolled 90 patients who underwent valve replacement surgery. SIRI was calculated using laboratory data on admission. Receiver operating characteristic (ROC) analysis was used to calculate the optimal cutoff values of SIRI for predicting mortality. Univariable and multivariable COX analysis was used to assess the relationship of SIRI with clinical outcomes.

RESULTS: 5-year mortality rate was higher in SIRI ≥1.55 group than SIRI <1.55 group [16 (38.1%) *vs*. 9 (18.8%)]. In receiver operating characteristic analysis, the optimal cutoff values for SIRI were 1.55 (area under the curve 0.654, *p*: 0.025). Univariable analysis revealed that SIRI [OR: 1.41, 95%CI (1.13-1.75), *p*<0.001] was an independent predictor of 5-years mortality. Multivariable analysis revealed that glomerular filtration rate (GFR) [OR: 0.98, 95%CI (0.97-0.99)] was an independent predictor of 5-years mortality.

CONCLUSIONS: Although SIRI is a preferable parameter for the detection of long-term mortality, it failed to predict in-hospital and 1-year mortality. Larger multi-center studies are needed to investigate effect of SIRI on prognosis.

Key Words:
Cardiac valve prostheses, Prognosis, Inflammation, Heart valve prosthesis implantation.

Introduction

Heart valve disease (HVD) is a common condition resulting from to rheumatic; infective or degenerative diseases and valve replacement or valvuloplasty under cardiopulmonary bypass (CPB) are the main operative procedure to treat HVD[1]. HVD is considered a dynamic and inflammatory process[2]. Thus, identifying the prognostic factors of the poor postoperative outcomes of HVD is of tremendous matter to improve prognosis.

Inflammatory markers, such as neutrophil/lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), as well as established pro-inflammatory biomarkers have been shown to predict mortality and morbidity after cardiac surgery[3,4]. The role of inflammatory markers have been described previously as independent predictors of mortality and morbidity in patients undergoing heart valve surgery[5]. Systemic immune-inflammation index (SII) is a novel biomarker that has been receiving increasing interest in recent years[6]. As similar systemic immune response index (SIRI) that integrates the characteristics of neutrophils, monocytes and lymphocytes could also provide prognostic value in recent studies[7]. Studies[7,8] have verified that a high SIRI score is related to the poor prognosis in the setting of large cerebral artery occlusion and aneurysmal subarachnoid hemorrhage.

As far as we know, there are no studies on whether SIRI can help as a predictive value for postoperative HVD having a poor prognosis. In this study, we investigated the prognostic value of SIRI as a predictor of long-term mortality in patients undergoing of valve replacement surgery.

Subjects and Methods

The study was designed as a cross-sectional, single-center, retrospective study and comprised patients that had a hemodynamically significant valve defects due to rheumatic, infective or degenerative disease at Dicle University Medical School Cardiovascular Surgery clinic between January 2016 and May 2022. Patients under 18 years of age, unwilling to participate, or diagnosis with hematological diseases, systemic inflam-

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matory diseases, malignancies, infections, chronic liver or kidney disease, autoimmune diseases were excluded from the study. The study protocol was approved by the Local Ethics Committee (Dicle University Medical Faculty ethical committee approval number and date: 199 and 12.05.2022).

Preoperative characteristics of the patients, such as age, gender, smoking, hypertension, diabetes mellitus (DM), hyperlipidemia, history of CAD, left ventricular ejection fraction (LVEF), history of cerebrovascular events (CVE) and atrial fibrillation (AF) were noted. The data on preoperative laboratory investigations, including white blood cell (WBC), monocytes, neutrophil counts, lymphocyte count, serum albumin and C-reactive protein (CRP) were obtained for every participant. From the monocytes, neutrophils and lymphocytes, systemic inflammation response index (SIRI) which is calculated with the formula (monocyte count x neutrophil count/lymphocyte count) were derived. Hematological parameters were measured from K_2EDTA samples using a Sysmex K-4500 (Sysmex, Japan) electronic counter.

132 patients were evaluated for outcome and their data were extracted from an electronic data-base and/or hospital record archive files. The flow chart for patient enrolment is illustrated in Figure 1.

Each patient was followed up for at least 30 days. A total of 90 procedures were performed *via* a midline sternotomy, five procedures *via* ministernotomy, and three procedures *via* a lateral thoracotomy incision, under general anesthesia in mild hypothermia. The primary endpoint was 5-years death from all causes. Secondary endpoints were considered as the presence of either in-hospital mortality, 1-year mortality or 5-years mortality. The follow-up of discharged patients was conducted through direct observation during hospitalization, telephone interviews, and/or at outpatient clinic visits 30 days after the cardiac operation.

Statistical Analysis

Data were analyzed using SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov test was used to determine normality distribution of data. Categorical variables were expressed as percentages (%) and were compared using Chi-square test or Fisher Exact test as appropriate. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and were compared using Student's *t*-test.

Continuous variables with nonparametric distribution were expressed as median (25^{th}-75^{th} percentile) and were compared with Mann-Whitney U test. Independent predictors of mortality were determined with univariable, and multivariable COX regression analysis and

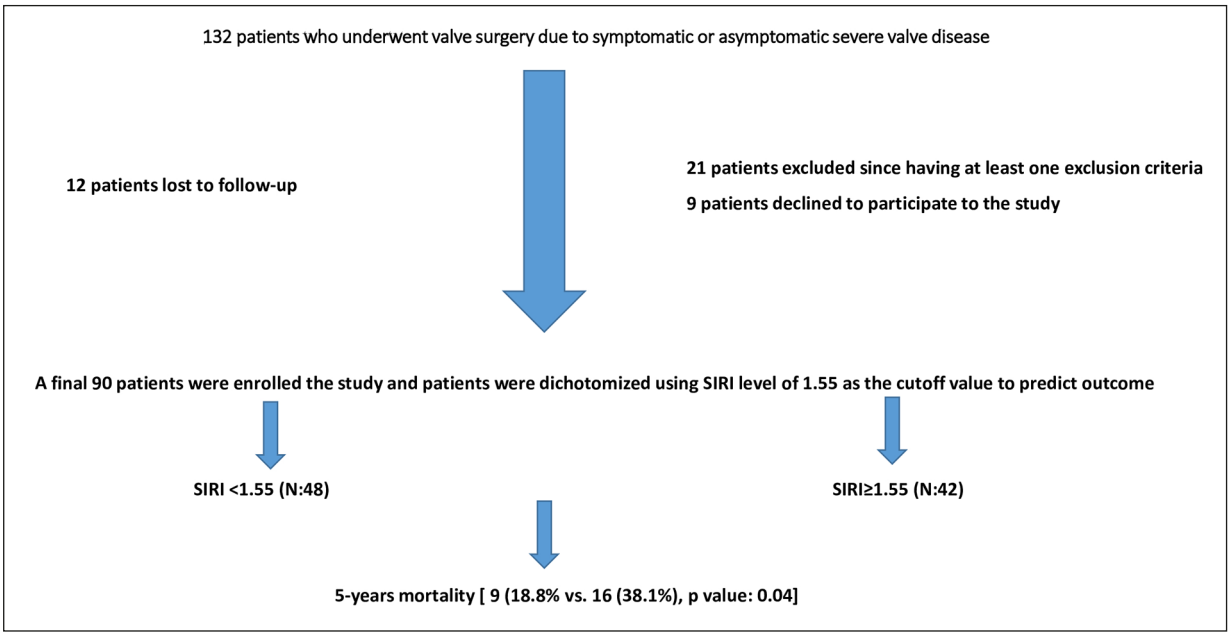

Figure 1. The study flow chart diagram.

the results were expressed with odds ratio (OR) and 95% confidence interval (CI). In univariable analysis the parameters with *p*-value <0.05 were added to the multivariable model. The cutoff of SIRI to the predict mortality was determined using receiver operating characteristic (ROC) curve analysis. Correlations were analyzed using with Pearson or Spearman's correlation coefficient according to the distribution characteristics. Survival analysis was performed using Kaplan-Meier analysis. A *p*-value of <0.05 was considered significant.

Results

The study included 90 patients with a mean age of 52±15 years. The female gender was 44 (48.8%). Median follow-up period was 43 (interquartile range [IQR]: 4.75-56) months. Patients were dichotomized using SIRI level of 1.55 as the cutoff value to predict outcome. Patients dichotomized two group as their SIRI values: (I) SIRI <1.55(n=48) and (II) SIRI ≥1.55 (n=42). Table I demonstrates the demographic, clinical characteristics, operation details and clinical out-

Table I. Demographic characteristics, laboratory parameters and clinical outcomes of the patients.

Parameters	SIRI <1.55 (n:48)	SIRI >1.55 (n:42)	*p*-value
Age, n	49±13	56±17	**0.01**
Female, n%	24 (50)	20 (47.6)	0.82
Hypertension, n%	19 (39.6)	22(52.4)	0.22
Diabetes Mellitus, n%	8 (16.7)	5 (11.9)	0.52
History of cerebrovascular diseases, n%	2 (4.2)	2 (4.8)	0.89
Smoking, n%	9 (18.8)	6 (14.3)	0.57
Dyslipidemia, n%	4 (8.3)	7 (16.7)	0.22
Coronary artery disease, n%	6 (12.5)	10 (23.8)	0.16
Atrial fibrillation, n%	8 (16.7)	6 (14.3)	0.75
Heart failure, n%	2 (4.2)	9 (21.4)	**0.01**
Ejection fraction,IQR, n%	60 (55-60)	60 (55-60)	0.81
Systolic pulmonary artery pressure mmHG, n	46±14	49±18	0.49
Left atrial diameter, mm, IQR	45 (39-53)	48 (43-55)	0.19
Operated target valve, n%			
Mitral valve	25 (52.1)	28 (66.7)	0.42
Aortic valve	19 (39.6)	10 (23.8)	
Tricuspid valve	0 (0)	1 (2.4)	
Aortic and mitral valve	2 (4.2)	1 (2.4)	
Mitral and tricuspid valve	2 (4.2)	2 (4.8)	
Etiology of valve disease, n%			
Infective endocarditis	6 (12.5)	9 (21.4)	0.34
Rheumatic disease	31 (64.6)	21 (50)	
Degenerative disease	11 (22.9)	12 (28.6)	
White blood cell count (× 103 µL)	7.8±1.8	9.5±2.2	**<0.01**
Platelets (× 103 µL)	240±73	235±81	0.77
Lymphocytes (× 103 µL)	2.5±0.8	2±0.8	**<0.01**
Neutrophils (× 103 µL)	4.4±1.2	6.5±1.8	**<0.01**
Monocytes (× 103 µL)	0.6±0.2	0.8±0.2	**<0.01**
GFR (ml/min/1,73 m^2)	91±27	80±37	0.09
Uric ascides (mg/dl), IQR	6.3 (4.9-7.8)	5.8 (5.2-7)	0.76
Serum albumin (g/dl), IQR	3.8 (3.5-4.2)	3.2 (2.9-3.9)	**<0.01**
SIRI (N*M/L)	1±0.3	2.8±1.4	**<0.01**
CRP, mg/dl, IQR	0.43 (0.12-0.95)	0.86 (0.6-2.5)	**<0.01**
In-hospital mortality, n%	5 (10.4)	6 (14.3)	0.57
1-year mortality, n%	7 (14.6)	12 (28.6)	0.10
5-year mortality, n%	9 (18.8)	16 (38.1)	**0.04**
Follow-up (month), n	43 (16-59)	42 (2.8-55)	0.37

Data are expressed as mean ± standard deviation (SD), frequencies (percentages) or as median (interquartile range) as appropriate. CRP; c reactive protein, GFR; glomerular filtration rate, IQR; interquartile range, SIRI; systemic inflammation response index is calculated with the formula "Monocytes* Neutrophils/ Lymphocytes".

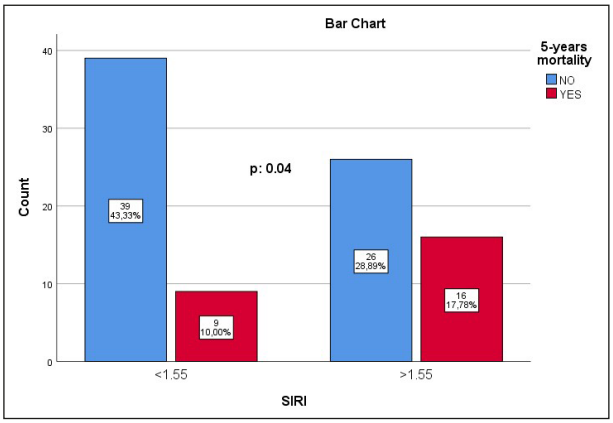

Figure 2. Bar chart graph of SIRI groups in terms of 5-years mortality.

comes of patients in both groups. Of all patients, 53 (59%) underwent prosthesis mitral valve replacement surgery, 29 (32%) underwent isolated prosthesis aortic valve replacement, one patient underwent tricuspid repair surgery, 3 (3.3%) underwent simultaneous aortic and mitral valve replacement and 4 (4.4%) underwent simultaneous mitral valve replacement and tricuspid repair surgery. The most common etiology undergoing prosthesis valve replacement was rheumatic valve disease [52 (57.7%), Table I]. Age, white blood cell (WBC), monocyte, and neutrophil counts, SIRI and CRP were significantly higher in group II (SIRI ≥1.55) compared to group I (SIRI <1.55). However, lymphocyte count and serum albumin level were significantly lower in group II (SIRI ≥1.55) as compared group I (SIRI <1.55). Additionally, heart failure and 5-years mortality (Figure 2) were higher in group II than those group I respectively (21.4% *vs.* 4.2% and 38.1% *vs.* 18.8%, Table I).

In univariable COX regression analysis, age, coronary artery disease, GFR, CRP, and SIRI were found to be independent predictors of long-term mortality (OR: 1.05, 95% CI: 1.02-1.09, p<0.001, OR: 2.58, 95% CI: 1.1-6, p: 0.02, OR: 0.97, 95% CI: 0.96-0.99, p<0.001, OR: 1.15, 95% CI: 1.05-1.25, p<0.001, OR: 1.41, 95% CI: 1.13-1.75, p<0.001, respectively; Table II). In multivariable COX regression analysis GFR was found to be an independent predictor of long-term mortality (OR: 0.98, 95%CI: 0.97-0.99, p<0.001, Table II). At a cutoff value of 1.55, SIRI predicted long-term mortality in undergoing valve surgery patients with a sensitivity of 64% and specificity of 60% (ROC area under curve [AUC]: 0.65, p: 0.02, Figure 3). There was positive correlation between SIRI and CRP as shown Figure 4A (r: 0.443, p<0.001) and negative correlation between SIRI and GFR as shown Figure 4B (r: -0.261, p: 0.17). Finally, the Kaplan-Meier analysis showed higher survival rates in group I (SIRI <1.55) (log rank=3.82, p: 0.05; Figure 5).

Discussion

This cross-sectional study was done to prove that the long-term prognostic value of inflammation assessed by the SIRI in heart valve replacement patients and the results indicated a higher prevalence of long-term mortality in higher SIRI (group II) patients compared with patients with lower SIRI patients (group I).

Heart valve replacement is associated with perioperative adverse events, such as death, pro-

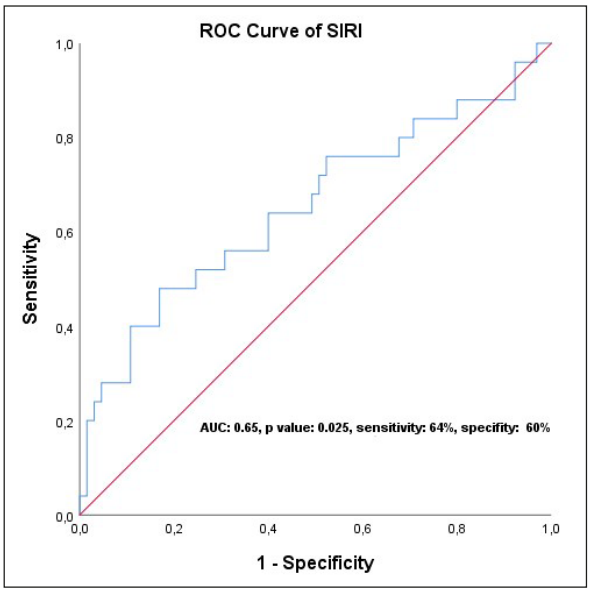

Figure 3. Receiver-operating-characteristics (ROC) curve analysis.

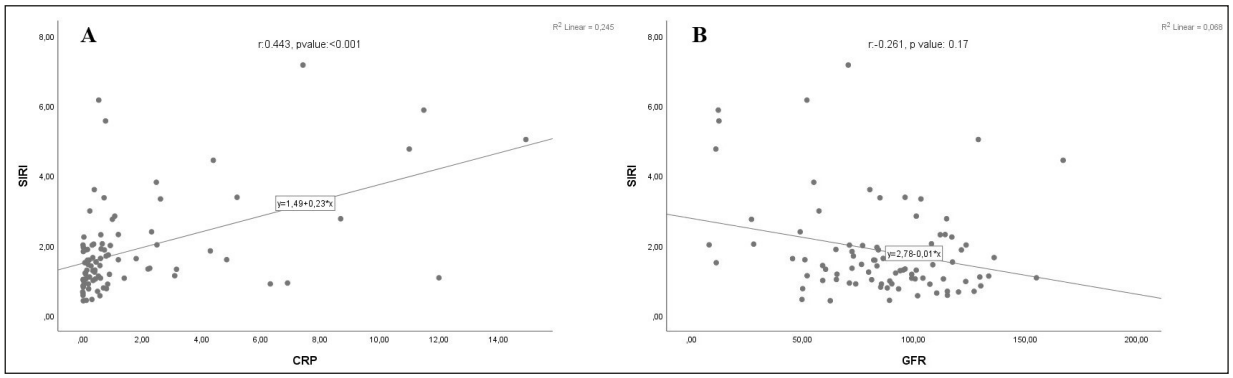

Figure 4. A, Correlation analysis of between SIRI and CRP. **B,** Correlation analysis of between SIRI and GFR.

longed hospitalization and increased healthcare cost. Several studies[9-12] have supported that the extensively used risk assessment tools, EuroSCORE II, EuroSCORE, and Society of Thoracic Surgeons (STS) have limitations due to inadequate calibration models. Therefore, it is vital to understand the exact mechanism which causes the poor prognosis after heart valve replacement surgery and prognostic markers linked with the underlying mechanisms.

Some studies[13,14] have indicated that age, preoperative liver function, renal function injury, LVEF and blood transfusion are significant factors affecting the prognosis in patients with HVD. We showed that preoperative SIRI was significantly associated with long-term prognosis, which have not been revealed in previous studies.

Alvarez et al[15] have been demonstrated that inflammation and immune responses are closely related to the occurrence, postoperative complications and mortality in patients with HVD. Migration of leukocytes to the destructed valves causes disease progression, suggesting that this inflammation plays an important role in the progression of valve disease[16]. Inflammation contributes to progress of HVD and leukocytes, including neutrophils, lymphocytes, and monocytes have different effects on inflammatory reaction. Neutrophils stimulate inflammatory response whereas monocytes lead to inflammatory and prothrombotic pathways by interacting with platelets and endothelial cells. On the contrary, lymphocytes have a downregulation effect on inflammation[17].

SIRI is a novel marker of inflammation consisting of 3 factors (neutrophil monocyte/lymphocyte) and provides a comprehensive assessment of inflammation. The prognostic significance of SIRI was investigated in recent studies[18,20,21]. Wei et al[18] showed that SIRI could be a useful marker of worse outcomes in patients with pancreatic cancer, gastric cancer, hepatocellular carcinoma, breast cancer, and metastatic cancer. Topkan et al[19] showed a significant correlation between lower SIRI and longer progression-free survival in pa-

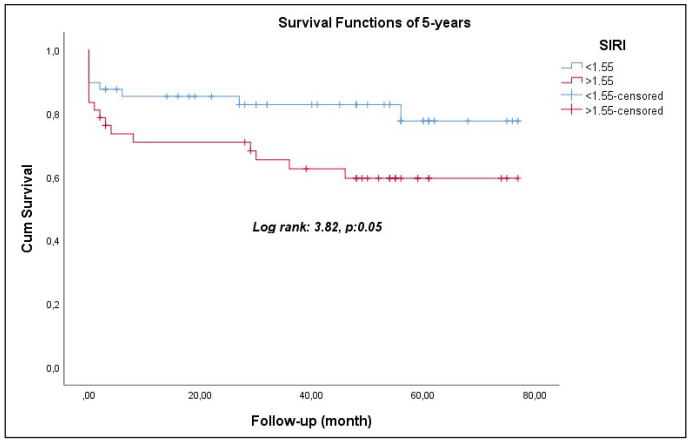

Figure 5. Kaplan-Meier analysis according to the SIRI groups.

Table II. Univariable and multivariable COX regression analyses to determine independent predictors of 5-year mortality.

	Univariable		Multivariable	
Parameter	**OR (95%CI)**	***p*-value**	**OR (95%CI)**	***p*-value**
Age	1.05 (1.02-1.09)	**<0.01**	1.04 (1-1.07)	0.17
Gender	0.85 (0.39-1.87)	0.69		
Hypertension	0.58 (0.25-1.34)	0.20		
Diabetes Mellitus	0.90 (0.27-3)	0.88		
Coronary artery disease	2.58 (1.11-6)	**0.02**	0.73 (0.24-2.25)	0.59
Cerebrovascular disease	1.63 (0.38-6.92)	0.50		
Heart failure	1.41 (0.48-4.12)	0.52		
Smoking	1.28 (0.48-3.42)	0.61		
Atrial fibrillation	1.35 (0.51-3.62)	0.54		
GFR	0.97 (0.96-0.99)	**<0.01**	0.98 (0.97-0.99)	**<0.01**
Albumin	1.002 (0.997-1.008)	0.33		
CRP	1.15 (1.05-1.25)	**<0.01**	1.13 (0.99-1.29)	0.05
Uric ascides	0.98 (0.92-1.03)	0.49		
SIRI	1.41 (1.13-1.75)	**<0.01**	0.96 (0.67-1.38)	0.85

CRP; c reactive protein, GFR; glomerular filtration rate, SIRI; systemic inflammation response index, OR; odds ratio, CI; confident interval.

tients with glioblastoma multiforme. Yun et al[20] indicated that elevated SIRI were associated with poor prognosis in patients with aneurysmal subarachnoid hemorrhage. Zhang et al[21] reported that elevated SIRI was associated with higher risk of mortality, sepsis and higher stroke severity. However, SIRI has not previously been investigated in patients with HVD undergoing valve replacement surgery. Although there was a significant difference in study population, our results are similar to their findings.

Our study determined that SIRI was associated with long-term mortality of patients who underwent valve replacement surgery. Therefore, physicians should use prognostic inflammatory markers in patients with HVD, such as SIRI, which is noninvasive, easily accessible, and cost-effective.

Limitations

As with any study, limitations are inherent in the present study. First, the retrospective nonblinded analysis induced bias and errors in data interpretation. Second, the study did not include other inflammatory markers or possible confounding variables, such as erythrocyte sedimentation rate (ESR) and interleukins. Third, we evaluated SIRI on admission and did not analyze the dynamic changes during follow-up periods.

Conclusions

Our findings suggest that elevated SIRI was associated with poor prognosis of patients with valve replacement surgery. SIRI was noninvasive and cost-effective serological inflammatory marker, represent potential prognostic predictors for clinical application in patients undergoing valve surgery. Further studies are warranted to confirm our findings.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

The authors declare that there is not any financial disclosure.

Informed Consent

The study was conducted with the informed consent of the patients.

Ethics Approval

The study protocol was approved by the Local Ethics Committee (Dicle University Medical Faculty Ethical Committee number and date: 199 and 12.05.2022).

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References

1) Muhamed B, Parks T, Sliwa K. Genetics of rheumatic fever and rheumatic heart disease. Nat Rev Cardiol 2020; 17: 145-154.
2) Bäck M, Gasser TC, Michel JB, Caligiuri G. Biomechanical factors in the biology of aortic wall and aortic valve diseases. Cardiovasc Res 2013; 99: 232-241.
3) Iliopoulos I, Alder MN, Cooper DS, Villarreal EG, Loomba R, Sahay RD, Fei L, Steele PE, Flores S. Pre-operative neutrophil-lymphocyte ratio predicts low cardiac output in children after cardiac surgery. Cardiol Young 2020; 30: 521-525.
4) Weedle RC, Da Costa M, Veerasingam D, Soo AWS. The use of neutrophil lymphocyte ratio to predict complications post cardiac surgery. Ann Transl Med 2019; 7: 778.
5) Xiang J, He L, Li D, Wei S, Wu Z. Value of the systemic immune-inflammation index in predicting poor postoperative outcomes and the short-term prognosis of heart valve diseases: a retrospective cohort study. BMJ Open 2022; 11: e064171.
6) Demir M, Özbek M. A novel predictor in patients with coronary chronic total occlusion: systemic immune-inflammation index: a single-center cross-sectional study. Rev Assoc Med Bras 1992 2022; 68: 579-585.
7) Yi HJ, Sung JH, Lee DH. Systemic Inflammation Response Index and Systemic Immune-Inflammation Index Are Associated with Clinical Outcomes in Patients Treated with Mechanical Thrombectomy for Large Artery Occlusion. World Neurosurg 2021; 153: e282-e289.
8) Yun S, Yi HJ, Lee DH, Sung JH. Systemic Inflammation Response Index and Systemic Immune-inflammation Index for Predicting the Prognosis of Patients with Aneurysmal Subarachnoid Hemorrhage. J Stroke Cerebrovasc Dis 2021; 30: 105861.
9) Kuwaki K, Inaba H, Yamamoto T, Dohi S, Matsumura T, Morita T, Amano A. Performance of the EuroSCORE II and the Society of Thoracic Surgeons Score in patients undergoing aortic valve replacement for aortic stenosis. J Cardiovasc Surg 2015; 56: 455-462.
10) Grant SW, Hickey GL, Dimarakis I, Cooper G, Jenkins DP, Uppal R, Buchan I, Bridgewater B. Performance of the EuroSCORE models in emergency cardiac surgery. Circ Cardiovasc Qual Outcomes 2013; 6: 178-185.
11) Chalmers J, Pullan M, Fabri B, McShane J, Shaw M, Mediratta N, Poullis M. Validation of EuroSCORE II in a modern cohort of patients undergoing cardiac surgery. Eur J Cardiothorac Surg 2013; 43: 688-694.
12) Parolari A, Pesce LL, Trezzi M, Cavallotti L, Kassem S, Loardi C, Pacini D, Tremoli E, Alamanni F. EuroSCORE performance in valve surgery: a meta-analysis. Ann Thorac Surg 2010; 89: 787-793.
13) Park HS, Laiz A, Sanchez-Vega J, Díaz Del Campo P, Martín-Martínez MA, Guerra-Rodríguez M, Corominas H. Valve Abnormalities. Risk Factors for Heart Valve Disease and Valve Replacement Surgery in Spondyloarthritis. A Systematic Review of the Literature. Front Cardiovasc Med 2021; 24; 8: 719523.
14) Xiang J, He L, Li D, Wei S, Wu Z. Value of the systemic immune-inflammation index in predicting poor postoperative outcomes and the short-term prognosis of heart valve diseases: a retrospective cohort study. BMJ Open 2022; 11; 12: e064171.
15) Mourino-Alvarez L, Baldan-Martin M, Gonzalez-Calero L, Martinez-Laborde C, Sastre-Oliva T, Moreno-Luna R, et al. Patients with calcific aortic stenosis exhibit systemic molecular evidence of ischemia, enhanced coagulation, oxidative stress and impaired cholesterol transport. Int J Cardiol 2016; 15; 225: 99-106.
16) Liesenborghs L, Meyers S, Lox M, Criel M, Claes J, Peetermans M, Trenson S, Vande Velde G, Vanden Berghe P, Baatsen P, Missiakas D, Schneewind O, Peetermans WE, Hoylaerts MF, Vanassche T, Verhamme P. Staphylococcus aureus endocarditis: distinct mechanisms of bacterial adhesion to damaged and inflamed heart valves. Eur Heart J 2019; 14; 40: 3248-3259.
17) Lux D, Alakbarzade V, Bridge L, Clark CN, Clarke B, Zhang L, Khan U, Pereira AC. The association of neutrophil-lymphocyte ratio and lymphocyte-monocyte ratio with 3-month clinical outcome after mechanical thrombectomy following stroke. J Neuroinflammation 2020; 18; 17: 60.
18) Wei L, Xie H, Yan P. Prognostic value of the systemic inflammation response index in human malignancy: A meta-analysis. Medicine 2020; 11; 99: e23486.
19) Topkan E, Kucuk A, Ozdemir Y, Mertsoylu H, Besen AA, Sezen D, Bolukbasi Y, Pehlivan B, Selek U. Systemic Inflammation Response Index Predicts Survival Outcomes in Glioblastoma Multiforme Patients Treated with Standard Stupp Protocol. J Immunol Res 2020; 14: 8628540.
20) Yun S, Yi HJ, Lee DH, Sung JH. Systemic Inflammation Response Index and Systemic Immune-inflammation Index for Predicting the Prognosis of Patients with Aneurysmal Subarachnoid Hemorrhage. J Stroke Cerebrovasc Dis 2021; 30: 105861.
21) Zhang Y, Xing Z, Zhou K, Jiang S. The Predictive Role of Systemic Inflammation Response Index (SIRI) in the Prognosis of Stroke Patients. Clin Interv Aging 2021; 16: 1997-2007.