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The Predictive Role of Systemic Immune Inflammation Index to the Aortic Valve Calcification in the Elderly Population with Chronic Renal Failure

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Abstract

Objectives: Aortic valve calcification (AVC) is a chronic, degenerative and progressive condition that results of endothelial injury, cholesterol deposition, myofibroblast differentiation and subsequent valve calcification, involving complex pathophysiological mechanisms such as the activation of inflammatory and immune system cells. The frequency of AVC increased in the presence of chronic renal failure (CRF) and with age. The study aimed to reveal the relationship between AVC and systemic immune inflammation index (SII) that includes peripheral neutrophil, lymphocyte and platelet counts in the elderly population with chronic renal failure.

Materials and Methods: Patients over 65 years of age who applied to the cardiology outpatient clinic with chronic renal failure between March 2018 and October 2022 were included in the study. The patients were divided into two groups as group 1 (control group- undetected AVC on echocardiography) (70 patients) and group 2 (AVC detected on echocardiography) (70 patients). SII of all patients was defined as: SII=neutrophil count × platelet count/lymphocyte count. Our study was a retrospective, observational study.

Results: The mean SII value was statistically significantly higher in group 2 (754.2±268.7) than group 1 (622.79±297.2, p=0.007). In the univariable regression analysis of the factors affecting AVC in elderly patients with CRF, neutrophil [odds

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ratio (OR): 0.752; 95% confidence interval (CI): 0.605-0.934, p=0.01], lymphocytes (OR: 2,197; 95% CI: 1,346-3,585, p=0.002), and SII (OR: 0.998; 95% CI: 0.997-1.000, p=0.009) were predictors. In the multivariable regression analysis: SII (OR: 1.002; 95% CI: 1.000-1.005, p=0.034), lymphocytes (OR: 5,660; 95% CI: 2,349-13,637, p<0.001) and neutrophil (OR: 497; 95% CI: 0.344-0.717, p<0.001) were found to be independent predictors. SII> 633.4, 64% sensitivity, and 65% specificity (receiver operating characteristic area under curve: 0.672, 95% CI: 0.582-0.762, p<0.001) are associated with aortic valve sclerosis.

Conclusion: High SII in the elderly with chronic renal failure is associated with the presence of AVCs.

Keywords: Aort calcification, systemic immune inflammation index, and predictivity

Introduction

Aortic valve calcification (AVC) is a chronic, degenerative and progressive condition that results of endothelial injury, cholesterol deposition, myofibroblast differentiation and subsequent valve calcification, involving complex pathophysiological mechanisms such as the activation of inflammatory and immune system cells. It is characterized by hyperechoic appearance on the valves and increased thickness of the valves on cardiac imaging (with echocardiography)[1]. Clinical factors associated with aortic sclerosis include risk factors similar to atherosclerotic heart disease. Persons prone to calcific aortic stenosis (AS) are patients with radiation exposure to the mediastinum, renal failure, familial hypercholesterolemia, or disorders of calcium metabolism[2,3]. The frequency of AVC increases in the presence of chronic renal failure and with age[4]. Progression in renal failure is a critical trigger for the initiation and progression of vascular/valve calcification[5]. The prevalence of calcific AVC in patients over 65 years of age is approximately 2-4%, and its frequency tends to increase with the aging population[6].

Recent studies have begun to show that inflammatory and immune system cells have an important role in the pathogenesis of atherosclerosis as well as play a role in the pathogenesis of heart valve calcification[7]. AVC pathophysiologically affected by the inflammatory process; studies predict the severity of aortic AS by looking at the ratio of blood cells such as neutrophils, lymphocytes, and platelets to each other[8].

Therefore, the systemic immune inflammation index (SII), which includes peripheral neutrophil, lymphocyte, and platelet counts, was developed[6]. In recent studies, high SII has been associated with negative outcomes in patients with oncology follow-up. This index has also been used as a predictive value for mortality in people with atherosclerotic cardiovascular disease[9,10].

The aim of the study aimed to reveal the relationship between AVC and SII in the elderly population with chronic renal failure.

Materials and Methods

Patients over 65 years of age who applied to the cardiology outpatient clinic with chronic renal failure between March 2018 and October 2022 were included in the study.

Exclusion criteria were defined as malignancy, active infection, chronic inflammatory disease, steroid use, severe kidney or liver failure, presence of a prosthetic heart valve, and in which cases could not be performed optimal echocardiographic examination. Demographic data, biochemical parameters, and imaging findings of the patients were recorded.

The patients were divided into two groups as group 1 (control group-undetected AVC on echocardiography) (70 patients) and group 2 (AVC detected on echocardiography) (70 patients). The hemogram and biochemical parameters of the patients at the time of admission were taken as a basis. SII of all patients was defined as: SII=neutrophil

count × platelet count/lymphocyte count. AVC was defined as a dense echocardiographic structure with highly echogenicity features localized to the valves in the parasternal long/short axis, apical five-three-chamber views.

The study was designed as a retrospective and observational. The İzmir Bakırçay University Non-Interventional Ethics Committee approved the study with decision number 2022/753.

Statistical Analysis

The IBM SPSS Statistics 24.0 Program was used for statistical analysis. Numerical variables are presented as mean and standard deviations. Categorical variables are reported as number (n) and frequency (%). In the comparison between the two groups, the independent sample t-test was used if the normal distribution was achieved, and the Mann-Whitney U test was used if the normal distribution could not be obtained. Then, regression analysis was performed to evaluate whether the SII was an independent predictor of AVC in elderly patients with CRF, and finally, receiver operating characteristic (ROC) curve analysis was performed for sensitivity and specificity, and the statistics were completed. The significance level for all hypotheses was accepted as <0.05.

Results

There was no statistically significant difference between the groups in terms of mean age, gender, and body mass index among the patients included in the study. Comorbidities of hypertension, diabetes, hyperlipidemia, and coronary artery disease were similar between the groups. In the echocardiography, the median and interquartile range (Q1-Q3) left ventricular ejection fraction (LVEF) value of the patients was 60% (55-60%), and there was no significant difference between the groups in terms of LVEF. Neutrophil values from biochemical parameters were lower in group 1 than in group 2 (5.24±1.46 vs 5.99±1.8, p=0.008, respectively). Lymphocyte values were higher in group 1 than in group 2 (2.62±0.87 vs 2.19±0.61, p=0.001, respectively). Cholesterol parameters were similar in the groups. The mean SII value was 688.5 (±289.9). It was statistically significantly higher in group 2 (754.2±268.7) than group 1 (622.79±297.2, p=0.007). All demographic data, laboratory results, and echocardiographic findings are shown in Table 1.

In the univariable regression analysis of the factors affecting AVC in elderly patients with CR, neutrophil [odds ratio (OR): 0.752; 95% confidence interval (CI): 0.605-0.934, p=0.01], lymphocytes (OR: 2,197; 95% CI: 1,346-3,585, p=0.002), and SII (OR: 0.998; 95% CI: 0.997-1,000, p=0.009) were predictors. In the multivariable regression analysis: SII (OR: 1,002; 95% CI: 1,000-1,005, p=0.034), lymphocytes (OR: 5,660; 95% CI: 2,349-13,637, p<0.001) and neutrophil (OR: 497; 95% CI: 0.344-0.717, p<0.001) parameters were found to be independent predictors of AVC (Table 2). SII> 633.4, 64% sensitivity and 65% specificity (ROC area under curve: 0.672, 95% CI: 0.582-0.762, p<0.001) are associated with AVC (Figure 1).

Discussion

According to the results of the study, higher SII is significantly associated with the presence of AVC in elderly patients with chronic renal failure.

In a study investigating the predictive value of SII in calcific severe AS, SII levels were found to be higher in the high flow-high gradient AS and low flow-low gradient AS group compared to the control group (525±188, 835±402 and 784±348, respectively) (p<0.001)[6]. In our study, the SII value was found to be higher in elderly patients with CRF with AVC compared to the other group. In a study on coronary artery disease in which inflammation is central to the etiopathogenesis such as heart valve calcification, the cut-off point value of SII ($694.3x10^9$) was revealed to predict major cardiovascular events better than traditional risk factors in patients with CAD after coronary intervention[9]. Similarly, in our study, the SII cut-off value was ($628.7x10^9$).

Notably the valves are usually calcified in aortic valve stenosis that occurs in elderly patients. Unlike rheumatic valve pathology, commissural fusion is not observed. Calcification usually starts from the base of the valve cusps and progresses toward the leaflets and restricts their movement. The calcification of the aortic valve cusps is quite common in the elderly. It is possible to detect AVC, a significant portion of the anatomical and functional changes, with a meticulous echocardiographic examination. Therefore, in our study, we used the echocardiography method in the diagnosis of AVC[11].

Chronic kidney disease is a disease with high renal and cardiovascular morbidity and mortality, negatively affecting the quality of life, and its incidence has increased significantly recently. In patients with CKD, calcification may occur in the myocardium, heart valves, and arteries due to calcium and phosphorus storage[12].

Table 1. Demographic, clinical, biochemical and imaging finding of study population

	Group 1 (n=70)	Group 2 (n=70)	Total (n=140)	p-value
Age (years) mean ± SD	73 (70-78)	71 (68-75)	72 (69-77)	0.15
Male sex, n (%)	30 (42.8)	39 (55.7)	69 (49.3)	0.12
Smoking, n (%)	8 (11.4)	9 (12.8)	17 (12.1)	0.79
BMI, kg/m^2, mean ± SD	24 (22-28)	24 (22-29)	24.2 (22.2-29)	0.7
Heart rate, /min	73.98±6.8	72.0±9.0	73.0±8.03	0.14
Hypertension, n (%)	39 (55.7)	34 (48.5)	73 (52.1)	0.39
DM, n (%)	13 (18.5)	12 (17.1)	25 (17.9)	0.82
CAD, n (%)	34 (48.5)	27 (38.5)	61 (43.5)	0.23
Hyperlipidemia, n (%)	26 (37.1)	24 (34.2)	50 (35.7)	0.72
Urea, mg/dL	37.15±14.69	36.5±15.31	36.82±14.95	0.79
Creatinine, mg/dL	1.96±0.56	1.88±0.57	1.92±0.56	0.42
WBC, × 10^9/L	8.61±2.17	9.12±3.58	8.85±2.91	0.33
Neutrophil, x10^9/L	5.24±1.46	5.99±1.8	5.62±1.68	**0.008**
Hemoglobin, g/dL	13.10±1.52	13.27±1.37	13.19±1.44	0.497
Platelet, x10^9/L	284.5±63.92	266±51.64	275.25±58.64	0.062
Lymphocyte, x10^9/L	2.62±0.87	2.19±0.61	2.41±0.78	**0.001**
Fasting blood sugar, mg/dL	104.61±21.05	108.42±22.8	106.52±21.95	0.3
SII	622.79±297.2	754.2±268.7	688.5±289.9	**0.007**
Total cholesterol, mg/dL	178.51±33.55	172.17±36.23	175.34±34.93	0.28
Triglyceride, mg/dL	181.37±100.6	194.27±99.32	187.82±99.82	0.44
HDL, mg/dL	44.34±15.99	40.18±9.17	42.26±13.15	0.06
LDL, mg/dL	102.41±27.66	97.57±29.17	99.99±28.43	0.31
Sodium, mEq/L	140.4±2.85	139.55±2.36	139.97±2.64	0.059
Potassium, mmol/L	4.38±0.41	4.33±0.42	4.35±0.41	0.42
Calcium, mg/dL	8.76±0.52	8.69±0.59	8.73±0.56	0.45
Phosphate, mg/dL	4.17±0.94	4.06±1.03	4.12±0.98	0.47
LVEF, % Median IQR (Q1-Q3)	60 (54-61)	59 (55-60)	60 (55-60)	0.20
LVEDD, mm	48 (45-51)	47 (44-50)	47.5 (45-50)	0.48
LVESD, mm	30 (26-34)	29 (26-33)	30 (26-34)	0.68
LA diameter, mm	38 (34-43)	38 (34-42)	38 (34-42)	0.92

BMI: Body mass index, DM: Diabetes mellitus, CAD: Coronary artery disease, WBC: White blood cell, SII: Systemic immune inflammation index, HDL: High density lipoprotein, LDL: Low density lipoprotein, LVEF: Left ventricle ejection fraction, LVEDD: Left ventricle end diastolic diameter, LVESD: Left ventricle end systolic diameter, LA: Left atrium, Group 1: Non-calcific aortic valve, Group 2: Calcific aortic valve

It has been shown that the inflammatory process is effective in the pathogenesis of AVC, and a fibrotic and calcific structure is formed on the valve with the contribution of proinflammatory cytokines and immune system cells[13]. Based on this information, different biomarkers have been used to predict the severity of valve calcification[14]. In recent studies, the prognostic values were investigated by calculating the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lymphocyte-monocyte ratio[15].

Neutrophil-lymphocyte ratio was found to be negative in mortality and 30-day results in patients who underwent aortic valve replacement[16]. In our current study, it was concluded that neutrophil values were high and lymphocyte values were low in the group with AVC, similar to other previous studies, i.e. is, the N/L ratio was high.

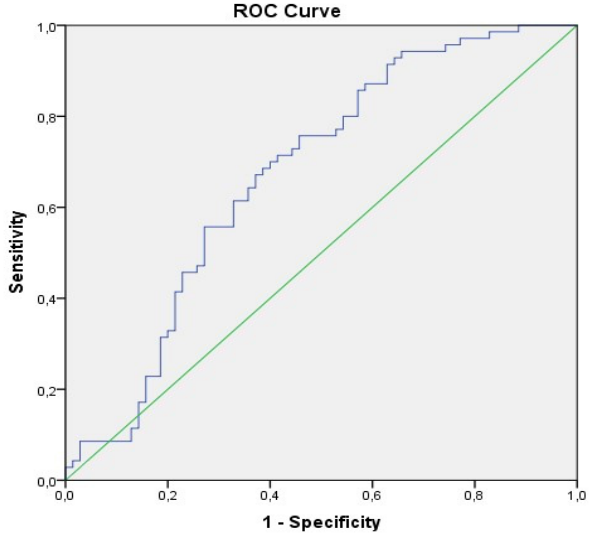

Figure 1. The cut-off value of the systemic immune inflammation index as a predictor of aortic valve calcification in the ROC curve
ROC: Receiver operating characteristic

As a component of the immune response, lymphocytes play an important role in the immune mechanisms. In patients with acute myocardial infarction, low lymphocyte concentration has been shown to be associated with adverse clinical outcomes in the progression of atherosclerosis (similar to the aortic calcification process)[17-19]. Increased lymphocyte apoptosis triggered by aggravated inflammation may decrease lymphocyte counts[20,21]. In conclusion, due to high neutrophil and platelet levels and decreased lymphocyte concentration, an elevated SII may be associated with increased inflammatory activity and therefore lead to poor clinical outcomes.

In a retrospective study conducted to reveal the relationship between mitral annular calcification (MAC) and the lymphocyte count was found to be borderline low in the MAC (+) group compared to the control group (1.86±0.63; 2.02 ±0.66, p=0.05)[22]. In our study, lymphocyte values were found to be lower in AVC group compared to other group.

Study Limitations

Apart from a retrospective feature, our study had limitations such as including a small patient population. Another limitation was that the SII value of the patients was calculated when the patients were admitted to the hospital, and there were no follow-up values.

Conclusion

High SII in the elderly with chronic renal failure is associated with the presence of AVCs. This study may lead to future large-scale randomized studies on the relationship of SII with AVC.

Table 2. Univariate and multivariate logistic regression analyzes in predicting aortic valve calcification in patients with CRF and elderly

	Univariate logistic regression			Multivariate logistic regression		
Variables	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Lymphocyte	2,197	1,346-3,585	**0.002**	5,660	2,349-13,637	**<0.001**
Neutrophil	0.752	0.605-0.934	**0.01**	0.497	0.344-0.717	**<0.001**
SII	0.998	0.997-1.000	**0.009**	1.002	1.000-1.005	**0.034**

SII: Systemic immune inflammation index, OR: Odds ratio, CI: Confidence interval

Ethics

Ethics Committee Approval: The İzmir Bakırçay University Non-Interventional Ethics Committee approved the study with decision number 2022/753.

Informed Consent: The study was designed as a retrospective and observational.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yurdam FS, Kış M, Concept: Yurdam FS, Design: Yurdam FS, Data Collection and/or Processing: Yurdam FS, Analysis and/or Interpretation: Kış M, Literature Search: Kış M, Writing: Yurdam FS.

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