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Original Article / Özgün Araştırma

Prognostic value of nutritional and inflammatory scores in Transcatheter aortic valve replacement patients

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Abstract

Background: Aortic Stenosis (AS) is a common heart valve disease that especially affects the elderly population and is seen with the aging of the society. In recent years Transcatheter aortic valve replacement patients (TAVR) has been increasingly applied worldwide as a procedure for the treatment of severe AS. Recently, various biomarkers and derived marker approaches have been studied in AS patient groups as in many cardiovascular diseases. Since it has been previously shown that increased inflammatory scores and poor nutritional scores are closely associated with the development process and prognosis of cardiovascular diseases, we hypothesized that these scores may be associated with prognosis after TAVR. Therefore, in this study, we aimed to make a detailed evaluation in terms of mortality determinants after TAVR.

Methods and Results: 118 TAVR patients were included in the analysis. Median follow-up of 118 patients was 40.5 months. In terms of inflammatory status scores, the systemic immune inflammatory (SII) score (p= 0.027), the neutrophil/lymphocyte ratio (NLR) score (p= 0.012), and the platelet/lymphocyte ratio (PLR) score (p= 0.012) in the death group was found to be significantly higher. As nutritional status scores, the prognostic nutritional index (PNI) score (p= 0.003) was lower in the death group and the median Controlling Nutritional Status (CONUT) score (p= 0.002)) found significantly higher.

Conclusion: In severe and high-risk AS patients undergoing TAVR, measurement of malnutrition with the CONUT score and increased inflammatory status with the SII score was associated with an increased risk of all causes mortality in long-term follow-up. It has been determined that the development of complications related to the procedure is an indicator of increased mortality not only in the short term but also in the long-term follow-up.

Key words: CONUT - SII - TAVI - PNI - NLR

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Transkateter aort kapak implantasyonu hastalarında beslenme ve inflamatuar skorların prognostik değeri

Öz

Amaç: Aort Darlığı (AD), özellikle yaşlı nüfusu etkileyen ve toplumun yaşlanmasıyla birlikte görülen yaygın bir kalp kapak hastalığıdır. Son yıllarda Transkateter aort kapak implantasyonu (TAVI), şiddetli AS tedavisi için bir prosedür olarak dünya çapında giderek daha fazla uygulanmaktadır. Son zamanlarda birçok kardiyovasküler hastalıkta olduğu gibi AD hasta gruplarında da çeşitli biyobelirteçler ve türetilmiş belirteç yaklaşımları araştırılmaktadır. Artmış inflamatuvar skorların ve kötü beslenme skorlarının kardiyovasküler hastalıkların gelişim süreci ve prognozu ile yakından ilişkili olduğu daha önce gösterildiğinden, bu skorların TAVI sonrası prognoz ile ilişkili olabileceğini varsaydık. Bu nedenle bu çalışmada TAVI sonrası mortalite belirleyicileri açısından detaylı bir değerlendirme yapmayı amaçladık.

Yöntemler ve Sonuçlar: 118 TAVI hastası analize dahil edildi. 118 hastanın medyan takip süresi 40.5 aydı. İnflamatuar durum skorları açısından, sistemik immün inflamatuar (SII) skoru (p= 0.027), nötrofil/lenfosit oranı (NLR) skoru (p= 0.012) ve trombosit/lenfosit oranı (PLR) skoru (p= 0.012)) ölüm grubunda anlamlı olarak daha yüksek bulundu. Beslenme durumu skoru olarak ölüm grubunda prognostik nütrisyon indeksi (PNI) skoru (p= 0.003) daha düşüktü ve medyan CONUT skoru (p= 0.002) anlamlı olarak daha yüksek bulundu.

Sonuç: TAVI uygulanan şiddetli ve yüksek riskli AD hastalarında, CONUT skoru ile malnütrisyon ölçümü ve SII skoru ile artan inflamatuar durum, uzun dönem takipte tüm nedenlere bağlı mortalite riskinin artmasıyla ilişkilendirildi. İşleme bağlı komplikasyonların gelişmesinin sadece kısa dönemde değil uzun dönemde de mortalite artışının bir göstergesi olduğu belirlenmiştir.

Anahtar kelimeler: CONUT - SII - TAVR- PNI - NLR

INTRODUCTION

Aortic Stenosis (AS) is a common heart valve disease that especially affects the elderly population and is seen with the aging of the society[1]. The process of forming lesions of the aortic valve is due to the accumulation of lipids, especially with aging, the migration of inflammatory cells to the endothelium of the aortic valves, and stimulation of calcification processes. Aortic stenosis is characterized by progressive obstruction of the left ventricular outflow tract, resulting in insufficient cardiac output, heart failure, and possibly death[2].

In recent years, transcatheter aortic valve replacement (TAVR) has been rapidly applied worldwide as a procedure for the treatment of severe AS[3]. Successful TAVR has a shorter hospital stay and a higher probability of being discharged home compared with traditional surgical aortic valve replacement (SAVR)[4].

Endothelial dysfunction and inflammation may play an important role in the development of many diseases, and some biomarkers involved in these stages have become increasingly important parameters in the determination of the prognosis of inflammatory diseases[5]. Recently, many hematological and biomarker scores have been studied in AS patient groups, as in many cardiovascular diseases[6].

Since it has been previously shown that increased inflammatory scores and poor nutritional scores are closely associated with the development process and prognosis of cardiovascular diseases, we hypothesized that these scores may be associated with prognosis after TAVR. Therefore, in this study, we aimed to make a detailed evaluation in terms of mortality determinants after TAVR.

METHODS

Patients and study protocol

Our study is a single-center, observational study examining patients with severe AS. Patients who underwent TAVR procedure in our clinic between January 2014 and January 2020 were included in the study in a randomized retrospective manner. Exclusion criteria were malignancy and systemic

inflammatory disease. Our study was approved by the local ethics committee of our university.

Echocardiographic Analysis

Each patient was evaluated using resting transthoracic echocardiography as a standard procedure. While the patient was in the left lateral decubitus position, examination was performed with VIVID S5 ultrasound. Gradient measurement on the aortic valve was taken with a CW doppler at the level of the aortic valve in the apical five-chamber. Aortic valve area (AVA) was calculated with the continuity equation in accordance with the guidelines. Severe AS was defined as AVA ≤ 1.0 cm2 or a mean gradient ≥ 40 mmHg obtained with CW Doppler in the aortic valve[7].

Biochemical and hematological parameters

Standard techniques were employed for routine biochemical and hematological tests. Neutrophil/lymphocyte ratio (NLR), monocyte/HDL cholesterol ratio (MHR), platelet/lymphocyte ratio (PLR), CRP/Albumin ratio (CAR) were obtained by dividing the relevant values. The systemic immune inflammation index (SII) score was obtained by dividing the multiplication of neutrophil and platelet counts by the lymphocyte count.

The CONUT score was calculated from three variables in blood samples taken from TAVR patients at admission.

Albumin score: If albumin level ≥3.5 g/dL=0 point, if albumin level between 3.0–3.4 g/dL=2 points, if albumin level between 2.5–2.9 g/dL=4 points, if albumin level <2.5 g/dL=6 points.

Lymphocyte score: If lymphocyte count ≥1600 count/mL=0 point, if lymphocyte count between 1200–1599 count/mL=1 point, if lymphocyte count between 800–1199 count/mL=2 points, if lymphocyte count <800 count/mL=3 points.

Cholesterol score: If cholesterol level ≥180 mg/dL=0 point, if cholesterol level between140–179 mg/dL=1 point, if cholesterol level between 100–139 mg/dL=2 points, if cholesterol level <100 mg/dL=3 points.

CONUT score was calculated by albumin score + lymphocyte score + cholesterol score.

The prognostic nutritional index (PNI) score was calculated from two blood sample variables found in blood samples taken on admission from blood samples taken from TAVR patients. PNI was calculated according to this formula: PNI score=[10×serum albumin level in g/dL+0.005×total lymphocyte count in mm3].

Follow-up and endpoint

All patients were evaluated by a team and it was decided to perform TAVR. Transfemoral access was preferred in all patients. TAVR was performed in the catheterization laboratory.

The primary endpoint of the study was all-cause death during follow-up. Follow-up was defined as the time from TAVR to death or the last clinical contact. All patients were followed up after TAVR until January 2022 or death. Detection of endpoint data was obtained blindly through scanning medical records or telephone conversations with the patient or their relatives.

Statistical Analysis

Version 23.0 of SPSS software was used. Continuous variables were expressed as mean ± standard deviation (SD) or median according to the first and second percentiles (Q1-Q3) and distribution patterns of the data. Categorical variables were expressed as percentage (%) and frequency (n). Continuous variables were compared using the Student's t-test or Mann-Whitney U test as appropriate. The normal distribution of data was analyzed using Shapiro-Wilk tests or Kolmogorov-Smirnov. We then performed multivariate cox regression analyzes to identify independent predictors of all-cause mortality in TAVR patients during follow-up. We used Kaplan-Meier analysis for mortality and survival analysis by calculating the total follow-up time. A value of <0.05 was considered significant for the p value.

RESULTS

Among 136 patients who underwent TAVR between the specified dates, 118 had blood

parameters containing data to determine preprocedural variables and were included in the analysis. The demographic, echocardiographic, laboratory, and prognostic scores of the patients and the results of univariate and multivariate cox regression models of the study population, which were categorized according to the groups deceased or survived, are listed in Table-I. 58.5% were women and the mean age was 79.4 years. The mean STS score of the patients was calculated as 10%.

Table I: The demographic, echocardiographic, laboratory, and inflammatory parameters of the patients and the results of univariate and multivariate cox regression models

Demographic, Echocardigraphic, Laboratory and Inflammatory Parameters of the Patients				
Parameter	**Total n:118**	**Deceased n:66**	**Survived n:52**	***P value***
Age	79.4±7.2	80.5±7.2	78±6.8	***0.042***
Female gender, n%	69 (58.5)	33 (50)	36 (69.2)	***0.035***
STS	10±2.8	10.5±2.5	9.4±3	***0.033***
Euro Score	27.9±8	29±8.4	26.2±7.2	0.071
In hospital time(days)	3 (1)	3 (2)	3 (1)	0.504
Complications	28 (23.7)	21 (31.8)	7 (13.5)	***0.020***
EF%, IQR	60 (15)	60 (14)	52 (15)	0.242
Aortic valve maximum gradient (mmHg)	80±18	78±19	81±17	0.343
Aortic valve mean gradient (mmHg)	50±10	49.5±11.2	50±10	0.777
Valve size (mm)	27.7±2.8	27.8±3	27.7±2.6	0.863
Type of Valve Balon expandable Self expandable	 29 (26.1) 41 (36.9)	 24 (36.9) 41 (63,1)	 5 (10.9) 41 (89.1)	***0.002***
WBC (× 10^3 µL)	7.9±2.3	7.8±2.1	8±2.5	0.695
Hemoglobin (g/dl)	12.2±1.9	12±1.9	12.4±2	0.278
RDW (%)	13±1.7	13.4±2	12.6±1	***0.009***
Platelets (× 10^3 µL)	231±79	232±74	231±85	0.996
Neutrophils (× 10^3 µL)	5.3±2.3	5.4±2.4	5±2.1	0.404
Lymphocytes (× 10^3 µL)	1.8±0.7	1.6±0.5	2±0.8	***0.004***
Glucose (mg/dl)	129±57	133±60	123±51	0.347
Urea (mg/dl)	47±19	51±21	42±15	***0.009***
Creatine (mg/dl)	0.9±0.3	0.95±0.3	0.8±0.2	***0.005***
Lactate dehydrogenase (U/L)	315±169	341±195	284±123	***0.070***
Serum albumin (g/dl)	3.37±0.44	3.26±0.5	3.5±0.34	***0.003***
Total cholesterol (mg/dl)	178±45	173±44	184±47	0.174
LDL (mg/dl)	110±36	108±37	112±35	0.515
HDL (mg/dl)	43±12	41±12	46±12	0.050
Triglyserides (mg/dl)	122±71	118±58	126±84	0.550
CRP (mg/dl), IQR	0.48 (1.62)	0.55 (2.63)	0.43 (0.81)	0.222
SII	780±558	880±615	653±450	***0.027***
CAR, IQR	0.13 (0.45)	0.18 (0.9)	0.12 (0.22)	0.159
NLR	3.4±2.1	3.82±2.43	2.85±1.45	***0.012***
PLR	143±64	156±69	112±53	***0.012***
MHR	16.3±10.2	17±12	15±6	0.273
PNI	34±4.5	33±5	35±3.4	***0.003***
CONUT, IQR	2 (3)	3 (3)	2 (4)	***0.002***
Univairate and Multivariate COX Regression Model				
	Univariate analysis		**Multivariate analysis**	
Parameter	**OR (95%CI)**	***p***	**OR (95%CI)**	***p***
Age	1.043(1.006-1.082)	***0.023***	1.043 (0.999-1.090)	0.056
Gender	1.419 (0.873-2.309)	0.158		
Complication	1.845 (1.089-3.127)	***0.023***	1.613 (0.892-2.915)	0.113
STS	1.101 (1.010-1.200)	***0.028***	1.084 (0.986-1.192)	0.096
NLR	1.155 (1.037-1.285)	***0.009***	1.125 (0.889-1.424)	0.326
PLR	1.004 (1.001-1.008)	***0.023***	1.002 (0.994-1.010)	0.602
CAR	1.232 (0.995-1.524)	***0.056***	0.893 (0.657-1.212)	0.467
LnSII	1.518 (1.012-2.278)	***0.044***	0.834 (0.261-2.669)	0.760
PNI	0.896 (0.850-0.945)	***<0.001***	0.959 (0.855-1.077)	0.483
CONUT	1.271 (1.132-1.427)	***<0.001***	1.169 (0.897-1.524)	0.247

CAR: CRP/Albumin ratio, CONUT: Controlling Nutritional score, CRP: C-reactive Protein, EF: Ejection Fraction, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, LnSII:logaritmik systemic immune-inflammation index , MHR: monocyte/HDL cholesterol ratio, NLR: neutrophil/lymphocyte ratio, PLR: Platelet/Lymphocyte ratio, PNI: prognostic nutritional index, SII: systemic immune-inflammation index,

STS: Society of Thoracic Surgeons Score, WBC: White Blood Cell,

The median follow-up of 118 patients was 40.5 months. The all-cause mortality occurred in 66 (55.9%) patients. It was observed that the STS score was significantly higher in the deceased group compared to the survived group (10.5±2.5% vs. 9.4±3%, p=0.033).

In terms of inflammatory status scores, the SII score (880±615 versus 653±450, p= 0.027), the NLR score (3.82±2.43 versus 2.85±1.45, p= 0.012), and the PLR score (156±69 versus 112±53, p= 0.012) in the deceased group was found to be significantly higher.

It was observed that the median CAR score (0.18(0.9) vs. 0.12 (0.22), p= 0.159) and MHR score (17±12 vs. 15±6, p= 0.273) were higher in the deceased group but not significantly.

As nutritional status scores, the PNI score (33±5 vs. 35±3.4, p= 0.003) was lower in the deceased group and the median CONUT score (3 (3) vs. 2 (4), p= 0.002)) found significantly higher.

Complication evolution data and Kaplan-Meier analysis

Complication development data and details of complications related to the intervention are given in Figure-1. It was determined that complications developed in 28 (23.7%) patients and 21 of the patients who developed this complication had all-cause mortality during the follow-up. AV complete block in 7 patients, cerebrovascular events in 3 patients, hospital infection in 4 patients, infective endocarditis in 1 patient, access way complication in 9 patients, Coronary embolism in 1 patient, free wall rupture and pericardial tamponade in 4 patients were detected.

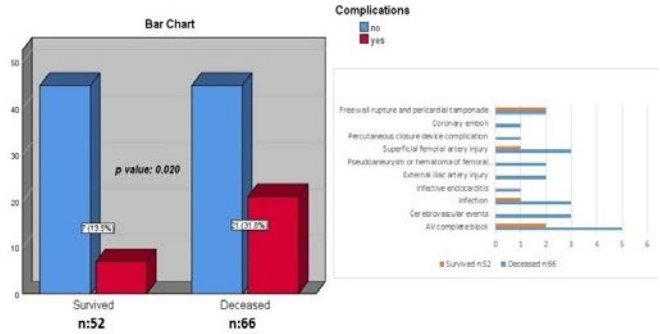

Figure 1. The complication development data related to the procedure

In Figure-2, Kaplan-Meier analysis is given for the development of all-cause mortality in the groups with and without complications during the follow-up period. According to Kaplan Meier's analysis, a significant difference was observed between the group with complications and the group without complications in terms of all-cause mortality at follow-up (Log-Rank test: 5.5, p<0.019).

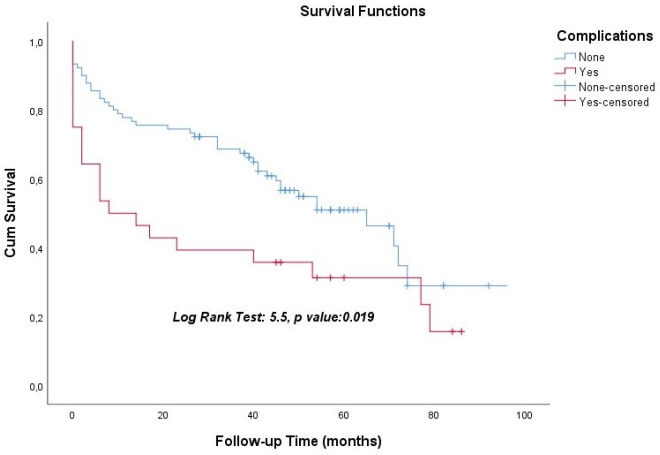

Figure 2. The Kaplan-Meier analysis of the groups with and without complications

Receiver operating characteristic (ROC) analysis of SII, NLR, and CONUT scores of the patients was performed. As a mortality predictor, the optimum CONUT score cut-off value was determined as ≥1.5 by ROC analysis.

The optimum SII score cut-off value as a mortality predictor was determined as ≥574.9 by ROC analysis. The optimum NLR score cut-off value as a mortality predictor was determined as ≥2.72 by ROC analysis.

DISCUSSION

This cross-sectional study was conducted to demonstrate the effect of complications, inflammatory parameters, and malnutrition on poor prognosis in patients with severe aortic stenosis treated with TAVR. The study showed three main findings. First, the presence of any complication related to the procedure is associated with all-cause mortality during the long-term follow-up as well as its early effects. Secondly, our study is the first to show the relationship between high NLR and PLR scores, which are among the inflammatory parameters previously shown to be associated with prognosis, and high SII value with prognosis. Thirdly, the relationship between high CONUT and low PNI scores, which are accepted as objective indicators of malnutrition, and prognosis after the TAVR procedure continues in long-term follow-up.

The development and progression of AS is partly related to active processes in atherosclerotic disease that have also been accepted as etiologically[8]. With recent evidence, AS is considered to involve an inflammatory atherosclerotic process similar to CAD[9]. In a recent study, it was shown that an increase in the monocyte/HDL ratio in patients with chronic total occlusion of coronary artery was associated with all-cause mortality[10]. Therefore, it was right to expect that high inflammatory scores and malnutrition markers, which have been previously shown to be associated with the development of CAD and its prognosis, would also be associated with prognosis in the TAVR group.

In a recent well-designed study, a high SII score predicted major endpoints after coronary intervention more accurately than known risk factors in CAD patients[11]. NLR and PLR have emerged as novel inflammatory prognostic markers that have been associated with both development and cardiovascular outcomes in various cardiovascular pathologies[12,13]. Another recent study investigated PLR and NLR in predicting poor procedural outcomes in patients undergoing TAVI and found that high PLR and NLR levels were associated with poor short-term outcomes[14]. It has been stated that these higher NLR and PLR levels can determine the proinflammatory state in calcific aortic stenosis as well as the prothrombotic state in patients. Considering its close relationship with NLR, our study is the first to show the relationship between high SII score, and poor prognosis after TAVR.

In two recent studies, it has been shown that malnutrition, which is determined by a low PNI score calculated with pre-procedural blood parameters and high CONUT scores, is closely associated with a 1-year poor prognosis after TAVR[15,16]. Our study provided data supporting the relationship between the determination of malnutrition status by two parameters calculated with simple blood parameters and the prognosis after TAVR. Since TAVR is a form of treatment, we think that monitoring the improvement after TAVR with these parameters and determining the relationship between prognosis can be an important indicator.

Conduction disorders, cerebral embolism, and complications related to percutaneous access sites continue to be common complications of TAVR that may bad influence the prognosis of patients[17-19]. These complications result in worse recovery of left ventricular function and a higher episode of readmission. Our study provided important information by showing that these complications are not only associated with short-term prognosis, but also with long-term prognosis. We think that we have

conducted a study that shows how important studies to prevent the development of complications can become.

Data with prognostic effects before and after TAVR is still a subject to be examined. Prospective new studies are needed in terms of the prognostic effects of the use of inflammatory and nutritional scores in follow-up and their acceptance as correctable risk factors.

Limitations

Our retrospective, partially well-designed study, of which we are confident of data reliability, has potential limitations. First of them retrospective, observational study with a small number of patients and therefore we cannot completely exclude potential selection and detection bias. In general, our findings should be considered to be informative for future studies. Second, due to the retrospective evaluation of the data, our study was insufficient to detect clinically relevant differences in challenging clinical outcomes. Third, although potential confounders were included in the multivariate model, additional confounders or unmeasured factors were not fully evaluated. In addition, since the same parameters are used in the calculation of the scores, we cannot say that the independent variable determination was done correctly. Finally, our study included the population of a particular region, and the prediction of other ethnic and cultural groups by these data may be limited.

CONCLUSİON

In severe and high-risk AS patients undergoing TAVR, measurement of malnutrition with the CONUT score and increased inflammatory status with the SII score was associated with an increased risk of death from all causes in long-term follow-up. It has been determined that the development of complications related to the procedure is an indicator of increased mortality not only in the short term but also in the long-term follow-up. This shows that the complication is not a situation that should be dealt with only in the acute period, but that it continues to be effective in the chronic period as well, and that closer follow-up of this patient group in the chronic period may be important to prevent negative consequences.

Ethics Committee Approval: The study was unanimously approved by local Ethics Committee on 03.02.2020. Verbal and written consent was obtained from the patients for participation in the study. The study was conducted in accordance with the Helsinki Declaration and was approved by the local ethics committee.

Conflict of Interest: The author declares no conflict of interest.

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