Predictive effect of nutritional scores assessment for 1-year mortality in patients with severe aortic stenosis treated with SAVR or TAVR

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Abstract. – OBJECTIVE: As treatment modalities of severe AS, interventional treatments such as SAVR or TAVR with the decision of the heart team have been performed recently. Controlling nutritional status (CONUT) score and prognostic nutritional index (PNI) have a very important place among the scores that provide a simple, effective, and objective evaluation of prognosis. In our study, we aimed to investigate the short-term prognostic results of severe AS patients who underwent TAVR or SAVR by comparing the CONUT and PNI results of the patients.

PATIENTS AND METHODS: 258 patients who underwent percutaneous TAVR or SAVR in our clinic between December 2012 and December 2020 were included in the study in a randomized retrospective manner. The primary endpoint of the study was in-hospital and 1-year all-cause death. The results of all patient groups were compared by dividing them into 2 groups as all-cause death group (deceased group) and non-all-cause death group (survived group) within 1 year.

RESULTS: All-cause mortality occurred in 57 (29%) patients within 1 year. As nutritional status scores, the PNI score (39.9±7.4 *vs.* 46.5±6.9, *p*<0.001) was lower in the deceased group and the median CONUT score [4(4) *vs.* 1(3) *p*<0.001] was found significantly higher. NLR score was also found to be significantly higher in the deceased group (*p*<0.001). They were divided into 3 tertiles containing an equal number of patients and compared according to the nutritional scores. Significantly higher 1-year mortality was observed in the high CONUT [10 (12%) deaths in T1, 12 (14%) in T2, and 35 (41%) deaths in T3, respectively, *p*<0.001] and low PNI [37 (43%) deaths in T1, 13 (15%) in T2, and 7 (8%) deaths in T3, respectively, *p*<0.001] groups, which can be considered as the worse nutritional group.

CONCLUSIONS: In the surgical or transarterial treatment of symptomatic severe aortic stenosis, we found that a high CONUT score and a low PNI score were predictors of all-cause mortality at 1-year follow-up, regardless of the type of treatment. We think that checking patients with scores like the abovementioned procedure and making the necessary corrections will lead to positive results in terms of prognosis.

Key Words:
TAVR, SAVR, Aortic stenosis, CONUT, PNI.

Introduction

Severe aortic stenosis (AS) is a very common disease in adults over 75 years of age[1]. Symptomatic aortic stenosis, which tends to be seen especially in the elderly population, is considered a highly mortal disease. If left untreated, the mortality rate is quite high, with an average life expectancy of 2 to 3 years[2].

Transcatheter aortic valve replacement (TAVR) is considered an alternative to surgical aortic valve replacement (SAVR) in the treatment of severe AS in patients at high surgical risk. As treatment modalities of severe AS, interventional treatments such as SAVR or TAVR with the decision of the heart team have been performed recently[3].

Numerous studies[4,5] have been conducted on the prognostic importance of nutritional status in different patient groups with cardiovascular disease. In addition, different scoring systems consisting of many parameters have been defined to evaluate this nutritional status. Controlling nutritional status (CONUT) score[6] and prognostic nutritional index (PNI)[7] have a very important place among the scores that provide a simple, effective, and objective evaluation of these issues.

In our study, we aimed to investigate the short-term prognostic results of severe AS patients who underwent TAVR or SAVR by comparing the

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CONUT and PNI results of the patients. Since we think it would not be right to directly compare the two treatment groups because there are patients in different risk groups, we aimed to evaluate the treatment groups according to their nutritional scores and the total patients, including all treatment groups in terms of prognosis.

Patients and Methods

Patients and Study Protocol

The study was unanimously approved by the Dicle University Faculty of Medicine Clinical Research Ethics Committee with the decision number 110 on 03.02.2020. Our study is a single-center, observational study examining patients with severe AS who underwent interventional therapy. Patients who underwent percutaneous TAVR or SAVR in our clinic between December 2012 and December 2020 were included in the study in a randomized retrospective manner.

Echocardiographic Analysis

As a result of the admission of symptomatic patients, standard procedures were performed using transthoracic echocardiography. The patients were examined with Vivid S6 (GE Medical Systems, Tampa, FL, USA) ultrasonography in the appropriate position. Gradient measurement in the aortic valve was made with continued wave doppler. Aortic valve area (AVA) was routinely calculated with the continuity equation. Severe AS was defined as AVA obtained with CW Doppler on the aortic valve ≤ 1.0 cm^2 or mean gradient ≥ 40 mmHg[8]. Society of Thoracic Surgeons (STS) score and European System for Cardiac Operative Risk Evaluation (EUROSCORE) of the patients were calculated. It was decided to apply TAVR or SAVR to the patients by the heart team and procedures were performed under appropriate conditions.

Biochemical and Hematological Parameters

Patients whose blood samples were routinely taken from venous blood during hospitalization were included in the study. Complete blood count (CBC) was performed with an automated system and hematological indices were calculated for each patient. Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and other biochemical levels were measured. The CONUT score was calculated from the blood samples at the time of first hospitalization in both the TAVR group and the SAVR group.

If the serum albumin level is ≥3.5 g/dL 0 point, if the serum albumin level is 3.0-3.4 g/dL 2 points, and if the albumin level is 2.5-2.9 g/dL 4 points, if the albumin level was <2.5 g/dL 6 points was accepted as the albumin score. If the lymphocyte count is ≥1600 count/mL 0 point, if the lymphocyte count is 1200-1599 count/mL 1 point, if the lymphocyte count is 800-1199 count/mL 2 points, if the lymphocyte count is <800 count/mL 3 points accepted as the lymphocyte score. If the cholesterol level is ≥180 mg/dL 0 point, if the cholesterol level is 140-179 mg/dL 1 point, if the cholesterol level is 100-139 mg/dL 2 points, and if the cholesterol level is <100 mg/dL 3 points accepted as the cholesterol score. Total CONUT score was calculated as albumin score + lymphocyte score + cholesterol score[9].

The prognostic nutritional index (PNI) score was calculated from blood samples taken at the time of first hospitalization in both groups of patients. PNI was calculated according to the formula: PNI score= [10×serum albumin level g/dL+0.005×total lymphocyte count mm^3][10].

According to their PNI scores, patients were categorized as: (1) <35; severe malnutrition, (2) 35-38; moderate malnutrition and (3) >38; There is no malnutrition. According to CONUT scores, patients were categorized as: (1) <2; no malnutrition, (2) 2-4; mild malnutrition, (3) 5-8; moderate malnutrition and (4) >8; severe malnutrition.

Main Outcome Measures

The primary endpoint of the study was in-hospital and 1-year all-cause death. Follow-up was defined as death or at least 1 year after TAVR or SAVR interventional treatments. The results of all patient groups were compared by dividing them into 2 groups as all-cause death group (deceased group) and non-all-cause death group (survived group) within 1 year.

Statistical Analysis

We analyzed our data using SPSS version 23 (IBM Corp., Armonk, NY, USA). First, we analyzed whether the distribution of our data was normal. We expressed abnormally distributed variables as IQR (interquartile range). We used the Chi-square test to analyze categorical variables and expressed the variables as a percentage (%). In the case of more than one group, we compared groups using one-way analysis of variance (ANOVA) or Kruskal-Wallis' test, as appropriate. We used univariate and multivariate analyzes with logistic regression models to identify predictors of in-hospital mortality and 1-year mortality. The scores and all data of the groups with and without death of the patients who underwent TAVR were tested with appropriate tests, then the scores and all data of the groups with and without death of the patients who underwent SAVR were tested with appropriate tests. Finally, the nutritional scores and all data of the groups with and without death of total patients were compared. Based on the results of the first univariate analysis, we determined the independent variables (NLR score, CONUT score, PNI score, STS score, EUROSCORE) that we should investigate. We included this in the next regression model. Receiver operating curve (ROC) analysis was used to determine the cut-off point for the effects of nutrition scores on mortality. We then performed multivariate logistic regression analyzes to identify independent predictors of primary endpoints. A *p*-value of <0.05 was considered significant.

Results

Between the specified dates, blood parameters and risk scores of 139 patients who underwent TAVR and 119 patients who underwent SAVR were included in the analysis for the use of pre-procedural variables in terms of prognosis. Basic demographic, laboratory and clinical characteristics of both individual treatment groups and total patients according to different treatment methods are listed in Table I.

When the treatment groups were evaluated among themselves, there was no difference in age between the dead and surviving groups in terms of 1-year mortality, but when the whole group was evaluated together, the age was found to be significantly higher in the deceased group (p=0.021).

All-cause mortality occurred in 57 (29%) patients within 1 year. STS and EUROSCORE scores in the deceased group were found to be significantly higher than in the living group (*p*-values 0.001 and 0.004, respectively).

It was observed that the GFR value was lower in the deceased group in the entire patient group, regardless of the type of treatment.

As nutritional status scores, the PNI score (39.9±7.4 *vs.* 46.5±6.9, p< 0.001) was lower in the deceased group and the median CONUT score [4(4) *vs.*1(3) p< 0.001)] found significantly higher. NLR score was also found to be significantly higher in the deceased group (p<0.001).

Different Scores in Prognosis

Receiver operating characteristic (ROC) analysis of PNI, NLR, and CONUT scores of the patients was performed. ROC results are given in Figure 1. Sensitivity and specificity values, which can be considered quite significant and powerful, were determined. It was determined that the cut-off values of the scores were a significant predictor of both in-hospital mortality and 1-year mortality.

Demographic, laboratory, and clinical characteristics of 3 equal nutrition groups formed by random ordering of CONUT and PNI scores from smallest to largest were compared in Table II. They were divided into 3 tertiles containing an equal number of patients and compared according to the nutritional scores. Significantly higher 1-year mortality was observed in the high CONUT [10 (12%) deaths in T1, 12 (14%) in T2, and 35 (41%) deaths in T3, respectively, p<0.001] and low PNI [37 (43%) deaths in T1, 13 (15%) in T2, and 7 (8%) deaths in T3, respectively, p<0.001] groups, which can be considered as the worse nutritional group.

In univariate and multivariate regression analysis, both in-hospital and 1-year mortality predictors of the whole group are shown in Table III. Low PNI score [OR: 0.889 95%CI (0.831-0.951) p =0.001], high NLR [OR: 1.160 95% CI (1.024-1.314) p =0.019] and high CONUT scores [OR: 1.346 95% CI (1.319-1.590) p <0.001] were determined as independent predictors of in-hospital mortality. Low GFR [OR: 0.973 95% CI (0.959-0.988) p <0.001], low PNI score [OR: 0.878 95% CI (0.830-0.928) p <0.001], high NLR [OR: 1.183 95% CI (1.049-1.334) p =0.006] and high CONUT [OR: 1.409 95% CI (1.222-1.625) p <0.001] scores were found as independent predictors of 1-year mortality.

Discussion

In our study, we found the following important results in patients treated surgically or percutaneously for symptomatic severe aortic stenosis: 1) CONUT and PNI scores, which allow the evalu-

Table I. Basic Demographic, laboratory and clinical characteristics of total patients according to different treatment modalities.

Variables			
All Patients	**Deseased group (n = 57)**	**Survived group (n=201)**	***p*-value**
Age (years)	72.9 ± 15.4	62.1 ± 16.9	0.021
Gender (male) n (%)	26 (46)	100 (50)	0.559
COPD, n (%)	4 (7)	22 (11)	0.379
Hypertension, n (%)	32 (56)	108 (54)	0.775
Diabetes mellitus, n (%)	9 (16)	49 (25)	0.165
Coronary Artery Disease, n (%)	23 (40)	67 (34)	0.339
Serum glucose (mg/dl)	137 ± 61.1	128 ± 45.5	0.239
Glomerular Filtration Rate (ml/min)	66.8 ± 30.9	86.1 ± 23.4	< 0.001
Hemoglobin (g/dl)	12.1 ± 2.1	12.8 ± 1.9	0.032
Neutrophil ($\times 10^3$ µL) (IQR)	5,150 (3,159)	4,905 (2,223)	0.061
Platelet ($\times 10^3$ µL) (IQR)	232 (107)	228 (97)	0.853
Lymphocyte ($\times 10^3$ µL) (IQR)	1,650 (915)	2,000 (990)	0.001
Monocytes ($\times 10^3$ µL) (IQR)	600 (315)	624 (276)	0.424
Serum albumin (g/dl)	3.13 ± 0.52	3.61 ± 0.46	< 0.001
Total cholesterol (mg/dl)	165 ± 45	181 ± 43	0.018
Triglyceride (mg/dl)	121 ± 65	137 ± 73	0.126
High Density Lipoprotein (mg/dl)	41 ± 13	45 ± 11	0.038
Low Density Lipoprotein (mg/dl)	101 ± 35	111 ± 35	0.063
STS SCORE (IQR)	10 (6.94)	5.4 (8.75)	0.001
EUROSCORE (IQR)	21(22.4)	20 (26.7)	0.004
CONUT Score (IQR)	4 (4)	1 (3)	< 0.001
PNI Score	39.9 ± 7.4	46.5 ± 6.9	< 0.001
NLR (IQR)	3.40 (2.91)	2.37 (1.57)	< 0.001
TAVR Group	**Deseased group (n = 35)**	**Survived group (n = 104)**	
Age (years)	80.7 ± 7	79.0 ± 6.7	0.119
STS SCORE	11 ± 2.87	10.1 ± 2.87	0.112
EUROSCORE	28.4 ± 8.5	28.6 ± 8.0	0.886
Glomerular Filtration Rate (ml/min)	64.8 ± 17.4	80.9 ± 18.6	< 0.001
CONUT Score (IQR)	4 (4)	2 (2)	< 0.001
PNI Score	38.5 ± 6.3	44.9 ± 5.6	< 0.001
NLR (IQR)	3.17 (2.86)	2.59 (1.77)	0.009
SAVR Group	**Deseased group (n = 22)**	**Survived group (n = 97)**	
Age (years)	60.4 ± 16.9	54.4 ± 15.2	0.138
STS SCORE (IQR)	2.40 (2.95)	1.24 (1.30)	0.001
EUROSCORE (IQR)	2.80 (8.79)	1.08 (1.08)	< 0.001
Glomerular Filtration Rate (IQR)	71 (72)	91 (35)	0.004
CONUT Score (IQR)	4 (6)	1 (3)	0.012
PNI Score	42.1 ± 8.5	48.1 ± 7.9	0.005
NLR (IQR)	3.63 (3.31)	2.25 (1.47)	0.009

Data are expressed as mean ± SD, frequencies (percentages) or median (interquartile range: IQR) as appropriate. CONUT: Controlling Nutritional Status; COPD: Chronic Obstructive Pulmonary Disease; NLR: Neutrophil Lymphocyte Ratio; PNI: Prognostic Nutritional Score.

ation of nutritional status with simple blood parameters, were shown to predict death in-hospital and at 1-year follow-up, 2) A high NLR score has been shown to have prognostic significance in patients with severe aortic stenosis, 3) it has been shown to have a low GFR value and poor prognosis in patients with symptomatic severe aortic stenosis treated by any interventional route.

In a recent study[11], the association of 30-day and 1-year mortality with high CONUT and low PNI after SAVR applied to the elderly population has been shown. We compared the treatment groups within themselves and as a total group that includes both, since we think that it would not be accurate to compare the patients who underwent TAVR directly and those who

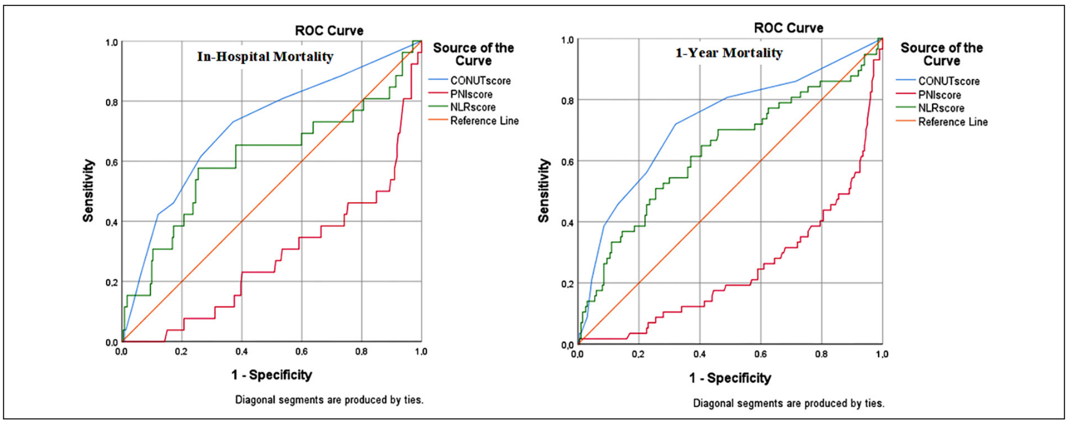

Figure 1. Receiver operating characteristic (ROC) analysis of PNI, NLR, and CONUT scores of the patients. In-hospital mortality: CONUT score >2.5 AUC: 0.715, 95% CI (0.605-0.825) Sensitivity 73%, Specificity 63% (*p*<0.001). PNI score <42.72 AUC: 0.720, 95% CI (0.612-0.827) Sensitivity 66%, Specificity 66% (*p*<0.001). NLR score >2.89 AUC: 0.608, 95% CI (0.474-0.742) Sensitivity 65%, Specificity 62% (*p*=0.070). 1-year mortality: CONUT score >2.5 AUC: 0.726, 95%CI (0.646-0.806) Sensitivity 71%, Specificity 68% (*p*<0.001), PNI score <43.3 AUC: 0.756, 95% CI (0.682-0.830) Sensitivity 70%, Specificity 69% (*p*<0.001), NLR score >2.73 AUC: 0.631, 95% CI (0.542-0.720) Sensitivity 65%, Specificity 60% (*p*=0.003).

Table II. CONUT and PNI divided into 3 tertiles containing an equal number of patients and compared according to the nutritional scores.

Variable	T1 CONUT (n = 86)	T2 CONUT (n = 86)	T3 CONUT (n = 86)	*p*-value
Age (years)	68.7 ± 14.9	67.2 ± 19.1	69.2 ± 15.8	0.020
Gender (male) n (%)	32 (37)	49 (57)	45 (52)	0.025
COPD, n (%)	10 (12)	9 (11)	7 (8)	0.741
Hypertension, n (%)	50 (58)	44 (51)	47 (55)	0.656
Diabetes mellitus, n (%)	25 (29)	18 (21)	15 (17)	0.173
Coronary Artery Disease, n (%)	26 (30)	30 (35)	34 (40)	0.044
Glomerular Filtration Rate (ml/min)	85.7 ± 22.8	81.5 ± 24	77.2 ± 31.8	0.057
Hemoglobin (g/dl)	13.1 ± 1.7	12.7 ± 1.9	12 ± 2.2	0.028
Neutrophil (× 10^3 µL)	5,136 ± 1,708	5,500 ± 2,685	5,756 ± 2,566	0.016
Platelet (× 10^3 µL)	251 ± 71	238 ± 83	227 ± 86	0.512
Monocytes (× 10^3 µL) (IQR)	647 (607)	728 (567)	755 (569)	0.272
STS SCORE (IQR)	6.25 (5.2)	6.49 (5.4)	7.19 (5.7)	0.760
EUROSCORE (IQR)	15.4 (12.4)	16.7 (13.4)	18.7 (15.1)	0.739
In-hospital mortality, n (%)	4 (5)	5 (6)	17 (20)	0.001
In-1 year mortality, n (%)	10 (12)	12 (14)	35 (41)	< 0.001
	T1 PNI (n = 86)	**T2 PNI (n = 86)**	**T3 PNI (n = 86)**	***p*-value**
Age (years)	71.6 ± 14.9	72 ± 15.1	61.5 ± 17.8	0.018
Gender (male) n (%)	48 (56)	36 (42)	42 (49)	0.187
COPD, n (%)	9 (11)	11 (13)	6 (7)	0.444
Hypertension, n (%)	51 (59)	44 (51)	46 (54)	0.543
Diabetes mellitus, n (%)	13 (15)	23 (27)	22 (26)	0.132
Coronary Artery Disease, n (%)	36 (42)	34 (40)	20 (23)	0.020
Glomerular Filtration Rate (ml/min)	76 ± 21	80 ± 22	88 ± 24	0.094
Hemoglobin (g/dl)	12 ± 2.1	13 ± 1.8	12.9 ± 1.8	0.173
Neutrophil (× 10^3 µL)	5,985 ± 2,837	5,070 ± 1,876	5,337 ± 2,212	0.020
Platelet (× 10^3 µL)	227 ± 92	242 ± 80	246 ± 68	0.410
Monocytes (× 10^3 µL) (IQR)	776 (571)	590 (541)	774 (616)	0.442
STS SCORE (IQR)	8.1 (6.62)	7.25 (6.3)	4.58 (3.56)	0.446
EUROSCORE (IQR)	21.2 (17.7)	18.8 (15.8)	10.8 (7.9)	0.214
In-hospital mortality, n (%)	16 (19)	7 (8)	3 (4)	0.003
In-1 year mortality, n (%)	37 (43)	13 (15)	7 (8)	< 0.001

Table III. Predictors of mortality in univariate and multivariate regression analysis.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
In-hospital mortality all patients				
Gender	1.922 (0.823-4.487)	0.131	1.918 (0.758-4.850)	0.169
Age	1.004 (0.979-1.029)	0.761		
Diabetes mellitus	0.872 (0.384-1.979)	0.743		
Hypertension	0.804 (0.289-2.235)	0.676		
Coronary artery disease	1.187 (0.515-2.737)	0.687		
Glomerular Filtration Rate (ml/min)	0.978 (0.963-0.994)	0.008	0.987 (0.970-1.003)	0.121
STS Score	1.060 (0.998-1.125)	0.060	1.060 (0.944-1.190)	0.325
EUROSCORE	1.016 (0.989-1.043)	0.245	0.981 (0.928-1.037)	0.506
NLR score	1.139 (1.012-1.281)	0.031	1.160 (1.024-1.314)	0.019
PNI score	0.892 (0.840-0.947)	< 0.001	0.889 (0.831-0.951)	0.001
CONUT score	1.330 (1.145-1.546)	< 0.001	1.346 (1.319-1.590)	< 0.001
1-year mortality all patients				
Gender	1.192 (0.661-2.152)	0.559		
Age	1.024 (1.003-1.045)	0.023	1.008 (0.977-1.040)	0.602
Diabetes mellitus	0.578 (0.264-1.262)	0.169		
Hypertension	1.090 (0.603-1.972)	0.775		
Coronary artery disease	1.343 (0.733-2.459)	0.340		
Glomerular Filtration Rate (ml/min)	0.969 (0.956-0.982)	< 0.001	0.973 (0.959-0.988)	< 0.001
STS Score	1.096 (1.033-1.162)	0.002	1.090 (0.961-1.236)	0.182
EUROSCORE	1.029 (1.009-1.049)	0.005	0.981 (0.940-1.023)	0.365
NLR score	1.165 (1.040-1.305)	0.008	1.183 (1.049-1.334)	0.006
PNI score	0.875 (0.833-0.919)	< 0.001	0.878 (0.830-0.928)	< 0.001
CONUT score	1.398 (1.234-1.584)	< 0.001	1.409 (1.222-1.625)	< 0.001

OR: Odds ratio, CI: Confident interval, ASPECTS: Alberta Stroke Program Early CT Score. CONUT: Controlling Nutritional Status, NIHSS: National Institutes of Stroke Scale.

underwent SAVR due to the different life expectancies of the applied populations. We examined the prognostic factors of patients with severe aortic stenosis who were treated in accordance with the guidelines in our clinic. We found that poor nutritional scores were associated with poor prognosis in all groups.

In a potentially important study[12] investigating patients undergoing TAVR and SAVR and investigating follow-up NLR values, high baseline NLR was shown to be independently associated with mortality and rehospitalization after TAVR or SAVR. Also, the observed reduction in NLR after TAVR or SAVR was associated with improved outcomes. In our study, it was shown that higher NLR values at admission were associated with increased 1-year mortality. Considering that nutritional scores are more effective on prognosis than NLR in our study, it will be seen once again how important nutrition is in patients. Similar to the previous study, we think that the follow-up of nutritional scores will be a very important determinant in terms of prognosis.

In patients with severe aortic stenosis and chronic kidney disease (CKD), TAVR and SAVR were found to be prognostically similar at 5-year follow-up[13]. It has been shown that baseline impaired renal function and occurrence of periprocedural acute kidney injury are strong predictors of 30-day and 1-year mortality after TAVI, regardless of whether renal function improves or it doesn't[14]. Considering the poor prognostic power of patients with low GFR in our study group, especially at 1-year follow-up, we think that it is very important to evaluate renal function values in both types of interventional treatment of severe aortic stenosis.

Limitations

This study had some limitations. It had a retrospective design and was a single-center study. Since there is no data on the functional limitation status of the patients after the procedure, the improvement in quality of life may be lacking in terms of provider research. Patients could also be evaluated with other nutritional scores that provide more detailed data and investigated according to their changes in follow-up.

Conclusions

In the surgical or transarterial treatment of symptomatic severe aortic stenosis, we found that a high CONUT score and a low PNI score were predictors of all-cause mortality at 1-year follow-up, regardless of the type of treatment. We think that it is very important to be able to determine both nutritional status and inflammatory status with simple blood parameters. We think that checking patients with scores like these before the procedure and making the necessary corrections will lead to positive results in terms of prognosis. We think that the prognostic parameters of all patients who are planned for interventional treatment should also be evaluated, such as the evaluation of their existing diseases.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of Data and Materials

Data available on request due to privacy/ethical restrictions.

Ethics Approval

The study was unanimously approved by the Dicle University Faculty of Medicine Clinical Research Ethics Committee with the decision number 110 on 03.02.2020. The study was performed in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee.

Informed Consent

Oral and written consent was obtained from the patients for participation in the study.

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Authors' Contribution

Significant contributions to the concept or design of the business; or obtaining, analyzing or interpreting data for study: M.O., M.K. Drafting the work or critically reviewing it for important intellectual content: M.O., M.K. Final approval of the version to be published: M.O., M.K. An agreement to be responsible for all aspects of the business to ensure that questions regarding the accuracy or completeness of any part of the business are properly investigated and resolved: M.O., M.K.

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