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The relationship between the serum uric acid/creatinine ratio and prognosis in patients with transcatheter aortic valve implantation

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Abstract. – OBJECTIVE: Aortic valve stenosis is a common valve disease in developed countries where the elderly population is high. Aortic valve stenosis is not a simple calcification; it is a dynamic process in which uric acid plays a serious role. We investigated the role of the serum uric acid/creatinine (SUA/Cr) ratio, which is an indicator of uric acid level independent of renal function, in determining the prognosis in patients who had undergone transcatheter aortic valve implantation (TAVI).

PATIENTS AND METHODS: In this retrospective cohort study, 357 patients who underwent TAVI for symptomatic severe aortic stenosis between March 2019 and March 2022 were retrospectively analyzed. After applying exclusion criteria, the remaining 269 patients were included in the study. According to the Valve Academic Research Consortium criteria, major adverse cardiac and cerebrovascular events (MACCE) defined the endpoint of the study. Therefore, patients were divided into two groups: the MACCE group and the no MACCE group.

RESULTS: Serum uric acid level was significantly higher in the MACCE group (7.0 ± 2.6) than in the no MACCE group (6.0 ± 1.7) (p = 0.008). SUA/Cr ratio was significantly higher in the MACCE group (6.7 ± 2.3) than in the no MACCE group (5.9 ± 1.1) (p = 0.007).

CONCLUSIONS: The serum UA/creatinine ratio is important in determining the prognosis of patients undergoing TAVI.

Key Words:
Uric acid, Transcatheter aortic valve replacement, Aortic valve stenosis, Prognosis, Mortality.

Introduction

Aortic stenosis (AS) has become a common valve disease in adults worldwide as a result of the increasing life expectancy and an increasing elderly population[1,2]. Transcatheter aortic valve implantation (TAVI) is a proven treatment option for patients with symptomatic severe AS who are not suitable for surgery or are considered at high surgical risk[1]. AS is a dynamic process that begins with progressive fibrocalcific degeneration and thickening of the aortic valve leaflets and progresses to valve stenosis over time[2]. The underlying pathophysiology is complex, such as atherosclerosis: endothelial dysfunction, chronic inflammation, immune cell proliferation, myofibroblast proliferation, and osteoblast differentiation occur, and calcification ensues[2]. AS is the result of a dynamic inflammatory and oxidative process; therefore, inflammatory, and oxidative markers have been proposed[3] to predict prognostic outcomes in patients undergoing TAVI.

Uric acid (UA) may have an opposite role in oxidative stress, depending on whether it is intracellular or extracellular. It is an antioxidant while it is intracellular and a pro-oxidant while it is extracellular. UA accounts for 50% of the total antioxidant capacity in body fluids in humans[4]. When UA is in acidic/hydrophobic cell cytoplasm or in atherosclerotic plaques, it transforms into a pro-oxidant substance and increases oxidative stress and plays a role in the pathophysiology of many diseases, especially cardiovascular diseases[4].

Most, if not all, epidemiological studies[5] have demonstrated an association between elevated serum UA and many diseases, including coronary heart disease, ischemic stroke, heart failure, hypertension, and atrial fibrillation. Therefore, serum UA level is considered to be associated[6] with cardiovascular mortality. Although the relationship between serum UA and cardiovascular diseases is not fully known, it is estimated[4] that serum UA plays an important role in the pathophysiology of cardiovascular diseases by mediat-

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ing or enhancing the deleterious effects of known cardiovascular disease risk factors on arteries and myocardium.

UA may affect the aorta and other large arteries besides coronary arteries. Some previous studies and analyses[7,8] have suggested that serum UA levels may be associated with aortic arch calcification and spontaneous aortic dissection. UA plays a role in the development of aortic valve calcification, which was previously believed to be a simple calcification but is now understood to occur through a dynamic process similar to atherosclerosis. Epidemiological studies[9] in the Chinese population have shown that serum UA levels are associated with aortic valve calcification. In a small study[10], UA levels were found to be correlated with the echocardiographic valve area in patients with aortic stenosis. However, no large-scale studies have compared TAVI outcomes and serum UA levels in patients with severe aortic stenosis undergoing TAVI.

Some studies[11,12] have shown that serum UA levels are associated with renal functions, however, there are also studies in the literature that did not find a relationship between UA and renal functions. As age increases, kidney functions decrease, and this may change the serum UA level. Therefore, the ratio of serum UA/creatinine (SUA/Cr) is more reliable than UA; it shows the actual/corrected UA level independently of kidney function. The easy-to-calculate SUA/Cr ratio estimates the actual/corrected serum UA level that has previously been shown[13] to be associated with cardiovascular events and eliminates the confounding effect of renal function.

UA plays a serious role in the pathogenesis of both aortic valve calcification and diseases of the ascending aorta. In this study, we investigated the prognostic role of the preprocedural SUA/Cr ratio in patients with severe aortic stenosis who underwent TAVI.

Patients and Methods

In this retrospective cohort study, 357 patients who underwent TAVI between March 2019 and March 2022 for symptomatic severe aortic stenosis in Ankara City Hospital's Heart Center were analyzed. After applying exclusion criteria, 269 patients were included in the study. The patients were divided into two groups based on whether they had major adverse cardiac and cerebrovascular events (MACCE) or not (Figure 1).

Echocardiography measurements were evaluated by a cardiac imaging specialist. Patients were diagnosed with severe aortic stenosis when the aortic mean gradient was $\geq$ 40 mmHg, peak velocity was $\geq$ 4.0 m/s or the valve area was $\leq$ 1 cm^2 ($\leq$ 0.6 cm^2/m^2). TAVI was performed on patients who were considered high risk for surgery or were inoperable due to comorbidities. Our hospital's heart team consists of at least two clinical cardiologists, two invasive cardiologists, two cardiovascular surgeons, and anesthesiologists, all of whom are experts in their fields. In some cases, pulmonologists, oncologists, endocrinologists and/or other specialists are consulted according to a patient's condition.

Routine blood tests including serum UA and creatinine values were obtained from the antecubital vein within 24 hours of the procedure from all patients included in the study. The SUA/Cr ratio was calculated by dividing the serum UA (mg/dL) level by the serum creatinine (mg/dL) level. Patients who underwent emergency TAVI, non-transfemoral access TAVI and valve-in-valve TAVI patients were not included in the study. Pa-

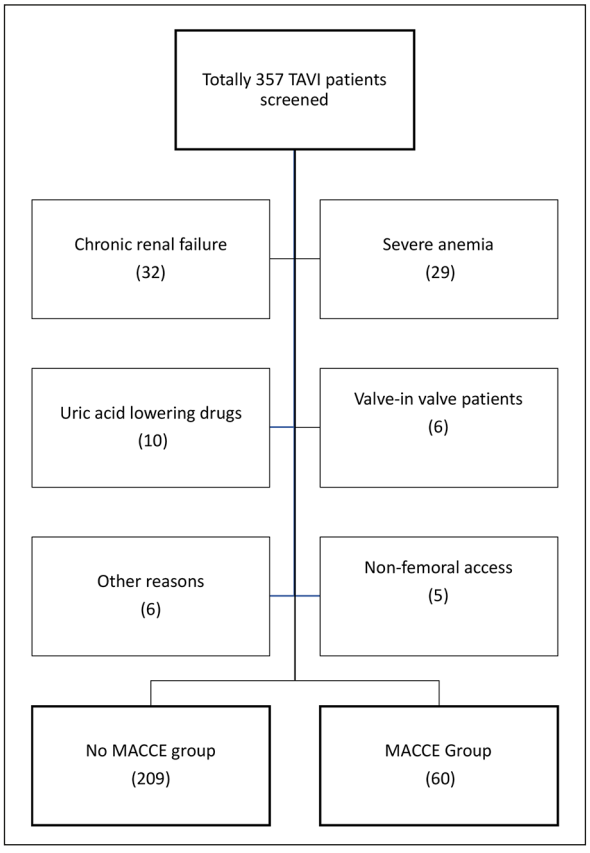

Figure 1. Study flow diagram

tients were also excluded if they had severe anemia (hemoglobin < 10 g/dL), a low platelet count (≤ 100,000/dL), a chronic renal failure glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2, liver cirrhosis (Child-Pugh class C), active infection or sepsis, active malignancies or were taking UA-lowering drugs (e.g., allopurinol, febuxostat) or chemotherapy drugs.

The study was approved by the Ankara City Hospital's Research Ethics Committee (Date: 18 January 2023; No.: E2-23-3191). Informed consent was not obtained because patient information data were anonymized. The study was performed under the principles of the Declaration of Helsinki.

Demographic and baseline characteristics of the patients, laboratory and echocardiography results and information about the TAVI access site and valve type were recorded. We also documented whether an emergency pacemaker was required during the procedure, whether there was any in-hospital mortality, whether there were any post-discharge complications such as bleeding, stroke, or acute coronary syndrome and whether there was a need for a permanent pacemaker. Mortality data were followed up with a hospital database integrated with the nationwide health and mortality system. Before the TAVI decision, the surgical risk was calculated with the EuroSCORE II risk calculator (available at: EuroSCORE.org/index.php?id=17).

Endpoints

According to the Valve Academic Research Consortium (VARC)[14], MACCE is associated with all-cause mortality in one-month, all-cause mortality in 12 months, peri-procedural blood transfusion, emergency pacemaker implantation, re-hospitalization, pacemaker requirement in follow-up, major bleeding, acute renal failure, major vascular complications, stroke, transient ischemic attack, hemorrhagic stroke, and acute coronary syndrome. One-month mortality was defined as death from any cause in the first month after TAVI or death in patients who stayed in the hospital longer than one month after TAVI and died during that hospitalization.

Statistical Analysis

SPSS for Windows (v. 23.0; IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Parametric variables are given as mean ± SD, nonparametric variables as medians with interquartile ranges and categorical variables as percentages. Continuous variables were analyzed for normal distribution using the Kolmogorov-Smirnov test. Depending on whether the continuous variables were normally distributed, differences between the groups were evaluated using Student's *t*-test or the Mann-Whitney U test. A Chi-square test was used to compare categorical variables between groups. Univariate and multivariate logistic regression analyses were performed to investigate predictors of MACCE in the study population. Variables that were significant at $p < 0.05$ in the univariate analysis were included in the multivariate logistic regression analysis to identify independent predictors of one-year MACCE (blood transfusion, pacemaker requirement in follow-up, urgent pacemaker requirement, intra-procedure stroke, acute renal failure, major bleeding, ischemic stroke, hemorrhagic stroke, acute myocardial infarction, all-cause death in 1-month, all-cause death in 1 year). The covariates included in the analysis were hemoglobin, SUA/Cr ratio, blood transfusion, urgent pacemaker need, acute renal failure, and albumin level.

Results

352 patients were included in our study group, 88 patients were excluded according to the exclusion criteria. Of these patients, 32 were excluded due to chronic renal failure, 29 due to severe anemia, 10 because they were using UA-lowering drugs, six because of valve-in-valve TAVI, five because of non-transfemoral access TAVI. Additionally, six patients were excluded for other reasons, two due to thrombocytopenia, and one due to chronic liver disease.

The mean age of patients was 76.5 ± 7.5 years, and 48.0% of patients were male. No differences were found between the groups according to sex or age. Both groups' demographic, clinical, and laboratory characteristics were similar except those regarding serum UA, serum albumin, and SUA/Cr ratio (Table I). Serum UA level was significantly higher in the MACCE group (7.0 ± 2.6) than in the no MACCE group (6.0 ± 1.7) ($p = 0.008$). SUA/Cr ratio was significantly higher in the MACCE group (6.7 ± 2.3) compared to the no MACCE group (5.9 ± 1.1) ($p = 0.007$). Serum albumin level was significantly lower in the MACCE group (37.6 ± 5.8) than in the no MACCE group (40.0 ± 5.5) ($p = 0.008$).

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

Variables	All (269)	No MACCEs (209)	MACCEs (60)	p
Age	76.5 ± 7.5	76.4 ± 7.2	76.7 ± 8.6	0.815
Male gender, n (%)	129 (48.0)	101 (48.3)	28 (46.7)	0.469
Hypertension, n (%)	243 (90.3)	187 (89.5)	56 (93.3)	0.268
Diabetes mellitus, n (%)	130 (48.3)	99 (47.4)	31 (51.7)	0.330
Chronic Lung Disease, n (%)	76 (28.3)	56 (26.8)	20 (33.3)	0.202
Hyperlipidemia, n (%)	108 (40.1)	88 (42.1)	20 (33.3)	0.142
Atrial fibrillation, n (%)	81 (30.1)	61 (29.2)	20 (33.3)	0.320
CVA, n (%)	22 (8.2)	16 (7.7)	6 (10.0)	0.362
Prior PCI, n (%)	90 (33.5)	74 (35.4)	16 (26.7)	0.133
Prior CABG, n (%)	45 (16.7)	34 (16.3)	11 (18.3)	0.419
Pacemaker/ICD presence, n (%)	17 (6.3)	12 (5.7)	5 (8.3)	0.321
Balloon Expandable Valve, n (%)	81 (31.0)	58 (28.7)	23 (39.0)	0.091
EuroSCORE, median (IQR)	5.9 (10.1)	5.4 (10.1)	7.3 (11.4)	0.052
AVA, cm^2	0.71 ± 0.16	0.71 ± 0.16	0.70 ± 0.18	0.880
LVEF, %	50.7 ± 12.6	50.4 ± 12.9	52.0 ± 11.4	0.307
Hemoglobin, g/dL	11.9 ± 1.7	11.9 ± 1.8	11.5 ± 1.4	0.052
Leukocyte count, ×1,000/uL	7.4 ± 2.4	7.3 ± 2.3	7.8 ± 2.7	0.180
Platelet count, ×1,000/uL	239.7 ± 85.4	237.2 ± 79.9	248.2 ± 102.5	0.447
Creatinine, mg/dL	1.07 ± 0.39	1.06 ± 0.37	1.10 ± 0.46	0.499
Serum Uric Acid, mg/dL	6.3 ± 2.0	6.0 ± 1.7	7.0 ± 2.6	**0.008**
Serum Albumin g/L	39.4 ± 5.6	40.0 ± 5.5	37.6 ± 5.8	**0.006**
SUA/Cr Ratio	6.1 ± 1.5	5.9 ± 1.1	6.7 ± 2.3	**0.007**

CVA: Cerebrovascular Accident, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Graft, ICD: Intracardiac Defibrillator, AVA: Aortic Valve Area, LVEF: Left ventricular ejection fraction, SUA/Cr: Serum Uric Acid/ Creatinine Ratio.

The procedural and postprocedural clinical outcomes of the patients at the one-year follow-up are shown in Table II. In the MACCE group, 15 died in the first month, and four died at the time of the procedure. Four patients died due to acute pericardial tamponade and five died due to peripheral vascular complications after the procedure. Within one month, two patients died at home after being discharged. Thirty-three additional patients died 2-12 months after discharge.

In the univariate analysis, hemoglobin level was not statistically significant in predicting MACCE; however, the following factors were statistically significant: increased SUA/Cr ratio (OR 1.470, 95% CI 1.192-1.812, $p < 0.001$), blood transfusion requirement (OR 3.244, 95% CI 1.641-6.414, $p = 0.001$), urgent pacemaker requirement (OR 2.876, 95% CI 1.352-6.120, $p = 0.006$), acute renal failure (OR 3.759, 95% CI 1.166-12.121, $p = 0.027$) and low albumin level (OR 0.929, 95% CI 0.883-0.978, $p = 0.005$). In the multiple logistic

Table II. Procedural and postprocedural clinical outcomes of the groups (one-year follow-up).

Variables	All (269)	No MACCEs (209)	MACCEs (60)	p
Blood transfusion, n (%)	45 (16.8)	26 (12.5)	19 (31.7)	**< 0.001**
Pacemaker, urgent, n (%)	34 (12.6)	20 (9.6)	14 (23.3)	**0.006**
Pacemaker need in follow-up n (%)	5 (1.9)	0 (0)	5 (8.3)	**< 0.001**
Stroke, intra-procedure, n (%)	9 (3.3)	3 (1.4)	6 (10.0)	**0.005**
Acute renal failure, n (%)	12 (4.5)	6 (2.9)	6 (10.0)	**0.029**
Major bleeding, n (%)	2 (0.7)	0 (0)	2 (3.3)	**0.049**
Ischemic stroke, n (%)	9 (3.3)	0 (0)	9 (15.0)	**< 0.001**
Hemorrhagic stroke, n (%)	1 (0.4)	0 (0)	1 (1.7)	0.223
Acute myocardial infarction, n (%)	0 (0)	0 (0)	0 (0)	
All-cause death 1 month, n (%)	15 (5.6)	0	15 (25.0)	**< 0.001**
All-cause death, 1 year, n (%)	33 (12.3)	0 (0)	33 (55.0)	**< 0.001**

MACCE: major adverse cardiac and cerebrovascular events.

regression analysis, the following factors were identified as independent predictors of MACCE: SUA/Cr ratio (OR 1.522, 95% CI 1.220-1.899, $p < 0.001$), blood transfusion requirement (OR 2.480, 95% CI 1.136-5.417, $p = 0.023$), acute renal failure (OR 4.675, 95% CI 1.198-18.239, $p = 0.026$) and low albumin level (OR 0.937, 95% CI 0.883-0.993, $p = 0.029$) (Table III).

Discussion

In this study, serum uric acid level and SUA/Cr ratio were found to be significantly higher in the patient group who developed MACCE after TAVI, and serum albumin levels were found to be lower than the other group.

This study emphasizes that serum UA level may be a prognostic factor independent of renal function and low albumin level in patients undergoing TAVI.

In the past, the pathology of aortic valve calcification was thought to be a passive, degenerative process that occurred with aging. Now, it is understood[15] that aortic valve calcification is a complex process involving inflammatory and metabolic processes, including calcium deposition, endothelial damage, inflammation, fibrosis, lipid accumulation, and matrix remodeling, similar to atherosclerosis. A high level of serum UA is considered to induce endothelial dysfunction and trigger the process of aortic valve calcification by accelerating the oxidation of low-density lipoprotein (LDL), thus promoting its progression[16]. Moreover, previous studies[17] have shown that serum UA levels correlate with the degree of aortic valve calcification. UA affects the valve structure and the vascular smooth muscle cells in the ascending aorta and is associated[8,18] with the dilatation and calcification of the thoracoabdominal aorta.

For many years, aortic valve replacement surgery had been the only option for the treatment of severe aortic stenosis, but approximately one-third of the patients are ineligible for the surgery because of advanced age, comorbidities, or frailty. The development of TAVI over the last 20 years has become an option for the treatment of intermediate and high-risk patients and patients who are not suitable for surgery[19]. TAVI is now considered an alternative to surgery, even in low-risk patients. However, issues such as in-hospital mortality, valve durability, risk of stroke, and procedural complications (e.g., bleeding, required pacemaker implantation, renal failure, paravalvular leak, and infective endocarditis) remain serious[20,21]. For example, the in-hospital mortality rate of TAVI varies between 1.84% and 9.09% depending on the experience of center[22].

In our study, the one-month mortality rate (death during the procedure, death from any cause in the first month after TAVI or death in patients who stayed in the hospital longer than one month after TAVI and died during that hospitalization) according to VARC-2 criteria[14] was 5.6%. According to the results of a large registry study[23] conducted in the USA, the one-year all-cause mortality rate after TAVI was 23.7%, and the stroke rate was 4.1%. In our study, the one-year all-cause mortality rate was 17.8%. Similar to current studies[24], the ischemic stroke rate was 3.3%. The median EuroSCORE II value of the patients was 5.9, indicating that many of the patients in our study were at intermediate or high surgical risk. Depending on the type of valve, implantation depth, and operator experience, the rate of arrhythmia requiring a pacemaker varies between 8% and 35%[20]. In our study, arrhythmia requiring a pacemaker rate was 12.6% before discharge and 1.9% at the one-year follow-up. The acute coronary syndrome was not observed at the one-year follow-up, which may be the result of routine coronary angiography and, if

Table III. Univariate and multivariate logistic regression analyses on the predictors of MACCE

	Univariate OR (95% confidence interval)	Multivariate OR (95% confidence interval)
Hgb	0.861 (0.727-1.020, $p = 0.084$)	0.961 (0.783-1.179, $p = 0.701$)
SUA/Cr ratio	1.470 (1.192-1.812, **$p < 0.001$**)	1.522 (1.220-1.899, **$p < 0.001$**)
Blood transfusion	3.244 (1.641-6.414, **$p = 0.001$**)	2.480 (1.136-5.417, **$p = 0.023$**)
Urgent Pacemaker	2.876 (1.352-6.120, **$p = 0.006$**)	2.275 (0.970-5.336, $p = 0.059$)
Acute Renal Failure	3.759 (1.166-12.121, **$p = 0.027$**)	4.675 (1.198-18.239, **$p = 0.026$**)
Serum Albumin	0.929 (0.883-0.978, **$p = 0.005$**)	0.937 (0.883-0.993, **$p = 0.029$**)

SUA/Cr: Serum Uric Acid/Creatinine Ratio.

necessary, revascularization in all patients prior to TAVI. However, as we do not routinely monitor troponin after TAVI, especially in this group of elderly patients, silent myocardial infarctions may have been overlooked. Blood transfusion requirement was 31.7% in the MACCE group and 12.5% in the no MACCE group. Like in previous studies[25], this rate was statistically significantly higher in the MACCE group. Acute renal failure is a significant cause of morbidity and mortality after TAVI[26]. In our study, 4.5% of all patients experienced acute renal failure, and the rate was significantly higher in the MACCE group. Balloon-expandable valves were used in 31% of patients. We used different manufacturer's balloon-expandable and self-expandable valves. No subgroup analysis was made between the valve types produced by different manufacturers.

Until now, no study has directly investigated the prognostic role of UA in TAVI patients. However, Biter and Tosu[27] investigated the relationship between the UA/albumin ratio and MACCE after TAVI in 150 patients and found that UA/albumin ratio helps to determine prognosis. The decrease in albumin along with the increase in uric acid plays an important role in the prognosis. Preprocedural albumin (measured 24 hours prior) is an important indicator of frailty, according to the VARC-2 frailty criteria. Hypoalbuminemia correlates with a bad prognosis and is indicative of all-cause mortality after TAVI[28,29]. In our study, albumin levels were significantly lower in the MACCE group than in the no MACCE group. Our study emphasizes that UA level is an important marker independent of albumin and creatinine in determining the prognosis in patients undergoing TAVI.

Limitations

The greatest limitation of our study is its retrospective nature and the fact that it is based on data accessed through the hospital information system. Also, our study was conducted in a single center and the sample size was small. Furthermore, the number of patients who reached the endpoint of the study was a small percentage. Finally, while analyzing one-year follow-up all-cause mortalities, no analysis was made about the cause of death.

Conclusions

Serum UA levels may be associated with cardiovascular diseases and all-cause mortality in many patient groups. It is not known whether serum UA is etiological or prognostic. In this study, we demonstrated that UA, which plays a role in the etiology of aortic valve calcification and ascending aorta diseases, may have a prognostic role in TAVI patients. However, larger prospective studies are needed to determine the extent of UA's prognostic role and whether UA can be used as a treatment target.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by Ankara City Ethics Committee (protocol code E2-23-3191 and 18.01.2023).

Informed Consent

Not applicable.

Data Availability

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to anonymized data.

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Authors' Contribution

H. Çiçekçioğlu is the principal author of this study and designed the study with resources acquisition, data collection and processing data, data analysis and interpretation, writing-original draft preparation, and editing. H. Çiçekçioğlu, A. Balun, Z.G. Cetin, B. Demirtaş, M. Cetin, K. Özbek; conceived the idea for the article, framing the hypothesis, designed the methods to generate results, data collection and processing data, data analysis and interpretation, writing-original draft preparation, critical review, and editing. All authors have read and approved the paper.

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