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Original Research

Can the Ratio of Calcium to Albumin Predict the Severity of Aortic Stenosis?

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ABSTRACT

Objective: Aortic sclerosis is observed in 25% of the elderly population, and 2.5% of these patients have severe aortic stenosis (AS). Numerous studies have reported a relationship between the serum calcium or albumin levels and AS. The present study investigated the relationship between the calcium toalbumin ratio (CAR) and AS.

Methods: Our study included 185 patients and 108 subjects as the control group. A routine transthoracic echocardiographic evaluation and laboratory examinations were performed inall participants. The corrected serum calcium levels were calculated using the most commonly used formula: corrected calcium=measured total calcium (mg/dL) + 0.8 (4.0−serum albumin [g/dL]).

Results: The serum C-reactive protein CRP, calcium, and corrected calcium levels were significantly different between the study groups ($p<0.05$), and the albumin levels were significantly decreased parallel withthe AS severity ($p<0.001$). Also, we detected a negative correlation between the albumin and corrected calcium levels and the EuroSCORE. CAR and corrected calcium to albumin ratio (cCAR) were significantly higher in the AS group, as expected ($p<0.01$). In the logistic regression analysis, albumin, CRP, low-density lipoprotein LDL, theCAR, and cCAR levels were found to be significantly and independently associated with the presence of AS ($p<0.05$). Moreover, in a regression analysis in the subgroup of AS only, albumin, the cCAR, and CAR were independently associated with the presence of very severe AS.

Conclusion: Our study showed an important relationship between the CAR and AS. Therefore, in clinical practice, this simple, inexpensive, and practical method may predict the severity of AS.

Keywords: Albumin, aortic stenosis, calcium, calcium to albumin ratio

INTRODUCTION

The best-known pathologies underlying aortic stenosis (AS) include aortic valve thickening and sclerosis, followed by progressive calcification causing obstruction. Aortic stenosis is observed in 25% of the elderly population (1), and changes on the cusp share similarities with the structure of atherosclerotic plaque (2). Approximately 2.5% of these patientsface severe AS, along with progressive calcification (3). Within this progressive process, the changes in the valve include bone cells in the osteoblastic phenotype, and in advanced AS cases, bone structures showing a lamellar structure (4, 5).

A previous study found that low serum calcium levels wereassociated with increasedcalcium hydroxyapatite deposition in native aortic valves in patients with severe calcific AS (6). On the other hand, another study demonstrated that serum calcium levels werehigher in patients with AS among subjects with normal renal function who did not have apparent atherosclerosis (7). In another study, while no significant relationship was detected between the severity of AS and serum calcium levels, it was reported that the increase in serum phosphate levels and the calcium-phosphate product levels have a negative relationship with the aortic valve area (AVA) (8). It has been previously shown that in patients with AS who underwent a transcatheter aortic valve implantation (TAVI) procedure, a low serum albumin level is an important prognostic factor for post-procedure mortality (9). Being an important marker of fragility, the serum albumin levels have been demonstrated to be lower in patients with AS, which is seen at an advanced age and in fragile patients (10). Additionally, inflammation has been demonstrated to play an active role in the progression of aortic sclerosis and calcific AS (11, 12). Also, albumin is known as a negative acute-phase reactant of which the blood level decreases during inflammation (13). Moreover, the most important transporter protein of calcium ions in the blood is albumin (14).

Our study explored the relationship of calcific AS with serum albumin, calcium, albumin-corrected calcium levels, and espe-

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cially the ratio of two closely interacting molecules, calcium and albumin.

METHODS

Our study included 185 patients admitted to our clinic between January 2014 and January 2017, diagnosed with severe AS, and 108 subjects who were admitted to our cardiology clinic for examination purposes and for whom no obstructive coronary artery disease (CAD) was detected after non-invasive tests, including the exercise test, myocardial perfusion scintigraphy, and computerized tomographic angiography, and no valvular pathology was detected byechocardiography. Patients with ahistory of acute coronary syndrome within the pastmonth; those with active malignancy;those who usedimmunosuppressive, steroid, or diuretic agents on regular basis, or external Vitamin D or calcium supplements;those who suffered fromchronic renal disease or renal disease requiring hemodialysis;those with aclinical presentation of infective endocarditis;those who suffered from anacute or chronic connective tissue disease;those who hadAS but with no available previous medical records; thosewho hadprimary hyperparathyroidism or inadequately treated thyroid issues;and those who hadaclinical presentation of Stage 3-4 cardiac failure were excluded from the study. Our study was designed in accordance with the Declaration of Helsinki, and the local ethical committee of Yıldırım Beyazıt University approved the study protocol (Date: 05.03.2018, No: 56). All patients were informed about the aims and the protocol of the study, and written informed consent was obtained.

Transthoracic Echocardiographic Evaluation

All patients underwent the echocardiographical examination, and the left ventricular ejection fraction was calculated using the modified Simpson method. It was performed using a lE33 echocardiography system (Philips Medical Systems, Eindhoven, The Netherlands) with a 3.5 MHz transducer by two experienced operators. The parasternal short- and long-axis, apical four-chamber, and subcostal four-chamber views were used as standard echocardiography. The aortic jet velocity was calculated by Doppler echocardiography. The transvalvular pressure gradient was determined by the Bernoulli formula, and AVA was calculated by the continuity equation. AS was defined as mild if the mean systolic transaortic gradient was <25 mmHg or the jet velocity was <3.0 m/s, moderate if the mean systolic transaortic gradient was 25-40 mmHg or jet velocity was 3.0-4.0 m/s, severe if the mean systolic transaortic gradient was >40 mmHg or jet velocity was >4.0 m/s, and very severe if the jet velocity wasgreater than 5.0 m/sn (15, 16).

Routine Laboratory Examinations

After 12 h of the fasting period, the blood for routine hematologic and biochemical tests was collected. The serum levels of fasting plasma glucose, lipid parameters, creatinine, and the hematological values were determined using the standard methods. The serum albumin and calcium levels were calculated using the COBAS INTEGRA Albumin Gen. 2/cobas c systems (Roche Diagnostics Corporation; Manheim, Germany). We used a reference range 3.5-5.2 g/dL and 8.8-10.2 mg/dL for albumin and calcium tests, respectively. The corrected serum calcium levels were calculated using the most commonly used formula in clinical practice, if the serum albumin level was <4 mg/dL: corrected calcium=measured total calcium (mg/dL) + 0.8 (4.0−serum albumin [g/dL]) (17).

Statistical Analysis

The data collected during the research were analyzed using the Statistical Package for the Social Sciences 15.0 statistical package program (SPSS Inc.; Chicago, IL, USA). Descriptive statistics were depicted as the mean±standard deviation or median (inter-quartile range) for continuous variables, and as the number of cases (n) and percentages (%) for categorical variables. The normality distribution was evaluated using the Kolmogorov-Smirnov test. Baseline characteristics were compared with the independent sample t-test, Mann-Whitney U test, chi-square test, or Fisher's exact test (wherever applicable). Pearson and Spearman's correlation test was used to assess the correlation between calcium, albumin, calcium/albumin ratio, and the mean systolic transaortic gradient and AVA. A logistic regression analysis was used to examine the association between AS, severe AS, and other variables. Variables with a p-value of <0.1 in a univariate logistic regression analysis were included in a multivariate logistic regression model. A p-value <0.05 was considered to be statistically significant.

RESULTS

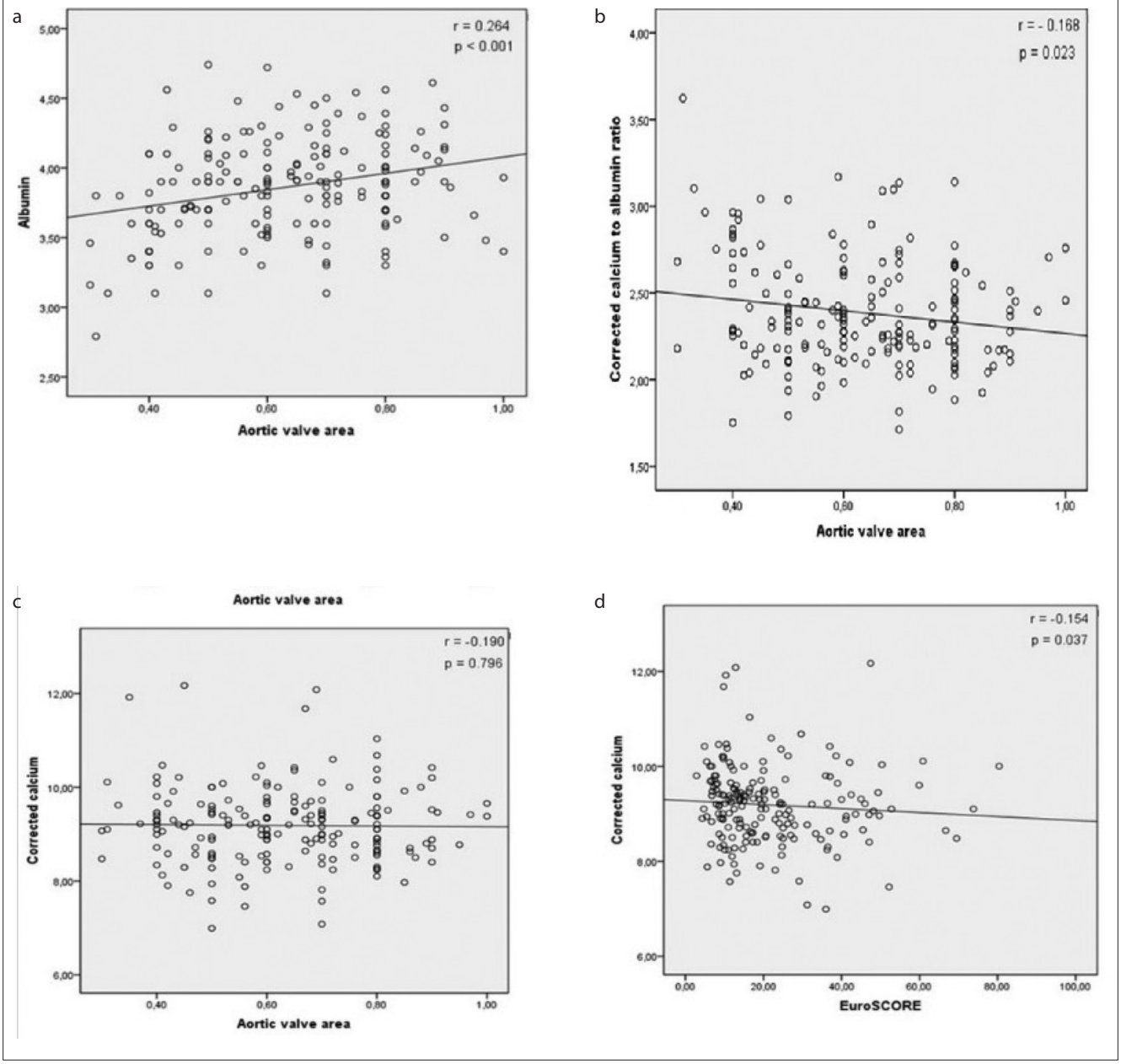
Clinical and demographic characteristics of the study groups are shown in Table 1. Hypertension and diabetes mellitus rates were higher, as expected, in the AS group (n=185) than in the control group (n=108), but there was no statistically significant difference in the subgroup between AS (n=145) and very severe AS group (n=40) (Table 2). The serum C-reactive protein (CRP), calcium, and corrected calcium levels were significantly different between the study groups (p<0.05), but only the serum CRP levels were still found to be significantly higher in the subgroup of AS (p=0.039). In addition, thealbumin level was significantly decreased parallel withthe severity of AS (4.49±0.51 in the control group, 3.90±0.34in the AS group, and 3.69±0.31in the very severe AS group; p<0.001). There was a significant positive correlation between albumin and AVA (r=0.264, p<0.001). Moreover, we did not observe a positive or negative correlation between AVA and neither calcium nor corrected calcium (respectively, r=0.05, p=0.485; and r=−0.190, p=0.796).Also, we detected a negative, but weak correlation between the albumin and corrected calcium levels and the EuroSCORE (Figure 1).

In addition, the calcium to albumin ratio (CAR) and correctedcalcium to albumin ratio (cCAR) were significantly higher in the AS group, as expected (p<0.01). Although the CAR and cCAR were detected as numerically higher in the very severe AS grup than the AS group, they were statistically insignificant (respectively, p-value 0.548 and 0.341). Also, the cCAR was positively correlated with the CRP level (r=0.197, p=0.019) and negatively correlated with AVA (r=−0.168, p=0.023) (Figure 2).

To determine the possible confounding factors for AS, a logistic regression analysis was performed. In the logistic regression analysis,the albumin, CRP, low-density lipoprotein (LDL), CAR, and

Figure 1. a-d. Correlation analysis of (a) serum albumin levels and AVA, (b) serum albumin levels and EuroSCORE, (c) serum calcium levels and AVA, and (d) serum calcium levels and EuroSCORE

AVA: aortic valve area



cCAR were found to be significantly and independently associated with the presence of AS (p<0.05). Moreover, the regression analysis in the AS only subgroup showed that albumin (odds ratio OR, 6.134; 95% confidence interval CI, 1.967-19.136; p=0.001) and cCAR (OR,4.613; 95% CI,0.930-22.876; p=0.0470) and CAR (OR,10.342; 95% CI, 1.252-24.296; p=0.030) were independently associated with the presence of very severe AS (Table 3).

DISCUSSION

The most important finding of our study is that AS is independently correlated with the CAR and albumin levels. To the best of our knowledge, this is the first large-scale study to investigate the association between the CAR and AS. We demonstrated that the CAR was significantly higher in patients with severe AS than in control subjects. Also, the CAR had a significantly positive correlation with CRP and negative correlation with AVA. Besides, we showed that the lower albumin levels and a higher CAR were also independently associated with the presence of very severe AS.

Aortic stenosis is a chronic disease thatshares similarities with atherosclerotic CAD, such as mechanical stress, chronic inflammation, calcification, and lipid deposition on valvular leaflets (2, 18). Being a commonly used and an importantmarkerof inflammation, it has been demonstrated that CRP levels are increased

Table 1. Baseline characteristics and laboratory parameters of the study groups

Variables	Control Group (n=108)	Aortic Stenosis (n=185)	p
Age, (years) (mean±std)	77.87±7.53	76.37±6.02	0.079
Hypertension, n (%)	45 (41.6)	143 (77.3)	<0.001
Diabetes mellitus, n (%)	10 (9.2)	59 (31.8)	<0.001
Creatinine, mg/dL, mean±std	0.84±0.21	0.97±0.4	0.06
LDL-C, mg/dL, (median-IQR)	119 (37-236)	100 (31-358)	<0.001
HDL-C, mg/dL, (median-IQR)	45 (23-80)	46 (12-103)	0.842
Triglyceride, mg/dL, mean±std	141 (34-584)	102 (30-511)	<0.001
CRP, (median-IQR)	3.61 (0.8-16)	4.62 (1.1-37)	0.042
Calcium (mg/dL) (median-IQR)	9.0 (6.91-12.17)	9.52(8.30-10.40)	<0.001
cCalcium (mg/dL) (median-IQR)	9.19 (6.9-12.17)	9.52 (8.5-10.40)	<0.001
Albumin (gr/dL) (mean±std)	4.49±0.51	3.88±0.35	<0.001
Calcium/albumin ratio	2.12±0.18	2.33±0.26	<0.001
Corrected calcium/albumin ratio	2.12±0.19	2.38±0.31	<0.001
LVEF, %, (mean±std)	61.46±4.64	53.07±14.30	<0.001
Maximum gradient,mmHg	-	82 (36-187)	-
Mean gradient, mmHg	-	49 (20-114)	-
Aortic valve area (cm^2), (median-IQR)	-	0.64 (0.30-1.0)	-
Logistic EuroSCORE (%)	-	16.54 (2.86-60)	-
Society of Thoracic Surgeons score (%)	-	5.7 (1.20-31.2)	-

CAD: coronary artery disease; cCalcium: corrected calcium; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; WBC: white blood cell

Figure 2. a, b. Correlation analysis of (a) cCAR and CRP, and (b) cCAR and AVA
AVA: aortic valve area; CRP: C-reactive protein; cCAR; corrected calcium to albumin artio

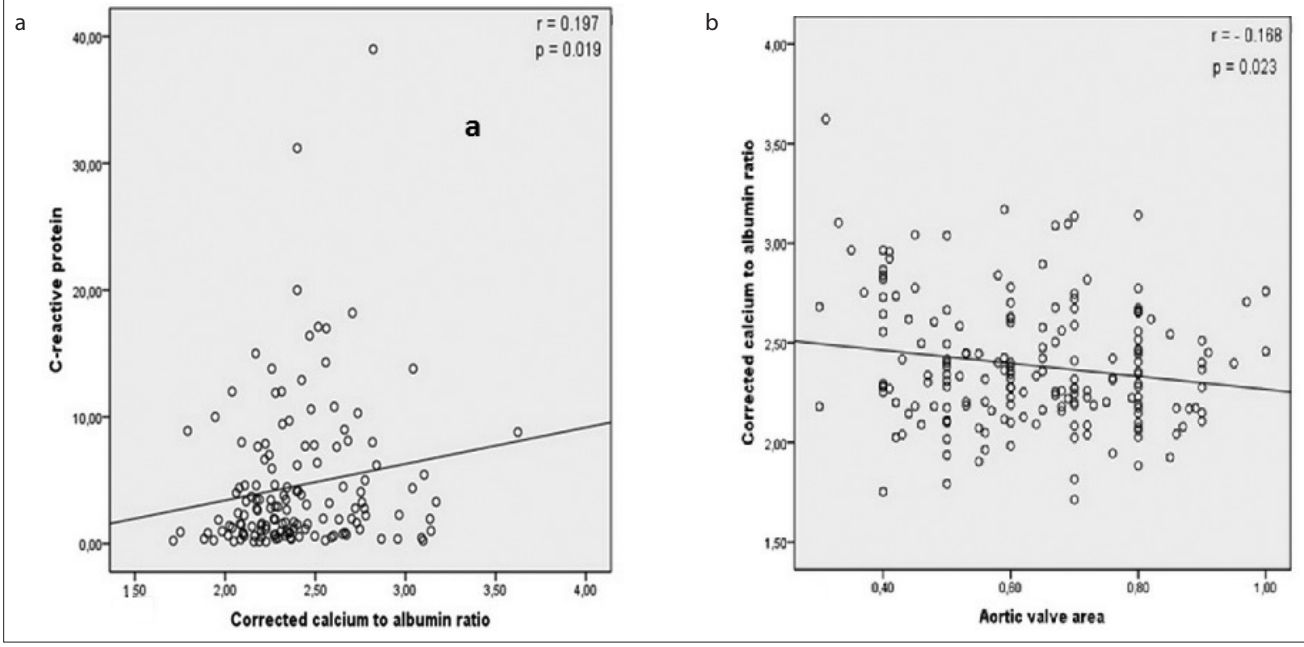


Table 2. Comprasion of baseline characteristic of severe and very severe aortic stenosis

Variables	Severe Aortic Stenosis (n=145)	Very Severe Aortic Stenosis (n=40)	p
Age, (years) (mean ±std)	77.68±7.47	78.55±7.78	0.532
Hypertension, n (%)	110 (75.8)	33 (82.5)	0.254
Diabetes mellitus, n (%)	13 (32.5)	46 (145)	0.534
Creatinine, mg/dl, (median–IQR)	0.93 (0.39–1.44)	0.89 (0.4–1.5)	0,351
LDL–C, mg/dl, (median–IQR)	98.58 (36.2–358)	103.10 (31.1–165)	0.644
HDL–C, mg/dL, (median–IQR)	46 (12–103)	47.5 (16–76)	0.765
Triglyceride, mg/dL, mean±std	102 (30–511)	99.5 (34–295)	0.999
CRP, (median–IQR)	4.3 (0.17–20)	5.79 (0.24–30)	0.039
Calcium (mg/dL) (median–IQR)	9 (7–12.17)	8.91 (6.91–11.36)	0.182
cCalcium (mg/dL) (median–IQR)	9.2 (7.08–12.17)	9.16 (6.99–11.92)	0.435
Albumin (gr/dL) (mean±std)	3.90±0.34	3.69±0.31	<0.001
Calcium/albumin ratio (mean±std)	2.33±0.25	2.36±0.33	0.548
Corrected calcium/albumin ratio (mean±std)	2.37±0.28	2.43±0.40	0.341
LVEF, %, (mean±std)	51.35±15.38	59.30±6.41	0.002
Maximum gradient, mmHg	77 (36–105)	132.5 (87–187)	<0.001
Mean gradient, mmHg	45 (20–64)	72 (58–114)	<0.001
Aortic valve area (cm^2), (median–IQR)	0.66±0.15	0.47±0.10	<0.001
Logistic EuroSCORE (%)	21.57±15.43	21.77±13.61	0.944
Society of Thoracic Surgeons score (%)	7.12±4.73	6.24±3.38	0.271

CAD: coronary artery disease; cCalcium: corrected calcium; CRP: C–reactive protein; HDL: high–density lipoprotein; LDL: low–density lipoprotein; LVEF: left ventricular ejection fraction; WBC: white blood cell

in patients with degenerative AS, such as atherosclerotic heart disease (19). A later study revealed that CRP levels measured at intervals in patients with asymptomatic AS playeda prognostic role in the severity, progression, and clinical outcomes of the disease. In the same study, it was also reported that long-term survival rates are lower in AS characterized byhigh CRP levels (20). Another important marker of chronic inflammation is albumin, which use has been recommended in clinical practice in recent years as it shows the fragility of AS patients (9, 10). Serum albumin, a negative acute-phase protein, is insufficiently produced by the liver during inflammation (13). Similarly, several other studies established that low albumin levels were related to an increased risk of cardiovascular mortality and morbidity (21). In their study that includedpatients who underwent TAVI for AS, Yamamoto et al. (22) detected higher all-cause and cardiovascular mortality rates after the procedure and during their 1-year follow-up in individuals whose pre-procedure albumin value was <3.5 mg/dL. Another striking point in this study is that the log EuroScore and the The Society of Thoracic Surgery Risk Score STS were considerably higher in the group with low albumin levels. However, different from our study, the peak velocity and the mean aortic gradient werefound to be higher in the group with high albumin levels, and the valvular area was observed to be comparable between both groups (22). In a study by Koifman et al. (23), while mean aortic gradients were found to be comparable in individuals with a low serum albumin level, AVA was found to be smaller in the group with a low albumin level. In their study, Bogdan et al. (9) have observed comparable mean and maximal aortic gradients and AVAs between the groups with low and high albumin levels. In our study, while the albumin level was negatively correlated with the mean and maximal aortic pressure, a positive correlation was observed with AVA. Recently, the Valve Academic Research Consortium committee hassuggested adding the"fragility"status of patients to classical pre-operative risk factors in patients treated for AS (10, 24). Aserum albumin level <3.5 g/dL has been accepted as a fragility indicator according to these criteria (10, 24).

Additionally, albumin is the most important transporter of calcium in the blood. Forty percent of calcium is transported as albuminbound. Therefore, for an exact assessment of the total calcium level in the blood, albumin levels should be also known

Table 3. Logistic regression analysis of predictive factors for AS

Variables	Odds Ratio (OR)	95% Confidence Interval for OR	p
Calcium (mg/dL)	1.315	0.833–2.075	0.240
cCalcium (mg/dL)	1.321	27.065–219.1	0.224
Albumin (gr/dL)	2.263	1.180–4.233	0.016
Corrected calcium/ albumin ratio	0.010	0.002–0.049	0.001
Calcium/albumin ratio	0.011	0.003–0.051	0.001
CRP (mg/dL)	0.991	0.899–1.093	0.042
LDL (mg/dL)	1.013	1.005–1.021	0.022

Logistic regresionanalysis of predictive factors for very severe aortic valve stenosis
in patients with severe aortic stenosis

Variables	Odds Ratio (OR)	95% Confidence Interval for OR	p
Calcium(mg/dL)	1.121	0.705–1.782	0.630
cCalcium (mg/dL)	1.189	0.749–1.887	0.462
Albumin (gr/dL)	6.134	1.967–19.136	0.001
Corrected calcium/ albumin ratio	4.613	0.930–22.876	0.047
Calcium/albumin ratio	10.342	1.252–24.296	0.030
CRP (mg/dL)	1.025	0.951–1.105	0.514
LDL (mg/dL)	0.999	0.989–1.008	0.817

*Values set in bold indicate p<0.05

(14). Calcific vascular and valvular heart diseases are known to have several characteristics in common with bone structure remodeling. Therefore, studies have been conducted showing the relationship between AS and theparathyroid hormone (PTH) and Vitamin D levels, which are the main actors of serum calcium, and the phosphorus levels and bone metabolism, which are the main components of the bone structure. In their study, Akat et al. (7) found higher calcium levels in patients withAS without CAD and with normal renal functions than in healthy individuals. Also, in the same study, it was observed that the ratio of the calcium level and the Vitamin D level to PTH washigher in patients with AS. In their study, again in individuals with normal renal functions, Linhartová et al. (25) detected higher serum PTH levels and lower Vitamin D levels in patients with AS. In the same study, while serum calcium levels showed a trend toward being higher, thisdid not reach statistical significance. At the end of this study, the authorsconcluded that the disregulation in the calcium and phosphate metabolism may be effective in the pathogenesis of AS (p=0.06). In AS patients, Yang et al. (26) found higher calcium, phosphate, alkaline phosphatase, PTH, and osteocalcin levels, which are important markers of the bone structure mineral turnover in the blood. Furthermore, a study in patients who used a regular calcium treatment did not detect progression in the aortic valve calcification on computerized tomographic assessment during a 4-year follow-up (27).

Albumin is quantitatively the most important plasma protein, and the synthesis and serum concentrations are regulated by a variety of factors. The decrease inalbumin levels reflects a variety of conditions, including malnutrition, systemic inflammation, heart failure, and hepatic and renal pathologies, and it is known that among patients with chronic diseases, including heart disease, lower serum albumin levels correlate with poor outcome (28, 29). Given that AS is also a chronic disease and, as mentionedabove, is an inflammatory process, low albumin levels in patients canbe expected. Considering that albumin is the most important transporter protein of calcium ions, assessing the albumin-corrected calcium levels during the blood calcium level measurement is important as it shows true calcium levels in this patient population. For the purposes of associating with chronic disease states, indicating albumin-corrected calcium levels may be more reasonable. It has been demonstrated that elevated calcium levels and the higher CAR emerged as novel parameters andwere strongly associated with all-cause mortality in patients with stable CAD. It can be assumed that the results of this study support our findings. However, more data are required to confirm the association between the all-cause mortality and the CAR in patients with AS (30). In daily practice, however, its measuring using an equation may be forgotten. In these patients, a simple CAR may be more important as it shows both the level of AS and inflammation state.

Our study has a few limitations. First, it is a single-center study with a retrospective design. The fact that Vitamin D and PTH levels, which are known to have an effect on calcium metabolism, were not studied in patient groups is an important drawback. Another important limitation is the low number of patients included into the study and the lack of patients with mild and moderate AS. Also, the fact that the serum calcium phosphate levels and phosphate levels were not studied may be considered as a drawback. Furthermore, the fact that only one serum level was studied in patients, that the mean of work-ups within the year was not used, and that other inflammation markers (interleukins, fibrinogen, etc.) were not studied may also be considered as limitation.

CONCLUSION

The present study detected an important relationship between the CAR and the severity of AS. We also detected itscorrelation with CRP and that it wasan important inflammation marker. Consequently, the CARthat emerged as a novel parameter can be calculated using simple biochemistry tests in daily practice andcould benefit other techniques for determining the severity of AS. Larger studies on this subject are needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yıldırım Beyazıt University (Date: 05.03.2018, No: 56).

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.S., Y.A.; Design - Y.A.; Supervision - E.B.; Data Collection and/or Processing - S.S., S.B.; Analysis and/or Interpretation - Y.A., H.A.; Literature Search - Y.A., S.S.; Writing Manuscript-Y.A.; Critical Review - E.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

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