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RESEARCH

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Correlation between staging classification of aortic stenosis based on the extent of cardiac damage and platelet indices

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Abstract

Background Platelets play a key role in the natural history of aortic stenosis (AS) and after transcatheter aortic valve implantation (TAVI). An echo-based staging system stratifies patients with severe AS into 5 groups according to the associated cardiac damage phenotype. We aimed to correlate these AS stages with platelet indices in post-TAVI patients.

Methods Patients with severe AS who underwent TAVI and were admitted to intensive cardiac care unit (ICCU) were prospectively identified and divided into 5 groups according to extra-valvular cardiac damage [no extravalvular cardiac damage (Stage 0), left ventricular damage (Stage 1), left atrial or mitral valve damage (Stage 2), pulmonary vasculature or tricuspid valve damage (Stage 3), or right ventricular damage (Stage 4)]. Baseline characteristics and complete blood count including mean platelet volume (MPV) and immature platelet fraction (IPF) were collected within 2 h after the procedure and analyzed in relation to aortic stenosis staging.

Results A total of 220 patients were included. The mean age was 81 years old and 112 (50.9%) were female. Two (1%) patients were classified in stage 0; 34 (15%) in stage 1; 48 (22%) in stage 2; 49 (22%) in stage 3 and 87 (40%) in stage 4. Higher mean MPV values were correlated with higher AS staging (10.8 fL, 11 fL, 11.3 fL and 10.8 fL in stages 1, 2, 3 and 4, respectively, $P=0.02$) as well as lower hemoglobin values (12 mg/dl, 11.6 mg/dl, 11 mg/dl and 11.3 mg/dl in stages 1, 2, 3 and 4, respectively $P=0.04$). Mean IPF values were 5.3%, 5.58%, 5.57% and 4.83% in stage 1, 2, 3 and 4, respectively ($P=0.4$). In a multivariate logistic regression model only MPV (OR = 2.6, $P=0.03$) and body mass index (BMI) (OR = 1.17, $P=0.004$) were correlated with higher staging (0–3) of AS.

Conclusions Although IPF and MPV levels increased in stages 0–3, there was a decrease in indices in stage 4, (probably due to bone marrow dysfunction) in this end-stage population. Higher levels of MPV and lower levels of hemoglobin were independently correlated with higher stages (0–3) of AS.

Keywords Aortic stenosis, TAVI, IPF, MPV

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Introduction

Aortic stenosis (AS), estimated to affect 3–5% of the elderly population in the western world, is characterized by progressive calcium deposition within the aortic valve that ultimately leads to leaflets deformation and a gradual reduction in orifice area [1]. Untreated symptomatic severe AS has significant morbidity and high mortality [2]. Unfortunately, there is no effective therapy to attenuate disease progression and aortic valve replacement remains the definitive treatment [3]. Until recently, surgical valve replacement was the standard of care for the treatment of symptomatic severe AS. However, since its introduction in 2002, transcatheter aortic valve implantation (TAVI) has emerged as an effective and less invasive alternative [4].

In recent years, growing evidence has revealed an important role of platelets in the natural history of aortic valve disease. The high shear stress and turbulent flow induced by a stenotic valve promote the local activation of the endothelium, which triggers and stimulates circulating thrombocytes. In turn, activated platelets amplify endothelial dysfunction which creates a self-perpetuating vicious cycle [5]. Initially, activated platelets are involved in the pathogenesis of aortic valve mineralization and calcification. Subsequently, platelets activation and dysfunction may contribute to the bleeding tendency seen in up to 20% of patients with AS [6]. After valve replacement, triggered thrombocytes may play a key role in bioprosthetic valve thrombosis and potentially in bioprosthesis failure [7].

Platelet size has been shown to correlate with platelet activity. Larger platelets are prothrombotic with a higher tendency for adhesion and aggregation than smaller platelets. Thus, platelet indices such as mean platelet volume (MPV) and immature platelet fraction (IPF) are useful indirect markers of platelet activation in the setting of cardiovascular disease [8–14]. Increased platelet dimensions are seen in a range of valvular heart diseases including mitral stenosis [15], bicuspid aortic valve disease [16], aortic valve sclerosis [17], AS [18], and bioprosthetic valve dysfunction [7]. Furthermore, altered platelet indices are associated with adverse outcomes in patients with cardiac diseases [8, 19, 20], including after TAVI [21–23].

An echocardiographic classification system for risk assessment in severe AS was recently introduced that stratifies patients into 5 groups (stages 0–4) according to the extent of cardiac damage resulting from chronically increased afterload [24]. Importantly, this staging system has prognostic implications including cardiac death and all-cause death for patients after aortic valve replacement [24]. The aim of the current study was to analyze platelet indices across the five stages of severe AS in patients who underwent TAVI.

Methods

Study population

The study was a prospective single-center cohort study at the Shaare Zedek Medical Center, a tertiary referral hospital and one of the two largest medical centers in Jerusalem.

AS Staging

All patients underwent transthoracic echocardiography before the procedure. Patients were categorized into 5 independent groups (Table 1) according to cardiac damage staging [24]: Stage 0—no cardiac damage; Stage 1—left ventricular (LV) damage defined as the presence of LV hypertrophy (LV mass index > 95 g/m^2 for women and > 115 g/m^2 for men), and/or diastolic dysfunction (E/e' > 14), and/or systolic dysfunction (LV ejection fraction < 50%); Stage 2—left atrial or mitral valve damage defined as left atrial dilation (indexed volume > 34 ml/m^2) and/or ≥ at least moderate mitral regurgitation and/or atrial fibrillation; Stage 3—pulmonary vasculature or tricuspid valve damage defined as systolic pulmonary hypertension ≥ 60 mmHg and/or ≥ moderate tricuspid regurgitation; and Stage 4—right ventricular (RV) damage defined as at least moderate RV systolic dysfunction [tricuspid annulus plane systolic excursion (TAPSE) < 17 mm] and tricuspid annulus velocity S' < 9.5 cm/s, and severe low-flow stroke volume index (< 30 ml/m^2). Due to the low number of patients in the 0-staging group in our patient population, group 0 and 1 were merged to stage 1.

Inclusion criteria

Patients with severe symptomatic AS who underwent TAVI and were admitted to a tertiary care center ICCU between August 2022 – May 2023 were enrolled and followed through July 2023.

Exclusion criteria

Patients with hematological disorders including myelodysplastic syndrome, severe anemia with hemoglobin values < 8 g/dL, platelet count < 80,000/μ, hematological malignancies, and patients who received recent (< 3 months) blood transfusions were excluded from the study.

Blood count parameters and Platelet Indices

Whole blood samples for complete blood count (in tripotassium ethylenediaminetetraacetic acid–anticoagulated blood) including MPV and IPF were drawn within 2 h after the procedure from peripheral venous blood. Blood samples were analyzed with Sysmex XN-2000 automated hematology analyzer (Sysmex, Kobe, Japan). IPF was measured by PLT-F (fluorescence) channel.

Table 1 Cardiac damage staging in patients with severe aortic stenosis

	Stage 0 No cardiac damage	Stage 1 LV damage	Stage 2 LA or MV damage	Stage 3 Pulmonary or TV damage	Stage 4 RV or RA damage
TTE	None	LV hypertrophy (LV mass index > 95 g/m^2 for women and > 115 g/m^2 for men), diastolic dysfunction (E/e'> 14), and/or systolic dysfunction (LVEF < 50%)	left atrial dilation (indexed volume > 34 ml/m^2) and/or ≥ moderate mitral regurgitation and\or atrial fibrillation	systolic pulmonary hypertension ≥ 60 mmHg and/or ≥ moderate TR	at least moderate RV systolic dysfunction: TAPSE < 17 and tricuspid annulus velocity S' < 9.5 cm/s

LV Left ventricle, *LVEF* Left ventricular ejection fraction, *LVEDP* Left ventricular end diastolic pressure, *LA* Left atrium, *MV* Mitral valve, *PA* Pulmonary artery, *TV* Tricuspid valve, *TR* Tricuspid regurgitation, *PVR* Pulmonary vascular resistance, *RV* Right ventricle, *TTE* Transthoracic echocardiography, *TAPSE* Tricuspid annulus plane systolic excursion, *RA* Right atrium

Measurements were performed according to the manufacturer's protocols.

The values of MPV and IPF were determined for every patient and mean MPV and IPF were then calculated for every AS staging severity group and were subsequently compared between the 4 groups (Fig. 1).

All patients received at least a single antiplatelet agent, generally aspirin, post procedure.

Data were checked for accuracy and out-of-range values by the study coordinator. Demographic data, presenting symptoms, ECG, comorbid conditions, and physical examination were systematically recorded. Laboratory, imaging, procedural results, and clinical data were collected as well. Data were anonymously documented in an electronic case report form (eCRF). Patients were followed-up up to 12 months.

Ethics and consent

This study complied with the Declaration of Helsinki and has been approved by the Shaare Zedek Medical Center Institutional Review Board (IRB) (IRB protocol number 0310–22-SZMC). Consent was deemed unnecessary according to national regulations.

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Statistical analysis

Patients' characteristics were presented as numbers (%) for categorical variables, means (SD) for normal distributed and medians (IQR) for non-normal distributed continuous variables. Comparison of categorical variables was done by Chi-squared test and Fisher's exact tests. For comparison of normally and non-normally distributed continuous variables, Student T-Test and Mann–Whitney tests were performed, respectively. Differences between the four AS groups were analyzed using one-way ANOVA for continuous variables that were normally distributed, while the Kruskal–Wallis test was used to compare continuous variables that did not adhere to a normal distribution. Multiple comparisons for continuous and categorical variables were tested using Bonferroni's correction. Survival curves were plotted, and the Kaplan–Meier log rank test was used to test the correlation of AS stage on mortality.

Stepwise logistic regression was performed to derive an equation that predicts AS staging. All the baseline characteristics that had a significant univariate association with AS staging were eligible for inclusion. The final model was adjusted for age, gender, various cardiac risk factors, co-morbidities, and platelet activity variables (IPF, MPV). Standard estimates were used to calculate odds ratios (ORs) and 95% CIs for each independent predictor. All tests were two-sided. $P<0.05$ was considered statistically significant. Analyses were carried out using R software, Version 4.2.0 (R Foundation for Statistical Computing.

Results

Patient characteristics

Two hundred and twenty consecutive patients were enrolled. The mean age was 81 years old and 112 (50.9%) were females. Patient distribution in each staging

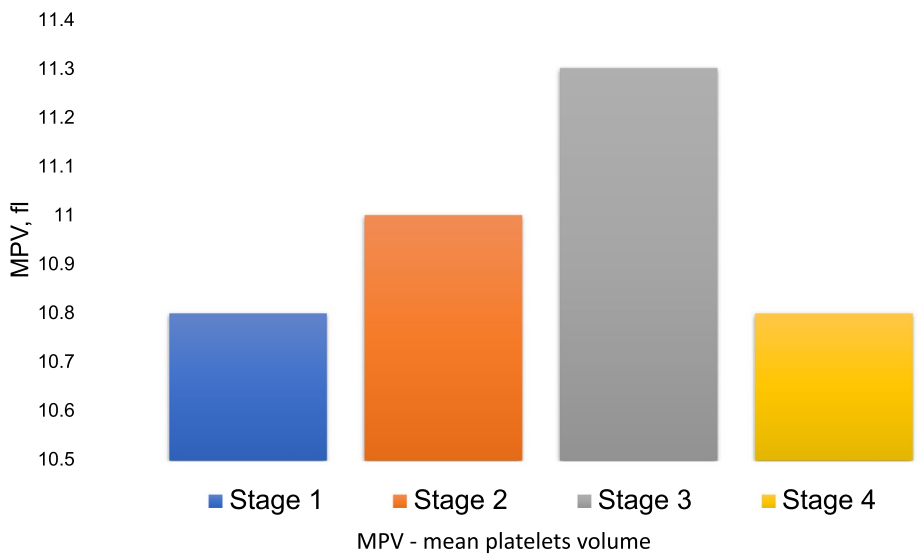

Fig. 1 MPV according to stage

category was as follows: 2 (1%) patients in stage 0; 34 (15%) in stage 1; 48 (22%) in stage 2; 49 (22%) in stage 3 and 87 (40%) in stage 4. Due to the low numbers of patients in stage 0, stages 0 and 1 were merged to stage 1.

One hundred and seventy-three (79%) patients had hypertension, 117 (53%) had dyslipidemia, and 88 (40%) had diabetes mellitus (DM). Patient characteristics are presented in Table 2.

Platelet indices

Mean MPV values were 10.8 fL, 11 fL, 11.3 fL and 10.8 fL in AS stages 1, 2, 3 and 4, respectively, ($P=0.02$) (Fig. 1).

Mean IPF values were 5.3%, 5.58%, 5.57% and 4.83% in AS stages 1, 2, 3 and 4, respectively ($P=0.4$). Hemoglobin values were 12 mg/dl, 11.6 mg/dl, 11 mg/dl and 11.3 mg/dl in AS stages 1, 2, 3 and 4, respectively, and were correlated with higher AS staging in stages 0–3 ($P=0.04$).

Multivariate logistic regression

In a multivariate logistic regression model [including age, sex, body mass index (BMI), hypertension, DM, dyslipidemia, anemia] only MPV levels (OR = 2.6 ± 0.33, $p=0.03$) and BMI (OR = 1.17 ± 0.55, $p=0.004$) associate with higher staging of AS (Table 3).

Mortality rate

During the follow-up period, mortality rate within each stage were 13.9% (5/36), 14.6% (7/48), 18.4% (9/49) and 25.3% (22/87) for stages 0 and 1, stage 2, stage 3 and stage 4, respectively. Kaplan Meier survival analysis demonstrated that the cumulative probability of death at 12 months follow-up was 8.1 ± 4.5%, 8.4 ± 5.4%, 16.6 ± 5.7%, and 22.7 ± 4.9% for each group respectively. Unadjusted Cox model demonstrated that patients with AS stage 4 were 1.8 times more likely to die compared to patients in stages 0–3 (HR 1.78 95% CI 0.98 – 3.24, $p=0.056$) (Fig. 2).

Table 3 Multivariate analysis

	OR	*P*-value
Age	1.07 ± 0.03	0.86
Sex	0.79 ± 0.49	0.62
BMI	1.17 ± 0.55	**0.004**
HTN	2.13 ± 1.84	0.21
Dyslipidemia	1.48 ± 0.48	0.51
Diabetes mellitus	1.18 ± 0.51	0.44
Hemoglobin	0.5 ± 0.2	0.21
MPV	2.6 ± 0.33	**0.03**

BMI Body mass index, *HTN* Hypertension, *MPV* Mean platelets volume

Discussion

In the present study we sought to evaluate the correlation between platelet reactivity indices and AS severity, based on the extent of the associated cardiac damage determined by an echocardiographic staging system. Our main findings were: 1) MPV levels correlate with higher AS stages; 2) the correlation between MPV levels and AS stages was not linear and decline at stage 4 AS, and 3) as expected, stage 4 AS was associated with the highest mortality rate. To our knowledge, this is the first study to describe the relationship between the grade of AS-induced cardiac damage and higher platelets indices.

The higher degree of platelet activation, evidenced by higher platelet indices seen in the cohort of patients with greater AS severity is somewhat expected. Previous studies have demonstrated that platelet reactivity is increased in patients with aortic stenosis, as a part of the pathophysiology of the disease [5, 23]. In-vitro studies have demonstrated that as stenosis severity progresses,

Table 2 Baseline* patient characteristics

	Stages 0 + 1 *N* = 36	Stage 2 *N* = 48	Stage 3 *N* = 49	Stage 4 *N* = 87	*P*-value
Age, mean	78.4 ± 7.04	79.9 ± 6.92	81.4 ± 8.31	81.7 ± 8.2	0.138
Sex (female)	19 (52.8%)	22 (45.8%)	28 (57.1%)	43 (49.4%)	0.709
BMI	26.5 ± 4.8	27.7 ± 4.94	27.6 ± 6.78	28.2 ± 5.35	0.491
Hypertension	26 (72.2%)	34 (70.8%)	42 (85.7%)	71 (81.6%)	0.209
Dyslipidemia	20 (55.6%)	24 (50%)	23 (46.9%)	50 (57.5%)	0.64
Diabetes mellitus	12 (33.3%)	23 (47.9%)	15 (30.6%)	38 (43.7%)	0.24
Hemoglobin[a] (mg/dl), mean	12 ± 1.46	11.6 ± 1.8	11 ± 1.62	11.3 ± 1.78	**0.04**
PLT[a], mean	201 ± 72.3	194 ± 87.1	188 ± 79.2	202 ± 82.6	0.792
MPV[a] (fl), mean	10.8 ± 1.17	11 ± 1.01	11.3 ± 0.982	10.8 ± 0.946	**0.02**
IPF[a] (%), mean	5.3 ± 3.26	5.58 ± 3.19	5.57 ± 2.54	4.83 ± 2.86	0.397

[a] Baseline blood samples for complete blood count, including MPV and IPF, were drawn within 2 h after the procedure

BMI Body mass index, *PLT* Platelets, *MPV* Mean platelets volume, *IPF* Immature platelets fraction

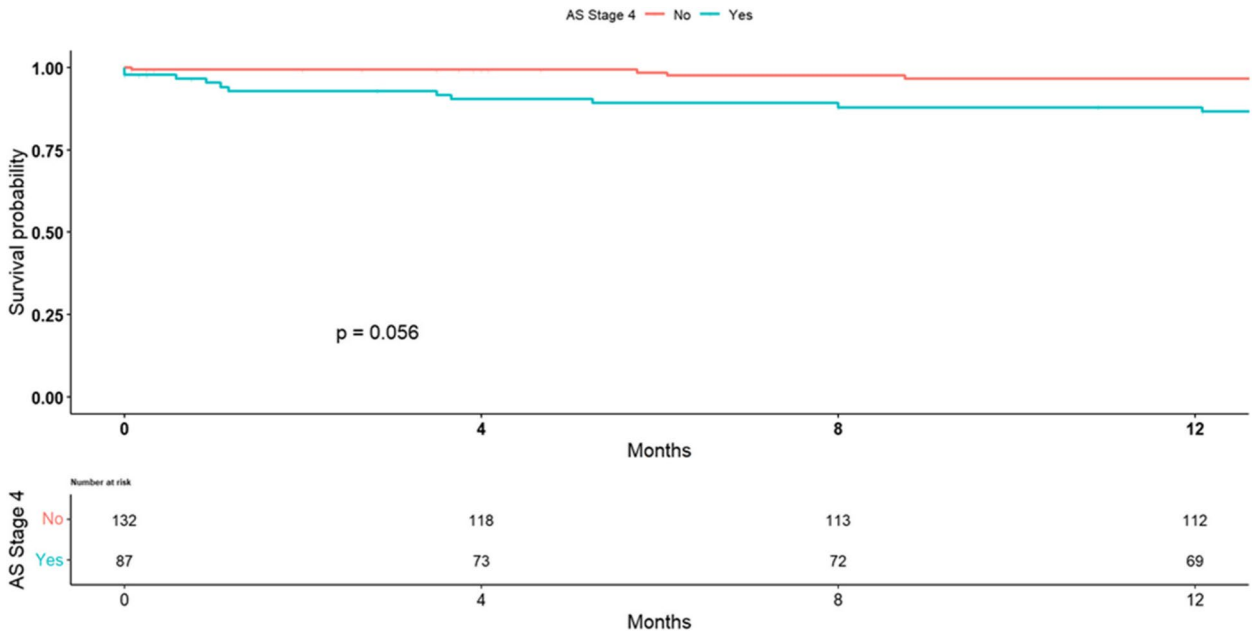

Fig. 2 Unadjusted Cox model survival in patients with severe AS stage 4

shear stress across the valve substantially increases and further promotes platelet activation and valvular damage [25, 26]. Likewise, animal models of AS have shown that higher levels of shear stress, are correlated with increased platelet activation [26]. However, no difference in baseline platelets indices were noted in patients with severe AS and peak pressure gradient > 100 mmHg when compared to patients with severe AS and peak pressure gradient < 100 mmHg. In contrast, when platelets indices are monitored before and after aortic valve replacement, an initial post-procedural increase in platelets dimensions is followed by a significant decrease when compared to pre-procedural dimensions [27].

In our analysis IPF values gradually increased from stage 1 to 3 and remained low in stage 4. However, these differences were not statistically significant. In contrast, a significant change between stages in MPV values were noted. In a multivariate analysis evaluating multiple variables, only MPV levels and BMI were correlated with higher stage of AS (Table 3).

As predicted, hemoglobin levels were highest in patients who had less cardiac damage and lowest in patients with more extensive cardiac remodeling. In contrast, mean platelet count remained relatively unchanged. These findings are in accordance with previously published data regarding the interaction of heart failure and bone marrow function. Cardiac insufficiency alters the bone marrow composition, adversely affects hematopoiesis potential, and impairs cellular responses to injury [28]. Not surprisingly, the extent of bone marrow dysfunction is related to the severity of heart failure [29]. Chronic low-grade inflammation, endothelial and microvasculature dysfunction, and the presence of circulating hematopoiesis inhibitory factors, alone or in combination, are the potential culprits. However, the exact mechanism of bone marrow dysfunction in heart failure remains unclear [29, 30]. Hence, the low platelet indices and hemoglobin levels documented in our analysis may be explained, at least in part, by the bone marrow dysfunction characteristic of the more advanced heart failure state, although this hypothesis remains speculative.

Finally, we noted increased mortality rate in patients with advanced cardiac damage. These findings are in accordance with the data published by Tastet and Généreux that reported a stepwise increase in mortality rates according to AS severity stage, regardless of the presence of symptoms. Notably, for each stage increment, 1-year mortality risk increased by ~45% [24, 31].

In our study, patients assigned a AS stage 4 were 1.8 times more likely to die at 1.5-year follow-up as compared with patients in stages 0–3 (Fig. 2).

The present study has several limitations. First, we did not include an extended follow-up of platelet indices. A longer period of monitoring could have potentially showed the effect of valve replacement on platelet indices. Furthermore, we did not include pre-procedure platelet index values. However, since blood for analysis was drawn shortly after the procedure, we believe that the change in platelet morphology between the pre- and the post-procedure are insignificant. Second, patients

were not stratified according to vascular access (i.e., trans-femoral vs. alternative access). Alternative TAVI access is usually associated with severe peripheral vascular disease and confers higher risk and poorer outcomes. Finally, pre-procedural factors that could affect platelets morphology and hemoglobin levels such as genetic factors, lifestyle, inflammation, and medications were impossible to fully accounted for.

Conclusion

Higher levels of MPV and lower levels of hemoglobin evidenced shortly after TAVI were correlated with higher preprocedural stages of AS severity. Although IPF and MPV levels increased in stages 1–3, there was a decrease in platelet dimensions in stage 4, probably due to combination of increased shear stress and platelets consumption, and bone marrow dysfunction likely present in this population with more advanced disease. Additional evidence is still needed to determine the correlation between platelet indices and AS severity stages of cardiac damage. These data may contribute to the risk stratification process of patients with severe AS and cardiac dysfunction.

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Clinical trial
Number – NA.

Authors' contributions
T.M, S.B - Wrote the main manuscript. R.L, G.B.Z- Statistics. S.C, L.T- Acquisition and analysis. P.S, M.G - Tables and Figures. L.S, D.D, M.S - Drafted the work. R.J, D.M – Analysis. N.P, N.L, I.A, R.H, M.S - Data collection. M.G, E.A - Resvised the manuscript . All authors reviewed the manuscript

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Data availability
Sequence data that support the findings of this study have been deposited in the Shaare Zedek Medical center.

Declarations

Ethics approval and consent to participate
This study complied with the Declaration of Helsinki and has been approved by the Institutional Review Board (IRB) at the Shaare Zedek Medical Center (IRB protocol number 0310–22-SZMC).

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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