Srce i krvni sudovi 2025; 44(3) : 47-54

Case report

Sex-Dependent Differences in Clinical and Echocardiographic Parameters in Asymptomatic Patients with Hemodynamically Significant Aortic Stenosis

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Abstract

Introduction: Aortic stenosis (AS) is the most common valvular disease in developed countries, and its course and clinical presentation can significantly vary depending on the patient's gender.
The aim of this study was to identify sex-specific differences in morphological, functional, and prognostic characteristics in asymptomatic patients with hemodynamically severe AS. Methods: This retrospective observational study included 116 patients (50 female and 66 male) with asymptomatic severe AS (AVA < 1.5cm², V_{max} > 3.5 m/s, P_{mean} > 30 mmHg). All participants underwent transthoracic echocardiography, and morphological, functional, and hemodynamic parameters were analyzed, as well as patterns of left ventricular remodeling and diastolic function. Patients were followed for 24 months, and predictors of mortality and major adverse cardiovascular events (MACE) were evaluated.
Results: Male had larger dimensions and volumes of the left ventricle, while female exhibited more pronounced transmitral flows and a higher cardiac index. The indexed aortic valve area (AVAi) was the most significant predictor of mortality in male. Survival during follow-up was low in both groups, with no statistically significant difference between sexes. However, a trend toward shorter survival was observed in female.
Conclusion: Although male and female with severe AS have a similar hemodynamic profile, they differ in patterns of remodeling and functional adaptation. Clinical management should be sex-specific, focusing on structural changes in male and on functional parameters and symptoms in female, in order to timely identify high-risk patients and optimize the timing of intervention.

Key-words aortic stenosis, sex differences, echocardiography, remodeling, survival

Introduction

Aortic stenosis (AS) is the most common valvular heart disease in developed countries, with a rising prevalence due to population aging[1]. Severe AS occurs in approximately 3–4% of individuals over the age of 75–80, while some degree of AS is present in more than 10% of elderly individuals[1]. In older patients, the most frequent cause is degenerative calcification of the aortic valve, whereas in younger individuals, the primary etiology is congenital bicuspid aortic valve (prevalence ~1%), which is 3–4 times more common in male[2,3]. Consequently, younger patients with AS are predominantly male, while female comprise the majority of patients with severe AS in advanced age[2,3].
AS typically has a prolonged asymptomatic course: the valve gradually undergoes fibrosis and calcification, narrowing the orifice. Symptoms (angina, syncope, dyspnea) emerge only in the stage of severe stenosis, marking the transition to a high-risk phase of the disease. Without valve replacement, prognosis is extremely poor—annual mortality exceeds 30%, and about half of patients with angina or syncope die within ~5 years, while those with signs of heart failure have an average life expectancy of ~2 years[4].
Asymptomatic severe AS has a more favorable short-term prognosis, but it is not without risk: sudden cardiac death occurs in ~1% annually, and many patients develop symptoms within a few years[4]. Guidelines therefore recommend close monitoring of such patients (follow-up visits and echocardiography every 6–12 months)[2]. Traditionally, intervention was deferred until symptom onset or decline in systolic function (ejection fraction – EF <50%), based on the assumption that surgical risk outweighed benefit in asymptomatic individuals. However, modern therapy, reduced mortality from surgical valve replacement, and the introduction of transcatheter aortic valve implantation (TAVI) have prompted reconsideration of the "wait and follow" strategy[4]. Other clinical trials have also explored whether early valve replacement in asymptomatic severe AS may improve outcomes compared to delayed intervention after symptom onset[5].
Patient sex significantly influences the course of AS[6]. Male are more often diagnosed with AS earlier in midlife, while female tend to present with severe AS later in old age[7]. At diagnosis, female exhibit a different clinical

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profile—less pronounced coronary or peripheral atherosclerosis, more frequent long-standing hypertension, more pronounced left ventricular hypertrophy, and smaller body size[8]. Additionally, male accumulate more calcification on the valve for the same severity of stenosis, whereas female have a higher proportion of fibrosis in the valve tissue[6]. Studies have shown that thresholds for severe stenosis are lower in female (e.g., lower Agatston calcium scores on CT)[2], and that female progress more rapidly in valve calcification[10].

Female predominantly exhibit concentric left ventricular hypertrophy (thicker walls, smaller volume), while male more often develop eccentric hypertrophy (greater chamber dilation)[9]. Female myocardium tends to have more diffuse interstitial fibrosis, compared to more focal fibrotic changes in male, resulting in stiffer ventricles and higher filling pressures[11]. Consequently, female more frequently develop heart failure with preserved EF and are prone to so-called paradoxical "low-flow, low-gradient" AS—severe stenosis with disproportionately low flow and gradient despite preserved systolic function, commonly seen in elderly female with small, hypertrophic ventricles[9]. Clinically, female often experience more pronounced symptoms at similar stenosis severity (greater dyspnea and fatigue) and tend to be more frail (often older, with more chronic conditions, prone to complications and slower recovery) during evaluation8.

Despite these differences, current AS guidelines do not recommend sex-specific approaches; indications for monitoring and intervention are the same for male and female[2,13]. Sex is only sporadically mentioned in clinical guidelines and is not systematically incorporated into decision-making[2,6,12]. As a result, some high-risk features in female may go unrecognized, since severity criteria and surgical indications have been shaped by studies with predominantly male cohorts[12]. Moreover, studies show that female are less frequently referred for timely valve replacement, which is associated with poorer outcomes[7,15], although some analyses suggest that female achieve better long-term survival than male following TAVI procedures[14].

Therefore, the aim of this study is to identify sex-specific differences in clinical and echocardiographic parameters among asymptomatic patients with severe AS, to improve understanding and management of this condition.

Methods

This retrospective observational study included 116 asymptomatic patients (50 female and 66 male) with hemodynamically severe aortic stenosis, examined between May 2009 and October 2010. Patient data were collected from medical records and an electronic database, with strict adherence to anonymity protocols.

The study enrolled asymptomatic individuals with echocardiographically confirmed severe aortic stenosis, defined by aortic valve area (AVA) < 1.5 cm², peak transvalvular velocity (V_{max}) > 3.5 m/s, and mean pressure gradient (P_{mean}) > 30 mmHg. Patients with other significant valvular lesions, symptomatic AS, or comorbidities that could affect left ventricular geometry and function were excluded to isolate the effect of stenosis itself.

Upon admission, demographic data (age, sex, body surface area – BSA), vital signs (blood pressure, heart rate), cardiovascular risk factors (hypertension, diabetes, hyperlipoproteinemia, smoking, family history), and any symptoms suggestive of aortic stenosis were recorded.

All patients underwent standard transthoracic echocardiography (TTE), which included measurements of cardiac structure (left ventricular dimensions, wall thickness, indexed left ventricular myocardial mass – LVMi, relative wall thickness – RWT), systolic function (volumetric indices, ejection fraction, stroke volume, cardiac output), and key indicators of stenosis severity (left ventricular outflow tract diameter – LVOT, AVA and indexed AVA, V_{max}, peak – P_{max} and mean pressure gradients). TTE was essential for accurate assessment of stenosis severity; in addition to standard metrics (gradients and velocities), supplementary parameters were analyzed (flow index, stroke volume, visual assessment of valve calcification) to enhance diagnostic precision. As a non-invasive method, TTE also enabled repeated measurements for monitoring disease progression.

Symptoms characteristic of advanced AS (dyspnea, angina, syncope, fatigue) and typical physical signs of severe stenosis (diminished and delayed carotid pulse; harsh systolic ejection murmur radiating to the neck; attenuated second heart sound) were documented.

Based on calculated LVMi and RWT values, left ventricular geometry was classified according to standard criteria (normal geometry, concentric remodeling, concentric hypertrophy, eccentric hypertrophy). Sex-based differences in these remodeling patterns were analyzed.

Diastolic function was assessed using Doppler analysis of transmitral flow (E and A waves) and tissue Doppler imaging of the mitral annulus (septal and lateral e'), with calculation of the E/e' ratio as an indicator of left ventricular filling pressure. Diastolic dysfunction was defined by borderline findings: E/A ratio < 0.8 (or > 2.0), mean E/e' > 14, and septal e' < 7 cm/s. Each patient was evaluated against these criteria, and the prevalence of diastolic dysfunction was compared between sexes.

Follow-up lasted 24 months. Major Adverse Cardiovascular Events (MACE) were defined as a composite outcome including surgical intervention, rehospitalization due to cardiac decompensation, onset or worsening of symptoms, event-free status, and death. Outcomes were compared between female and male. This sex-based outcome analysis was included in light of existing evidence on gender differences in the treatment and prognosis of severe AS.

Statistical analysis was performed using SPSS software (version 27). Appropriate parametric or non-parametric tests were used to compare male and female groups depending on data distribution (t-test or Mann–Whitney U for continuous variables; χ^2 test or Fisher's exact test for categorical variables). Correlations between quantitative parameters were assessed using Pearson's coefficient (for normally distributed data) or Spearman's coefficient (for non-normal distributions). Logistic regression was applied to identify predictors of mortality, and 24-month

Table 1. Demographic, Clinical, Etiological, and Echocardiographic Comparison Between female and male With Hemodynamically Severe Aortic Stenosis

Parameter	Female (n = 50)	Male (n = 66)	p
Age (years, mean ± SD)	65.52 ± 9.53	66.45 ± 11.94	0.268
BSA (m^2)	1.80 ± 0.17	1.97 ± 0.15	< 0.001
Systolic Blood Pressure (mmHg)	148.40 ± 20.34	148.25 ± 18.90	0.987
Diastolic Blood Pressure (mmHg)	89.40 ± 10.18	89.54 ± 11.52	0.941
Heart Rate (beats/min)	73.62 ± 12.54	68.86 ± 12.17	0.023
Diabetes Mellitus (%)	18	19.7	1.000
Hypertension (%)	74	66.7	0.421
Hyperlipidemia (%)	52	42.4	0.350
Smoking (%)	4	13.6	0.111
Bicuspid Aortic Valve (%)	14	24.2	0.240
Degenerative Etiology (%)	76	69.7	0.532
Rheumatic Etiology (%)	10	6.1	0.496
LVEDd (cm)	4.89 ± 0.43	5.22 ± 0.50	< 0.001
LVESd (cm)	2.96 ± 0.47	3.34 ± 0.47	< 0.001
IVSd (cm)	1.28 ± 0.14	1.31 ± 0.14	0.271
Posterior Wall Thickness (PWd, cm)	1.20 ± 0.13	1.24 ± 0.14	0.095
Relative Wall Thickness (RWT)	0.49 ± 0.07	0.48 ± 0.07	0.323
LVOT Diameter (cm)	1.94 ± 0.20	2.13 ± 0.25	< 0.001
LVEDV(ml)	78.22 ± 22.17	94.09 ± 26.60	< 0.001
LV End-Systolic Volume (LVESV, ml)	21.65 ± 9.37	27.65 ± 13.75	0.015
Indexed LV Mass (LVMi, g/m^2)	132.28 ± 25.82	139.72 ± 27.68	0.138
Ejection Fraction (Biplane, %)	72.98 ± 5.67	71.63 ± 7.37	0.283
Left Atrium Diameter (LA, cm)	4.02 ± 0.64	4.27 ± 0.49	0.035
Aortic Valve Area (AVA, cm^2)	0.77 ± 0.22	0.88 ± 0.21	0.008
Indexed AVA (AVAi, cm^2/m^2)	0.43 ± 0.12	0.45 ± 0.10	0.497
Peak Velocity (V_{max}, m/s)	4.20 ± 0.51	4.27 ± 0.45	0.421
Peak Gradient (P_{max}, mmHg)	71.29 ± 17.74	73.78 ± 15.55	0.424
Mean Gradient (P_{mean}, mmHg)	41.53 ± 12.00	43.46 ± 9.98	0.347
LVOT/Aortic V_{max} Ratio	0.24 ± 0.05	0.23 ± 0.04	0.145
Stroke Volume Index (SVi, ml/m^2)	25.10 ± 5.22	24.04 ± 4.75	0.259
Zva (mmHg/ml/m^2)	7.52 ± 2.07	7.82 ± 1.78	0.414
Energy Loss Index (ELI, mmHg/cm^2)	0.47 ± 0.14	0.48 ± 0.12	0.599
E/A Ratio	0.83 ± 0.33	0.80 ± 0.39	0.443
IVRT (ms)	88.94 ± 34.29	97.93 ± 39.83	0.260
E/e' Mean Ratio	13.12 ± 4.80	11.93 ± 5.20	0.121

BSA = Body Surface Area; CVD = Cardiovascular Disease; LVEDd = Left Ventricular End-Diastolic Diameter; LVESd = Left Ventricular End-Systolic Diameter; IVSd = Interventricular Septum Thickness; LVEDV = Left Ventricular End-Diastolic Volume; LVOT = Left Ventricular Outflow Tract; Zva = Valvulo-Arterial Impedance; IVRT = Isovolumetric Relaxation Time;; E/e'mean = ratio of early diastolic transmitral flow velocity to mean mitral annular velocity;

survival was analyzed using the Kaplan–Meier method, with curve comparison via the Log-rank test. A p-value < 0.05 was considered statistically significant.

Results

The analysis revealed significant sex-related differences in clinical, morphological, and functional characteristics among patients with severe aortic stenosis. The average age did not differ between sexes (approximately 66 years, p=0.268). However, body surface area (BSA) was significantly lower in female (1.80±0.17 vs. 1.97±0.15 m^2; p<0.001), and heart rate was slightly higher (74 vs. 69 beats/min; p=0.023). Arterial pressure showed no difference. Comorbidities and risk factors were similarly distributed across both groups (hypertension ~70%, diabetes ~19%, hyperlipidemia ~50% vs. 42%, smoking ~4% vs. 14%, family history of cardiovascular disease ~18% vs. 6%; all without significant differences). The etiology of aortic stenosis also did not vary by sex—degenerative origin predominated (~70–76% in both groups), and the prevalence of bicuspid valve showed no significant difference (24% vs. 14%, p=0.240). Overall, both groups were clinically similar, with expected smaller body size and slightly faster heart rate in female. A detailed comparative overview is provided in **Table 1**.

Table 2. Parameters of Left Ventricular Diastolic Function in female and male

Parameter	Female (n = 55)	Male (n = 66)	p-value
E/A	0.83 ± 0.33	0.80 ± 0.39	0.443
E/e'_{mean}	13.12 ± 4.80	11.93 ± 5.20	0.121
e' septal (m/s)	0.05 ± 0.01	0.05 ± 0.01	0.166

E/A = ratio of early (E) to late (A) diastolic transmitral flow velocities; E/e'mean = ratio of early diastolic transmitral flow velocity to mean early diastolic mitral annular velocity; e' septal = early diastolic velocity of the septal side of the mitral annulu

Table 3. Left Ventricular Geometry in female and male

Sex	Normal Geometry	Concentric Remodeling	Eccentric Hypertrophy	Concentric Hypertrophy	p
Female (n = 50)	0.86%	1.72%	6.03%	34.48%	0.448
Male (n = 66)	1.72%	6.90%	8.62%	39.66%	

Table 4. Mean Survival Time

Sex	Mean Survival (months)	95% CI	Median (months)	95% CI
Female	10.25 ± 3.25	3.88 – 16.62	7.00 ± 3.50	0.14 – 13.86
Male	12.60 ± 2.98	6.77 – 18.43	11.00 ± 2.19	6.71 – 15.29

95% CI = 95% confidence interval, indicating the lower and upper bounds of the estimate.

Echocardiographic structural parameters showed clear sex-based differences. Male had larger left ventricular dimensions and volumes compared to female. LVEDd: 5.22±0.50 vs. 4.89±0.43 cm; LVESd: 3.34±0.47 vs. 2.96±0.47 cm (male vs. female; both p<0.001). Similarly, left ventricular end-diastolic and end-systolic volumes were higher in male (LVEDV ~94 vs. ~78 ml; p<0.001; LVESV ~27.6 vs. ~21.7 ml; p=0.015). Left ventricular myocardial mass (LVM) was greater in male (276±57 g vs. 239±48 g; p<0.001), but when adjusted for BSA (LVMi ~140 vs. ~132 g/m²), the difference was no longer significant (p=0.138). This suggests that male develop greater absolute hypertrophy and dilation (eccentric remodeling) of the left ventricle, while relative (indexed) hypertrophy is similar across sexes.

Systolic function (ejection fraction – EF) was preserved in both sexes. EF measured by M-mode was slightly higher in female (68.2±5.1% vs. 65.8±5.5%; p=0.014), while biplane Simpson EF showed no difference (72.98% vs. 71.63%; p=0.283). Left atrial size was slightly larger in male (4.27 vs. 4.02 cm; p=0.035), while right atrial size did not differ significantly (p=0.085). Septal and posterior wall thickness (IVSd, PWd), as well as relative wall thickness (RWT), were similar between sexes (p>0.09), indicating a comparable degree of concentric remodeling.

Hemodynamic parameters indicated that the severity of aortic stenosis was similar in female and male. Female had a smaller absolute aortic valve area (AVA: 0.77±0.22 vs. 0.88±0.21 cm²; p=0.008), but after adjustment for BSA (AVAi ~0.43 vs. 0.45 cm²/m²), the difference disappeared (p=0.497). Peak transvalvular velocity (V_{max} ~4.3 m/s) and pressure gradients (P_{max} ~73 mmHg, P_{mean} ~42 mmHg) were nearly identical between sexes (p>0.3), and net energy gradient (P_{net}) showed no difference. Other flow parameters were also consistent: ejection time (ET), aortic velocity-time integral (Ao VTI), LVOT VTI, LVOT/Ao velocity ratio, stroke volume (~46 ml), and indexed stroke volume (~24 ml/m²) were similar (p>0.1 for all). The only significant hemodynamic difference was in cardiac index (CI)—female had a higher CI (1.83 vs. 1.64 L/min/m²; p=0.008). As expected, male had a larger ascending aortic diameter (11.6 vs. 10.4 cm²; p=0.008), while integrated afterload indicators (valvuloarterial impedance, Zva ~7.6 mmHg·m²/ml; energy loss index, ELI ~0.47 mmHg/cm²) were similar. These findings highlight the importance of using indexed measures (such as AVAi) when assessing stenosis severity, especially in individuals with smaller body size.

Left ventricular diastolic function parameters showed minor sex differences. Female had slightly higher transmitral flow velocities: E wave 0.83±0.28 vs. 0.71±0.23 m/s, A wave 1.03±0.22 vs. 0.94±0.23 m/s (p=0.03–0.05). Despite this, the E/A ratio remained ~0.8 in both groups (p=0.443), and E wave deceleration time was similar (~250 ms; p=0.916). Male had prolonged isovolumetric contraction time (IVCT: 69.8 vs. 56.4 ms; p=0.016) and a slightly higher myocardial performance index (MPI: 0.57 vs. 0.48; p=0.016), while isovolumetric relaxation time did not differ (IVRT: p=0.260). Tissue Doppler velocities (septal and lateral e', a', s') and E/e' ratio showed no significant differences (all p>0.1). Diastolic dysfunction was present in both groups without significant difference in prevalence (**Table 2**). Subtle differences suggest that female exhibit higher transmitral velocities (indicating elevated filling pressures), while male have longer isovolumetric phases and higher MPI. Overall, left ventricular diastolic function was similarly impaired in both sexes.

Patterns of left ventricular remodeling were comparable between female and male. Concentric hypertrophy predominated in both groups (≈34% in female, 40% in male), while normal geometry was rare (<2%). The distribution of left ventricular geometry types did not differ significantly between sexes (p=0.448; **Table 3**).

To assess sex differences in MACE and mortality, Fisher's exact test showed no statistically significant difference ($\chi^2 = 2.188$, df = 5, p = 0.863). The following events were considered: surgery, rehospitalization due to cardiac symptoms, symptom onset, symptom worsening, event-free status, and death. The most common outcome in both sexes was surgery (female 19.8% vs. male 26.7%), while mortality was slightly higher in male (4.3% vs. 3.5% in female). Other events were rare and showed no significant sex-based differences.

Patient follow-up over 24 months revealed high mortality, with no significant difference between sexes. By month 12, approximately 20% of participants had survived, and by month 24, none remained (0% survival). Median survival was 7 months for female and 11 months for male (Table 4), without statistically significant difference. Kaplan–Meier survival curves (**Figure 1**) did not

differ between sexes (Log-rank p=0.520). Although a steeper decline in survival was visually observed in female during the first 12–15 months, sex was not identified as an independent predictor of outcome.
Univariate logistic regression analysis identified indexed aortic valve area (AVAi) as a key risk factor. Lower AVAi was associated with higher mortality risk in both male (p=0.037) and female (p=0.052), while age (p=0.083) and indexed left ventricular mass (LVMi, p>0.1) had no significant effect (**Figure 2**).
In summary, male and female with severe AS exhibit similar hemodynamic disease severity but differ in cardiac anatomy and certain functional adaptations. Male develop larger dimensions and greater absolute left ventricular hypertrophy, while female have smaller body surface area, faster heart rate, and more pronounced transmitral flow velocities for a given degree of stenosis. Survival did not differ statistically between sexes, and lower indexed aortic valve area (AVAi) emerged as the strongest predictor of poor outcome in both groups.
These findings suggest that clinical management should be tailored to sex—focusing on timely recognition and treatment of structural changes (hypertrophy/dilation) in male once AVAi reaches a critical threshold, while in female, greater emphasis should be placed on clinical manifestations (symptoms, diastolic function) and age when making intervention decisions.

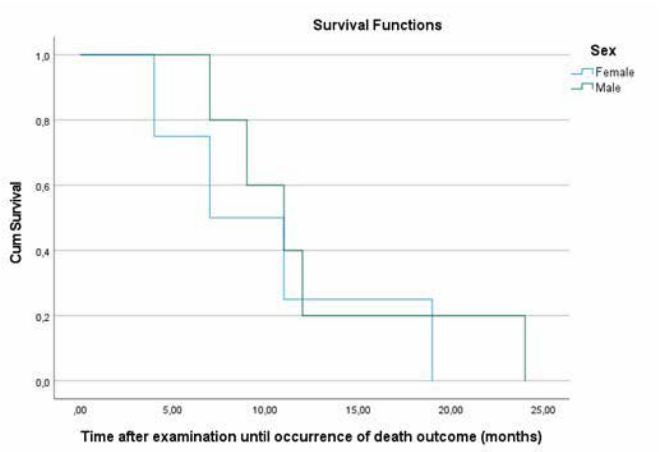

Figure 1. Comparative Survival in female and male over a 24-Month Follow-Up

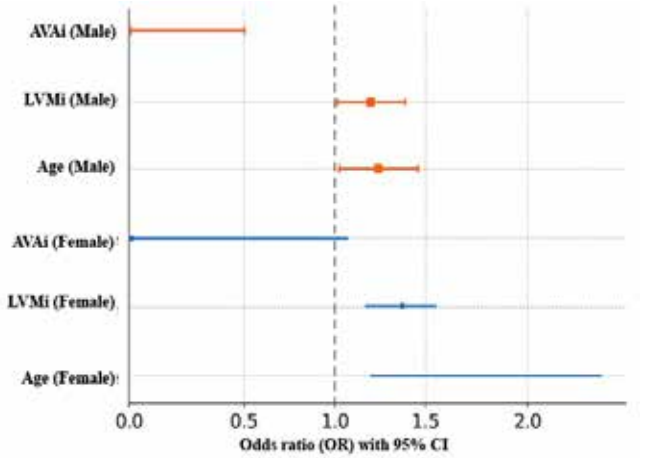

Figure 2. Mortality Predictors according to gender (Forest Plot)
AVAi = Indexed Aortic Valve Area; LVMi = Left Ventricular Mass Index; 95% CI = 95% confidence interval, indicating the lower and upper bounds of the estimate.

Discussion

Sex-related differences in patients with severe aortic stenosis (AS) are well documented in the literature, with female and male exhibiting distinct clinical profiles and myocardial adaptive mechanisms[16]. One of the most striking differences pertains to diastolic function—multiple studies have shown that female with AS more frequently develop impaired diastolic filling and elevated left ventricular end-diastolic pressure compared to male[17,18]. Nevertheless, despite these pathophysiological differences, most studies have not found significant differences in survival following aortic valve intervention between sexes; when timely and adequately treated, female and male have comparable outcomes[19,20]. This finding aligns with the results of our study.
Further analysis highlights sex-specific patterns of cardiac remodeling and hemodynamic response to pressure overload. Our findings, consistent with previous observations, confirm differences in left ventricular geometry: male generally have larger left ventricular dimensions and volumes, while female achieve similar systolic function with smaller chambers, thicker walls, and reduced cavity diameter[21,22]. This concentric hypertrophy pattern in female, as opposed to eccentric chamber dilation in male, is accompanied by relatively greater systolic load in female—they have a smaller outflow tract diameter and higher total peripheral impedance for the same stenosis severity[23]. At the same time, female maintain preserved ejection fraction (EF) despite pronounced wall hypertrophy[24]. However, preserved systolic function may mask subtle dysfunction; female more frequently exhibit elevated myocardial performance index (MPI) and prolonged isovolumetric contraction time, indicating globally reduced cardiac efficiency despite normal EF. Importantly, these structural-functional differences do not necessarily imply worse prognosis for female; on the contrary, some studies suggest that female fare equally well—or even better—after aortic valve replacement compared to male[25].
In our study, no difference in average age between sexes was observed, which contrasts with most previous research indicating that female with severe AS are typically diagnosed later in life[26]. A possible explanation lies in the inclusion criteria—only patients with pronounced hemodynamic stenosis were enrolled, resulting in a balanced age distribution. Additionally, the comorbidity profile was similar between sexes in our sample (including comparable rates of hypertension and diabetes), confirming that neither group had significantly greater burden of accompanying conditions. However, due to differences in body size (female had significantly lower BSA), interpretation of stenosis severity requires mandatory indexing of aortic valve area to body surface. This aligns with recommendations to always assess effective valve area relative to patient body size to avoid underestimating stenosis severity in smaller individuals[27]. In

this context, there is growing emphasis on sex-specific risk assessment and therapeutic decision-making. A recently proposed sex-specific risk stratification model better reflects differing risk factors in male and female following aortic valve replacement[28]. Analyses of TAVI populations have also shown that, although overall survival rates may be similar, perioperative risk profiles differ—e.g., female have higher incidence of vascular complications, while male more frequently present with concomitant coronary artery disease[29].

Differences in left ventricular remodeling patterns between sexes also influence disease progression and adaptation. Female predominantly exhibit concentric hypertrophy—thicker walls and smaller chamber volumes that help maintain cardiac output despite valve narrowing. This finding in our female patients corresponds with results from Petrov et al., who demonstrated that female have smaller LV cavities with thicker myocardium, while male develop more pronounced LV dilation and larger volumes[30]. Although concentric hypertrophy more effectively normalizes wall stress, it may lead to increased myocardial stiffness. Over time, chronic pressure overload exhausts compensatory mechanisms and leads to fibrosis, marking the transition to heart failure[31]. It is hypothesized that this transition occurs earlier in female as diastolic dysfunction, while male retain chamber dilatability longer before clinical deterioration. In our study, male also had significantly larger ascending aortic diameters. This may reflect larger body dimensions, but also the higher prevalence of bicuspid aortic valve in male, as confirmed by other studies on sex-related aortic anatomy differences[32]. A larger aortic diameter in male may influence prosthesis sizing (e.g., in TAVI), but was not accompanied by significantly higher valvulo-arterial impedance in our sample, suggesting similar overall hemodynamic load on the left ventricle.

Worsening diastolic function and elevated filling pressures are key prognostic factors in severe AS, particularly in female. Our female patients had higher mean E/e' ratios, indicating elevated diastolic filling pressures. The importance of this is supported by research showing that the combination of elevated E/e' and preserved EF identifies AS patients at increased risk of adverse outcomes[33]. In other words, even when systolic function is formally preserved, high diastolic pressures imply latent myocardial dysfunction. Additionally, left atrial function is becoming increasingly important in assessing disease severity. Recent studies suggest that reduced atrial contractility and reservoir function are poor prognostic indicators in severe AS[34]. Accordingly, parameters such as left atrial strain analysis are used to detect early signs of impaired cardiac filling capacity. Moreover, progression of myocardial fibrosis plays a central role in the transition from compensated to decompensated AS. Cardiovascular imaging evidence shows that cumulative myocardial fibrosis leads to gradual LV stiffness and onset of heart failure symptoms[35]. These changes may be subtle and particularly present in female with seemingly preserved systolic function, underscoring the need for comprehensive evaluation—including diastolic function, atrial performance, and fibrotic changes—as part of disease severity assessment.

Regarding final outcomes, 24-month follow-up revealed high mortality (all observed patients experienced adverse outcomes during this period, with no survivors at two years, reflecting the nature of the sample). Due to the relatively small number of patients followed (a total of 9, including 4 female and 5 male), sex differences in survival did not reach statistical significance. Kaplan–Meier survival analysis illustratively shows that survival curves for female and male are close and both decline steeply over 24 months. By the end of the first year (12 months), approximately one-fifth of patients remained alive (22.2%), and after two years, none. Median survival was 7 months for female and 11 months for male, with slightly longer average survival in male. Thus, male nominally had somewhat longer survival, but the difference was not statistically significant. Visually, a trend is observed where female lose survival more rapidly in early stages—the curve for female declines earlier and more steeply (e.g., after ~7–12 months, a smaller proportion of female remained alive compared to male). All female patients experienced mortality by month 19, while the last male death occurred at month 24. This resulted in male having slightly better survival toward the end of the follow-up period (e.g., at month 18, several male were still alive, compared to no female). However, due to the small sample size and overlapping confidence intervals, these differences cannot be considered reliably significant. The conclusion is that sex itself did not show a statistically significant impact on survival in this sample, although there is an indication that female may experience a more unfavorable early disease course. This trend—shorter survival in female—may be linked to the fact that female, as previously described, endure greater functional burden and symptoms earlier in the disease course[6,14,22,23,26,28,29,33]. In contrast, male may compensate for stenosis longer before terminal functional decline due to greater structural cardiac reserve.

Our study confirms that sex influences the morphological and functional manifestations of severe aortic stenosis—female have smaller, more hypertrophied left ventricles with preserved EF but greater diastolic burden, while male have larger cardiac dimensions and a different remodeling pattern. These findings point to the need for sex-specific approaches in monitoring and treating AS to ensure timely intervention and optimize outcomes for both sexes.

Study Limitations

Several key limitations of this study should be acknowledged. First, although 116 patients were included, stratification by sex and clinical outcomes (e.g., survival, need for surgery, or major adverse cardiovascular events – MACE) resulted in very small subgroups in certain analyses. This fragmentation reduces statistical power and makes it difficult to detect subtle but potentially clinically meaningful differences.

Second, the fact that this was a single-center, retrospective study introduces the risk of selection bias and limits the generalizability of the findings to broader populations.

Third, the 24-month follow-up period is relatively short for capturing the natural history of severe aortic stenosis, especially in patients managed conservatively. Due to the limited duration of follow-up, some outcomes—such as symptom development or rehospitalizations—were recorded in very small numbers, making it difficult to draw firm conclusions about long-term sex-based differences.

Fourth, the mortality analysis did not differentiate between cardiac and non-cardiac causes of death, which may reduce the precision of prognostic evaluations.

Finally, sex was considered exclusively in binary terms (male vs. female), without accounting for hormonal status, menopausal stage, or differences in pharmacological therapy. This simplified approach may overlook the influence of these factors on cardiac remodeling and disease progression. Given these limitations, the results should be interpreted with caution, and future studies with larger sample sizes and longer follow-up are needed to confirm and expand upon these findings.

Conclusion

This retrospective study provides a comprehensive insight into sex-specific differences in morphological, functional, hemodynamic, and prognostic parameters among asymptomatic patients with severe aortic stenosis. Analysis of 116 participants (50 female and 66 male) revealed that female and male respond differently to chronic hemodynamic stress, influencing disease presentation, diagnostic assessment, therapeutic decisions, and clinical outcomes.

This study underscores the importance of considering patient sex as a clinically relevant variable in the assessment of severe aortic stenosis. Future research should aim to develop sex-specific diagnostic algorithms, evaluate novel biomarkers, and apply predictive models to more precisely determine the optimal timing for intervention across different patient groups.

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Abstract

Polno zavisne razlike u kliničkim i ehokardiografskim parametrima kod asimptomatskih pacijenata sa hemodinamski značajnom aortnom stenozom

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Uvod: Aortna stenoza (AS) je najčešća valvularna bolest u razvijenim zemljama, a njen tok i klinička prezentacija mogu značajno varirati u zavisnosti od pola pacijenata. Cilj ove studije bio je da identifikuje polno specifične razlike u morfološkim, funkcionalnim i prognostičkim karakteristikama kod asimptomatskih pacijenata sa hemodinamski teškom AS. Metodi: U retrospektivnu opservacionu studiju uključeno je 116 pacijenata (50 žena i 66 muškaraca) sa asimptomatskom teškom AS (AVA < 1.5cm², Vmax > 3.5 m/s, Pmean > 30 mmHg). Svim ispitanicima urađen je transtorakalni ehokardiografski pregled, analizirani su morfološki, funkcionalni i hemodinamski parametri, kao i obrasci remodelovanja leve komore i dijastolna funkcija. Pacijenti su praćeni tokom 24 meseca, a analizirani su i prediktori mortaliteta i kombinovanih kardiovaskularnih događaja (MACE). Rezultati: Muškarci su imali veće dimenzije i zapremine leve komore, dok su žene imale izraženije transmitralne protoke i viši srčani indeks. Indeksirana površina aortnog ušća (AVAi) bila je najvažniji prediktor mortaliteta kod muškaraca. Preživljavanje tokom praćenja bilo je nisko u obe grupe, bez značajne razlike među polovima. Međutim, uočen je trend kraćeg preživljavanja kod žena. Zaključak: Iako muškarci i žene sa teškom AS imaju sličan hemodinamski profil, razlikuju se u obrascima remodelovanja i funkcionalnoj adaptaciji. Klinički pristup treba prilagoditi polu, kod muškaraca se fokusirati na strukturne promene, a kod žena na funkcionalne parametre i simptome, kako bi se pravovremeno identifikovali visokorizični pacijenti i optimizovao trenutak za intervenciju.

Ključne reči: *aortna stenoza, polne razlike, ehokardiografija, remodelovanje, preživljavanje*