Low-Flow, Low-Gradient Severe Aortic Stenosis: Cardiac Computed Tomography Findings and Clinical Outcomes After Aortic Valve Replacement

Se Jin Choi
University of Ulsan College of Medicine
Yura Ahn
University of Ulsan College of Medicine
Hyun Jung Koo (radkoo@amc.seoul.kr)
University of Ulsan College of Medicine
Dae-Hee Kim
University of Ulsan College of Medicine
Soyeon Lim
Ulsan University Hospital
Jun Bum Kim
University of Ulsan College of Medicine
Jong-Min Song
University of Ulsan College of Medicine
Duk-Hyun Kang
University of Ulsan College of Medicine
Jae-Kwan Song
University of Ulsan College of Medicine
Hwa Jung Kim
University of Ulsan College of Medicine
Joon-Won Kang
University of Ulsan College of Medicine
Dong Hyun Yang
University of Ulsan College of Medicine

Research Article

Keywords: cardiac computed tomographic, Aortic valve calcium, echocardiography, surgical AVR

Posted Date: December 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1151439/v1

Abstract

Aortic valve calcium scoring by cardiac computed tomographic (CT) has been recommended as an alternative to classify the AS severity, but it is unclear that whether CT findings can predict and have prognostic implication in low-flow, low-gradient aortic stenosis (LF-LG AS), which has fewer benefit from surgery among the AS subtypes. In this study, we examined the clinical and cardiac CT findings of LF-LG AS patients and evaluated factors affecting outcomes after surgical aortic valve replacement (AVR). This study included 511 (66.9±8.8 years, 55% men) consecutive patients with severe AS who underwent surgical AVR. Aortic valve area (AVA) was obtained by echocardiography (AVA_{echo}) and by CT (AVA_{CT}) using each modalities measurement of the left ventricular outflow tract. Patients with AS were classified as 1) high-gradient severe (n=438), 2) classic LF-LG (n=18), and 3) paradoxical LF-LG (n=55) based on echocardiography. Classic LF-LG AS patients had higher end-systolic and end-diastolic volume indices, lower left ventricular ejection fraction, larger AVA_{echo} and AVA_{CT}, and larger aortic annulus compared to high-gradient severe AS ($P<0.05$, for all). In classic LF-LG AS group, 27.8% of patients presented $AVA_{CT} \geq 1.2$ cm^2. After multivariable adjustment, old age (hazard ratio [HR], 1.04, P=0.049), high B-type natriuretic peptide (BNP) (HR, 1.005; P<0.001), preoperative atrial fibrillation (HR, 2.75; P=0.003), classic LF-LG AS (HR, 5.53, P=0.004), and small aortic annulus (HR, 0.57; P=0.002) were independently associated with major adverse cardiac and cerebrovascular events (MACCE). The classic LF-LG AS group presented larger AVA_{CT} and aortic annulus than those in high-gradient severe AS group and one third of them had $AVA_{CT} \geq 1.2$ cm^2. Old age, high BNP, atrial fibrillation, classic LF-LG AS, and small aortic annulus were associated with MACCE in severe AS patients after surgical AVR.

Introduction

Classic low-flow, low-gradient (LF-LG) severe aortic stenosis (AS) is defined by a small aortic valve (AV) area (AVA) on echocardiography ($AVA_{echo}<1$ cm^2), a low mean pressure gradient (PG<40 mmHg), and low flow (stroke volume [SV]<35 mL/m^2). The condition is characterised by low cardiac output due to a reduced left ventricular ejection fraction (LVEF< 50%).[1–5] Conversely, LF-LG AS may occur despite preserved LVEF and is classified as paradoxical LF-LG AS. Assessment of disease severity, management, and prediction of post-surgical outcome in patients with LF-LG AS is currently challenging. Since LF-LG AS presents fewer potential benefits from AV replacement (AVR) and considerable operation risks compared to true-severe AS, a classification for AS is important.[5]

Although the planimetry of the AVA using three-dimensional transoesophageal echocardiography has been reported to be more accurate than transthoracic echocardiography,[6] measurement issues still remain unresolved. Even in patients with normal systolic LV function, the grading of AS on echocardiography is inconsistent, and this is partly due to reduced SV.[7,8] In patients with low-flow state, AS severity may be underestimated due to lower mean PG, while incomplete opening of the AV may overestimate stenosis severity because of the reduced opening forces to the AV.[9] In patients with low-flow state, there can be a discrepancy between the EOA and the PG. Moreover, the continuity equation assumes circular LVOT which is elliptical shape, and echocardiography may underestimate LVOT. Additional diagnostic tests, dobutamine stress echocardiography (DSE) [2,10] and AV calcium score (AVC) obtained by computed tomography (CT) scan [11 12], have been used for the confirmation of severity and therapeutic guidance, and there is a chance that the patients with severe AS may be reclassified into the moderate range. However, reference standards used in these studies consisted of subjective assessment of the valve severity by cardiac surgeons and the AVC on CT images, which do not reflect hemodynamic severity.

Cardiac CT is recommended as an alternative to assess AS severity when DSE is inconclusive.[13] However, discrepancies have been reported between the measured AVA on cardiac CT (AVA_{CT}) and AVA_{echo}.[14,15] AVA_{CT} was significantly greater than the AVA_{echo} calculated by continuity equation, and suggested cut-off of AVA_{CT} for severe AS was <1.2 cm^2. Moreover, CT findings of LF-LG AS and imaging prognostic values remain undefined. Thus, we sought to (i) determine the CT characteristics of LF-LG AS, and (ii) evaluate prognostic factors affecting major adverse cardiovascular and cerebrovascular events (MACCE) of AS after AVR.

Results

Patient characteristics

High-gradient severe AS (85.7% [438/511]) was most common among patients, followed by paradoxical LF-LG AS (10.8% [55/511]) and classic LF-LG AS (3.5% [18/511]). (Supplementary Table 1). Half of the patients had tricuspid valves (48.1% [246/511]) and bicuspid valves were detected in the remaining patients. The median follow-up period for all patients was 4.12 (IQR, 3.19–5.50) years. MACCE occurred in 43 (8.4%) patients, and the overall mortality was 13.9% (n=71).

Among the groups with high-gradient severe AS, classic LF-LG AS, and paradoxical LF-LG AS, the age of patients were not statistically different (P=0.93) (Table 1). The number of concurrent percutaneous coronary artery intervention or CABG with AVR was highest in classic LF-LG AS group (50%, P=0.02). BNP was highest in classic LF-LG AS (median 944.5 pg/mL, P<0.001). MACCE was more common in the classic LF-LG AS than in the high-gradient severe AS (27.8 vs. 7.8%, P=0.01).

Table 1
Clinical and imaging characteristics of high-gradient severe, classic LF-LG, paradoxical LF-LG AS groups (n=511)

Characteristic	High-gradient severe AS	Classic LF-LG AS	Paradoxical LF-LG AS	P-value
No. of patients (%)	438 (85.7)	18 (3.5)	55 (10.8)	
Age, years	66.8 ± 8.8	66.8 ± 6.2	67.3 ± 9.4	0.93
Male	236 (53.9)	13 (72.2)	31 (56.4)	0.30
Body surface area, m^2	1.6 ± 0.2	1.7 ± 0.2	1.6 ± 0.2	0.56
Hypertension	231 (52.7)	12 (66.7)	30 (54.5)	0.50
Atrial fibrillation	65 (14.8)	4 (22.2)	4 (7.3)	0.20
PCI or CABG	94 (21.5)	9 (50.0)*	14 (25.5)	0.02
BNP, pg/mL	99.5 (43.0 – 280.5)	944.5 (304.8 – 3066.0)*	70.0 (35.0 – 190.0)	<0.001
lnBNP	4.6 (3.8 – 5.6)	6.8 (5.7 – 8.0)*	4.2 (3.6 – 5.2)	<0.001
Echocardiography				
LVEF, %	60.3 ± 10.0	36.0 ± 10.3*	62.6 ± 5.3	<0.001
Peak velocity, m/s	5.2 ± 0.7	3.6 ± 0.5*	3.5 ± 0.5†	<0.001
Peak PG, mmHg	108.5 ± 30.5	52.0 ± 13.1*	50.1 ± 16.0†	<0.001
Mean PG, mmHg	66.5 ± 19.4	29.8 ± 7.9*	28.0 ± 9.5†	<0.001
LVMI, gm/ m^2	135.4 ± 35.8	149.6 ± 31.1	124.9 ± 36.2	0.03
AV VTI, cm	124.6 ± 26.1	94.9 ± 33.3*	112.0 ± 27.7†	<0.001
LVOT VTI, cm	21.4 ± 4.1	16.0 ± 4.4*	21.2 ± 3.7	<0.001
LVOT diameter, mm	21.0 ± 1.5	21.8 ± 1.9	21.2 ± 1.6	0.06

Values are means ± standard deviations or numbers and percentages in parentheses. *Significant difference between patients with severe aortic stenosis and patients with classic low-flow, low-gradient, severe aortic stenosis (classic LF-LG AS) groups. †Significant difference between severe aortic stenosis and paradoxical LF-LG AS groups. AS, aortic stenosis; AVA, aortic valve area; AVC, aortic valve calcium score; BNP, B-type natriuretic peptide; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LF-LG, low-flow and low-gradient; lnBNP, log-transformed B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; MACCE, major adverse cardiac and cerebrovascular event; N/A, not available; PG, pressure gradient; SAC, systemic arterial compliance; VTI, velocity time integral; Zva, valvulo-arterial impedance.

Characteristic	High-gradient severe AS	Classic LF-LG AS	Paradoxical LF-LG AS	P-value
LVOT diameter/BSA	12.9 ± 1.3	13.1 ± 1.6	13.0 ± 1.3	0.55
AVA_{echo}, mm^2	61.3 ± 14.7	66.9 ± 15.1	69.5 ± 13.8†	<0.001
ESVI, mL/m^2	27.7 ± 16.8	63.4 ± 27.0*	24.5 ± 11.4	<0.001
EDVI, mL/m^2	66.8 ± 23.7	96.3 ± 29.3*	64.3 ± 24.5	<0.001
SAC, mL/m^2/mmHg	0.8 ± 0.3	0.7 ± 0.3	0.8 ± 0.3	0.28
Zva, mmHg/mL/m^2	5.3 ± 1.6	5.0 ± 1.9	4.4 ± 1.4†	<0.001
CT findings				
Valve morphology				0.04
Tricuspid	204 (46.6)	14 (77.8)	28 (50.9)	
Bicuspid with raphe	106 (24.2)	3 (16.7)	17 (30.9)	
Bicuspid without raphe	128 (29.2)	1 (5.6)	10 (18.2)	
AVC	3027.2 ± 1872.0	2895.5 ± 1624.5	2363.1 ± 1605.8*	0.04
LVOT mean diameter	24.8 ± 2.9	27.1 ± 2.7*	24.7 ± 2.6	0.003
AVA_{CT}, mm^2	84.9 ± 23.4	100.8 ± 22.7*	94.2 ± 25.0†	0.001
AVA_{plani}, mm^2	87.2 ± 23.2	99.7 ± 25.5*	97.5 ± 27.1†	0.003
Aortic annulus				
Circularity, %	81.6 ± 7.6	77.4 ± 6.6	82.3 ± 6.0	0.05
Maximal dimeter, mm	27.5 ± 3.2	30.4 ± 3.5*	27.4 ± 2.8	0.001
Mean diameter, mm	24.9 ± 2.6	26.9 ± 2.5*	25.0 ± 2.6	0.005

Values are means ± standard deviations or numbers and percentages in parentheses. *Significant difference between patients with severe aortic stenosis and patients with classic low-flow, low-gradient, severe aortic stenosis (classic LF-LG AS) groups. †Significant difference between severe aortic stenosis and paradoxical LF-LG AS groups. AS, aortic stenosis; AVA, aortic valve area; AVC, aortic valve calcium score; BNP, B-type natriuretic peptide; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LF-LG, low-flow and low-gradient; lnBNP, log-transformed B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; MACCE, major adverse cardiac and cerebrovascular event; N/A, not available; PG, pressure gradient; SAC, systemic arterial compliance; VTI, velocity time integral; Zva, valvulo-arterial impedance.

Characteristic	High-gradient severe AS	Classic LF-LG AS	Paradoxical LF-LG AS	P-value
Perimeter, mm	79.5 ± 8.4	85.4 ± 7.7*	80.0 ± 8.3	0.02
Area, mm^2	481.8 ± 102.4	554.8 ± 101.0*	489.5 ± 99.9	0.01
Sinus of Valsalva, mm	36.6 ± 4.5	38.4 ± 4.7	36.8 ± 5.0	0.25
ST junction, mm	30.9 ± 4.6	31.7 ± 3.3	31.5 ± 5.9	0.58
Ascending aorta tubular portion, mm	40.7 ± 6.3	38.4 ± 4.6	40.4 ± 7.7	0.31
Normalized to BSA				
AVA_{CT}, mm^2	51.7 ± 13.6	60.7 ± 15.8*	58.0 ± 15.6†	<0.001
AVA_{plani}, mm^2	52.6 ± 13.5	59.5 ± 17.5*	57.8 ± 15.2†	0.005
Aortic annulus				
Maximal dimeter, mm	16.8 ± 2.0	18.2 ± 2.6*	16.9 ± 1.7	0.01
Mean diameter, mm	15.2 ± 1.6	16.1 ± 1.9	15.4 ± 1.6	0.06
Perimeter, mm	48.7 ± 5.2	51.1 ± 5.8	49.2 ± 5.3	0.12
Area, mm^2	293.4 ± 55.5	331.0 ± 56.6*	299.7 ± 55.9	0.02
Sinus of Valsalva, mm	22.4 ± 2.9	23.0 ± 2.8	22.6 ± 2.9	0.65
ST junction diameter, mm	18.9 ± 2.9	18.9 ± 2.1	19.3 ± 3.2	0.69
Ascending aorta tubular portion, mm	25.0 ± 4.3	23.0 ± 2.9	24.8 ± 4.6	0.15
Surgical valve size, mm	22.1 ± 2.1	23.0 ± 2.1	22.3 ± 2.0	0.18
Surgical valve type				N/A
CE Magna	144	10	18	
ATSAP	82	4	8	

Values are means ± standard deviations or numbers and percentages in parentheses. *Significant difference between patients with severe aortic stenosis and patients with classic low-flow, low-gradient, severe aortic stenosis (classic LF-LG AS) groups. †Significant difference between severe aortic stenosis and paradoxical LF-LG AS groups. AS, aortic stenosis; AVA, aortic valve area; AVC, aortic valve calcium score; BNP, B-type natriuretic peptide; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LF-LG, low-flow and low-gradient; lnBNP, log-transformed B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; MACCE, major adverse cardiac and cerebrovascular event; N/A, not available; PG, pressure gradient; SAC, systemic arterial compliance; VTI, velocity time integral; Zva, valvulo-arterial impedance.

Characteristic	High-gradient severe AS	Classic LF-LG AS	Paradoxical LF-LG AS	P-value
Hancock	82	1	13	
St. Jude Regent	80	3	11	
Others	50	0	5	
Operator				0.47
Operator 1	170	5	18	
Operator 2	95	2	12	
Operator 3	81	4	15	
Operator 4	64	4	7	
Operator 5	28	3	3	
MACCE	34 (7.8)	5 (27.8) *	4 (7.3)	0.01
Overall mortality	57 (13.0)	6 (33.3)	8 (14.5)	0.05
Follow-up duration, d	1517.5 (1188.8 – 2026.5)	1134.0 (26.0 – 1682.0)	1455.0 (1112.0 – 1944.0)	0.007

Values are means ± standard deviations or numbers and percentages in parentheses. *Significant difference between patients with severe aortic stenosis and patients with classic low-flow, low-gradient, severe aortic stenosis (classic LF-LG AS) groups. †Significant difference between severe aortic stenosis and paradoxical LF-LG AS groups. AS, aortic stenosis; AVA, aortic valve area; AVC, aortic valve calcium score; BNP, B-type natriuretic peptide; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LF-LG, low-flow and low-gradient; lnBNP, log-transformed B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; MACCE, major adverse cardiac and cerebrovascular event; N/A, not available; PG, pressure gradient; SAC, systemic arterial compliance; VTI, velocity time integral; Zva, valvulo-arterial impedance.

Echocardiography

LVEF, transaortic peak velocity and PG were lower in the classic LF-LG AS group and reflected the characteristics of LF-LG AS (P<0.001, for all) (Table 1). The ESVI (63.4 vs. 27.7 mL/m^2, P<0.001) and EDVI (96.3 vs. 66.8 mL/m^2, P<0.001) were significantly larger in classic LF-LG AS, compared to the high-gradient severe AS group. SAC was not different among the groups (P=0.28), although Zva was lower in paradoxical LF-LG AS compared to others (P<0.001).

We found that AVA_{CT} ≥1.2 cm^2 was noted in 27.8% (5/18) of the patients with classic LF-LG AS (Figure 1). In classic LF-LG AS, AVA_{echo} was larger in patients with AVA_{CT}≥1.2 cm^2 than those with AVA_{CT}<1.2cm^2 (61.1 vs. 81.9 mm^2, P=0.005) (Supplementary Table 2). However, other echocardiography parameters such as LVEF, peak velocity, and PG were not statistically different between subgroups with

AVA_{CT}<1.2cm^2 and AVA_{CT}≥1.2 cm^2 (P>0.05, for all). In patients with paradoxical LF-LG AS, AVA_{echo} was larger in AVA_{CT}≥1.2cm^2 group (68.2 vs. 77.3 mm^2, P=0.08), but without statistical significance.

Computed tomography

Interobserver agreements for aortic root measurement on CT are high with the range of ICC from 89.2~97.0. (Supplementary Table 3). The pearson correlation coefficient for AVA_{echo} and AVA_{CT} was good (r=0.73, P<0.001). AVA_{CT} is larger than AVA_{echo} and the mean difference between AVA_{echo} and AVA_{CT} was 24.1 mm^2 (95% CI, −8.3 to 56.4 mm^2, P<0.001) (Figure 2A and 2B). Comparison of AVA_{echo} and AVA_{plani} is presented in Supplementary Figure 2. AVC was highest in patients with high-gradient severe S, and statistically lower in paradoxical LF-LG AS and moderate AS groups (P=0.0.04). LVOT dimeter measured on CT was longer in classic LF-LG AS group compared to that in high-gradient severe AS (24.8 vs. 27.1 mm, P=0.003). The mean AVA_{CT} was larger in the classic LF-LG AS group, compared to the high-gradient severe AS group (100.8 vs. 84.9 mm^2, P=0.001). Normalized aortic annulus maximal diameter was longer (16.8 mm vs. 18.2 mm, P=0.01) and aortic annulus area was larger (293.4 mm^2 vs. 331.0 mm^2, P=0.02) in classic LF-LG AS group compared to those in high-gradient severe AS.

In classic LF-LG AS group, mean AVC was higher in AVA_{CT}<1.2cm^2 group compared to that in AVA_{CT}≥1.2 cm^2 (3912.2 vs. 1360.1, P=0.002) (Table 2). AVA_{plani} was also smaller in AVA_{CT}<1.2cm^2 group compared to that in AVA_{CT}≥1.2 cm^2 (88.2 vs. 129.9 mm^2, P<0.001). The normalized annulus sizes and aortic root diameters on CT were not statistically different between AVA_{CT}<1.2cm^2 and AVA_{CT}≥1.2 cm^2 groups (P<0.05, for all). In paradoxical LF-LG AS patients, LVOT area normalized to BSA (289.3 vs. 345.5 mm^2, P=0.01), normalized sizes of aortic annulus area (292.7 vs. 341.4 mm^2, P=0.02), sinus of Valsalva (22.1 vs. 25.2 mm, P=0.003) and ST junction (30.6 vs. 36.7 mm, P=0.006) were larger in AVA_{CT}≥1.2 cm^2 group, compared to those measured in patients with AVA_{CT}<1.2cm^2.

Table 2
Subgroups of LF-LG AS according to AVA_{CT}

	Classic LF-LG AS (n = 18)			**Paradoxical LF-LG AS (n = 55)**		
Characteristic	AVA_{CT}<1.2cm^2	AVA_{CT}≥1.2 cm^2	P-value	AVA_{CT} <1.2 cm^2	AVA_{CT}≥1.2 cm^2	P-value
No. of patients (%)	13 (72.2)	5 (27.8)		47 (85.5)	8 (14.5)	
Age, years	66.1 ± 5.8	68.6 ± 7.7	0.46	67.3 ± 9.2	67.3 ± 10.9	0.99
Male	9 (69.2)	4 (80.0)	1.00	25 (53.2)	6 (75.0)	0.72
BSA, m^2	1.7 ± 0.2	1.6 ± 0.2	0.12	1.6 ± 0.2	1.7 ± 0.1	0.34
Hypertension	7 (53.8)	5 (100.0)	0.11	26 (55.3)	4 (50.0)	1.00
Atrial fibrillation	3 (23.1)	1 (20.0)	1.00	2 (4.3)	2 (25.0)	0.10
PCI or CABG	6 (46.2)	3 (60.0)	1.00	14 (25.5)	0 (0.0)	0.10
Rheumatic valvular disease	2 (15.4)	0 (0.0)	1.00	6 (12.8)	2 (25.0)	0.33
B-type natriuretic peptide, pg/mL	1118.0 (304.8 – 3066.0)	738.5 (239.3 – 3227.5)	0.80	59.0 (32.5 – 180.5)	200.5 (59.0 – 305.3)	0.38
lnBNP	7.0 (5.7 – 8.0)	6.6 (5.0 – 7.9)	0.60	4.1 (3.5 – 5.2)	5.2 (4.1 – 5.7)	0.12
Blood urea nitrogen, mg/dL	25.2 ± 16.7	18.6 ± 4.7	0.22	18.8 ± 8.5	18.0 ± 4.7	0.81
Creatinine, mg/dL	2.1 ± 2.3	1.9 ± 1.3	0.76	1.0 ± 0.4	0.9 ± 0.1	0.46
Echocardiography						
LVEF, %	36.9 ± 11.2	33.8 ± 8.0	0.59	62.8 ± 5.4	61.5 ± 4.6	0.53
Peak velocity, m/s	3.6 ± 0.4	3.4 ± 0.7	0.37	3.5 ± 0.5	3.6 ± 0.6	0.67
Peak PG, mmHg	53.5 ± 11.7	48.0 ± 17.0	0.44	49.5 ± 16.0	53.4 ± 16.9	0.53
Mean PG, mmHg	30.8 ± 6.8	27.2 ± 10.6	0.41	27.7 ± 9.4	29.8 ± 10.2	0.59

AS, aortic stenosis; AVA, aortic valve area; AVA_{CT}, AVA measured on CT; AVC, aortic valve calcium score; BSA, body surface area; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LF-LG, low-flow and low-gradient; lnBNP, log-transformed B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; MACCE, major adverse cardiac and cerebrovascular event; VTI, velocity time integral.

	Classic LF-LG AS (n = 18)			Paradoxical LF-LG AS (n = 55)		
LVMI, gm/ m^2	151.5 ± 33.5	144.7 ± 26.3	0.69	121.5 ± 32.7	144.6 ± 50.6	0.10
AV TVI, cm	101.3 ± 34.2	78.2 ± 26.9	0.20	114.2 ± 28.2	98.9 ± 21.3	0.15
LVOT TVI, cm	16.0 ± 4.8	16.2 ± 3.8	0.92	21.4 ± 3.6	19.7 ± 3.7	0.24
LVOT diameter, mm	22.1 ± 2.2	21.2 ± 0.2	0.22	21.0 ± 1.4	22.2 ± 2.2	0.18
LVOT diameter/BSA	12.9 ± 1.6	13.6 ± 1.4	0.40	13.0 ± 1.4	13.2 ± 1.2	0.75
AVA_{echo}, mm^2	61.1 ± 12.8	81.9 ± 9.1	0.005	68.2 ± 13.6	77.3 ± 12.7	0.08
ESVI	63.0 ± 30.0	64.4 ± 20.0	0.92	23.4 ± 10.6	30.7 ± 14.5	0.10
EDVI	96.4 ± 32.6	95.9 ± 21.3	0.98	62.0 ± 22.6	78.4 ± 31.5	0.08
SAC, $mL/m^2/mmHg$	0.7 ± 0.3	0.6 ± 0.1	0.52	0.7 ± 0.3	1.0 ± 0.5	0.21
Zva, $mmHg/mL/m^2$	4.7 ± 1.7	5.8 ± 2.2	0.82	4.5 ± 1.4	3.8 ± 1.5	0.21
CT findings						
Valve morphology			0.28			0.14
Tricuspid	9 (69.2)	5 (100.0)		26 (55.3)	2 (25.0)	
Bicuspid	4 (30.8)	0 (0.0)		21 (44.7)	6 (75.0)	
AVC	3912.2 (2247.0 – 4496.1)	1360.1 (960.1 – 2108.6)	0.002	2002.4 (1192.2 – 2841.6)	2584.3 (1306.5 – 5172.0)	0.12
AVA_{CT}	92.4 ± 15.5	122.7 ± 25.2	0.007	90.2 ± 22.4	117.7 ± 27.9	0.003
AVA_{plani}, mm^2	88.2 ± 20.0	129.9 ± 5.4	<0.001	90.1 ± 21.2	140.9 ± 13.8	<0.001

AS, aortic stenosis; AVA, aortic valve area; AVA_{CT}, AVA measured on CT; AVC, aortic valve calcium score; BSA, body surface area; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LF-LG, low-flow and low-gradient; lnBNP, log-transformed B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; MACCE, major adverse cardiac and cerebrovascular event; VTI, velocity time integral.

	Classic LF-LG AS (n = 18)			Paradoxical LF-LG AS (n = 55)		
LVOT area	587.5 ± 129.7	572.3 ± 79.9	0.81	468.9 ± 94.5	581.3 ± 94.9	0.003
Aortic annulus						
Maximum diameter, mm	30.6 ± 3.9	30.0 ± 2.1	0.77	27.1 ± 2.6	29.0 ± 3.6	0.05
Circularity, %	77.6 ± 7.5	76.9 ± 4.4	0.84	82.0 ± 5.7	83.8 ± 7.6	0.18
Mean diameter, mm	27.1 ± 2.9	26.5 ± 1.4	0.70	24.7 ± 2.3	27.0 ± 3.0	0.01
Perimeter, mm	86.0 ± 8.9	83.8 ± 3.7	0.46	78.7 ± 7.4	87.3 ± 10.0	0.01
Area, mm^2	563.3 ± 116.1	532.8 ± 45.9	0.44	475.2 ± 91.3	572.9 ± 113.2	0.009
Sinus of Valsalva, mm	39.3 ± 4.9	36.1 ± 3.4	0.20	35.9 ± 4.6	42.0 ± 4.2	0.001
ST junction, mm	32.1 ± 3.5	30.7 ± 2.8	0.44	30.6 ± 5.1	36.7 ± 7.7	0.006
Ascending aorta, mm	39.5 ± 4.4	35.5 ± 4.2	0.10	39.6 ± 7.1	45.1 ± 9.8	0.06
Normalized to BSA						
AVA_{CT}	53.9 ± 9.4	78.3 ± 16.1	0.001	55.9 ± 14.3	70.3 ± 17.9	0.01
AVA_{plani}, mm^2	51.5 ± 12.3	82.7 ± 6.0	<0.001	55.7 ± 12.7	84.1 ± 10.4	<0.001
LVOT area, mm^2	341.2 ± 69.4	365.5 ± 54.6	0.50	289.3 ± 55.3	345.5 ± 54.4	0.01
Aortic annulus						
Maximal dimeter, mm	17.9 ± 2.8	19.2 ± 2.0	0.35	16.8 ± 1.7	17.4 ± 1.6	0.37
Mean diameter, mm	15.8 ± 2.0	17.0 ± 1.7	0.27	15.3 ± 1.6	16.1 ± 1.6	0.20
Perimeter, mm	50.2 ± 6.0	53.6 ± 5.0	0.28	48.7 ± 4.9	52.0 ± 6.8	0.10

AS, aortic stenosis; AVA, aortic valve area; AVA_{CT}, AVA measured on CT; AVC, aortic valve calcium score; BSA, body surface area; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LF-LG, low-flow and low-gradient; lnBNP, log-transformed B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; MACCE, major adverse cardiac and cerebrovascular event; VTI, velocity time integral.

	Classic LF-LG AS (n = 18)			Paradoxical LF-LG AS (n = 55)		
Area, mm^2	327.6 ± 65.3	339.7 ± 26.4	0.70	292.7 ± 50.4	341.4 ± 71.4	0.02
Sinus of Valsalva	22.9 ± 3.0	23.0 ± 2.4	0.95	22.1 ± 2.6	25.1 ± 3.5	0.007
ST junction diameter	18.7 ± 1.9	19.6 ± 2.5	0.40	18.9 ± 2.5	21.9 ± 5.3	0.01
Ascending aorta tubular portion	23.1 ± 3.0	22.6 ± 2.9	0.78	24.5 ± 4.3	26.9 ± 5.7	0.18
Surgical valve size, mm	23.2 ± 2.3	22.6 ± 1.7	0.63	22.1 ± 2.1	23.3 ± 1.7	0.14
MACCE (cardiovascular death)	2 (15.4)	3 (60.0)	0.10	4 (8.5)	0 (0.0)	1.00
Overall mortality	4 (30.8)	2 (40.0)	1.00	7 (14.9)	1 (12.5)	1.00

AS, aortic stenosis; AVA, aortic valve area; AVA_{CT}, AVA measured on CT; AVC, aortic valve calcium score; BSA, body surface area; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LF-LG, low-flow and low-gradient; lnBNP, log-transformed B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; MACCE, major adverse cardiac and cerebrovascular event; VTI, velocity time integral.

Outcome analysis

MACCE were composed of arrhythmia (n=6), nonfatal cerebrovascular accident (CVA) (n=10), nonfatal myocardial infarction (n=4), heart failure (n=4), reoperation (n=1), and cardiovascular death (n=18). To identify clinical and radiological factors that affect MACCE, cox-proportional hazard regression analysis was performed (Table 3). In univariate analysis, older age, high BNP, high blood urea nitrogen and creatinine, presence of preoperative AF, tricuspid AV, classic LF-LG AS, small AV VTI and LVOT VTI, and small aortic annulus were factors significantly associated with MACCE ($P<0.05$, for all).

Table 3
Cox proportional hazard regression model for prediction of MACCE

	Univariate		Multivariable	
Parameter	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years	1.06 (1.02–1.10)	0.005	1.04 (1.00–1.09)	0.049
Body surface area, m^2	0.49 (0.08–3.15)	0.45		
B-type natriuretic peptide, 10 pg/mL	1.01 (1.003–1.01)	<0.001	1.005 (1.003–1.01)	<0.001
lnBNP	1.42 (1.13–1.77)	0.002		
Atrial fibrillation, (%)	3.22 (1.70–6.11)	<0.001	2.75 (1.40–5.40)	0.003
LVEF, %	0.98 (0.96–1.01)	0.20		
Peak velocity, m/s	0.80 (0.57–1.12)	0.19		
Mean PG, mmHg	0.99 (0.98–1.01)	0.21		
LVMI, gm/ m^2	0.99 (0.99–1.00)	0.18		
ESVI, mL/m^2	1.01 (0.99–1.02)	0.55		
EDVI, mL/m^2	1.00 (0.99–1.01)	0.90		
SAC, mL/m^2/mmHg	0.57 (0.21–1.53)	0.27		
Zva, mmHg/mL/m^2	1.00 (0.83–1.20)	0.98		
Bicuspid aortic valve	0.40 (0.21–0.77)	0.006		
Classic LF-LG AS	5.04 (1.98–12.84)	0.001	5.53 (1.74–17.56)	0.004
AVA_{echo}, m^2	1.01 (0.99–1.03)	0.60		
AV VTI, cm	0.98 (0.96–0.99)	<0.001		
LVOT VTI, cm	0.92 (0.86–0.99)	0.02		
lnAVC	0.89 (0.71–1.09)	0.26		

AS, aortic stenosis; AVA, aortic valve area; AVC, aortic valve calcium score; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; HR, hazard ratio; LF-LG, low-flow and low-gradient; lnBNP, log-transformed B-type natriuretic peptide;LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; MACCE, major adverse cardiac and cerebrovascular event; PG, Pressure gradient; SAC, systemic arterial compliance; VTI, velocity time integral; Zva, valvulo-arterial impedance.

	Univariate		Multivariable	
Normalized AVA_{plani}, mm^2	1.00 (0.98–1.03)	0.76		
Normalized AVA_{CT}, mm^2	1.02 (1.00–1.04)	0.50		
Annulus circularity, %	0.34 (0.01–18.69)	0.59		
Aortic annulus area, cm^2	0.73 (0.53 – 1.01)	0.06	0.57 (0.40 – 0.81)	0.002
Surgical valve size, mm	0.89 (0.77–1.04)	0.13		
Surgical valve type				
CE Magna	1	0.63		
ATSAP	0.55 (0.20 – 1.48)	0.24		
Hancock	1.09 (0.50 – 2.38)	0.83		
St. Jude Regent	0.63 (0.25 – 1.59)	0.32		
Others	0.85 (0.31 – 2.31)	0.75		
Operator				
Operator 1	1	0.33		
Operator 2	1.63 (0.78 – 3.38)	0.19		
Operator 3	0.37 (0.05 – 2. 76)	0.33		
Operator 4	0.94 (0.37 – 2.41)	0.90		
Operator 5	0.73 (0.30 – 1.78)	0.49		
AS, aortic stenosis; AVA, aortic valve area; AVC, aortic valve calcium score; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; HR, hazard ratio; LF-LG, low-flow and low-gradient; lnBNP, log-transformed B-type natriuretic peptide;LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; MACCE, major adverse cardiac and cerebrovascular event; PG, Pressure gradient; SAC, systemic arterial compliance; VTI, velocity time integral; Zva, valvulo-arterial impedance.				

On multivariable analysis, old age (hazard ratio [HR], 1.04, 95%CI, 1.00–1.09; P=0.049), high BNP (HR, 1.005; 95%CI, 1.003–1.01 P<0.001), AF (HR, 2.75; 95% CI, 1.40–5.40; P=0.003), classic LF LG AS (HR, 5.53; 95%CI, 1.74–17.56; P=0.004), and small aortic annulus area (cm^2), [HR, 0.57; 95%CI, 0.40–0.81; P=0.002]) were factors significantly associated with MACCE (Table 3). Normalized aortic annulus area (cm^2) (HR, 0.40; 95%CI, 0.22–0.74; P=0.004) was also a significantly associated factor when the parameter was substitute instead of aortic annulus area in multivariable analysis. When the normalized aortic sinus of Valsalva diameter instead of the aortic annulus size was substituted in the calculation, the weight of the other factors remained almost unchanged, while the normalized aortic sinus of Valsalva diameter (cm) (HR, 0.30; 95%CI, 0.09–0.98; P=0.04) was also identified as a significant factor.

Kaplan-Meier curves indicated significant mortality in the high BNP group (BNP>700 pg/mL) compared to the low BNP group (P=0.001) (Figure 3A). Furthermore, preoperative AF was also associated with significant mortality (Figure 3B) (P<0.001), and the outcome of classic LF-LG AS was worse in the cumulative survival curve (Figure 3C) (P=0.001).

Discussion

This study highlights the characteristics of LF-LG AS focusing on CT findings. The AVA_{CT} and aortic annulus were larger in classic LF-LG AS compared to those in high-gradient severe AS and 27.8% of classic LF-LG AS patients presented $AVA_{CT} \geq 1.2$ cm^2. High BNP, preoperative AF, classic LF-LG AS, and smaller aortic root were associated with MACCE after AVR.

Classic LF-LG AS patients demonstrated higher ESVI and EDVI, lower LVEF, larger AVA_{echo} and AVA_{CT}, and larger aortic annulus compared to high-gradient severe AS. The key messages of this study are demonstrated in Figure 4. In a previous study, patients with severe AS had significantly larger aortic annulus and ST junction diameters compared with those measured in control groups.[16] This could be attributed to aortic root remodelling: as severe AS progresses ESVI and EDVI increase to compensate, and dilated LV cavity may lead to dilatation of the aortic annulus. Failure to compensate may result in heart failure. Since the BNP was higher in classic LF-LG AS and the group presented poor outcome compared to high-gradient severe AS, classic LF-LG AS may be a compensation failure of high-gradient severe AS. Paradoxical LF-LG AS presented preserved ESVI, EDVI, and LVEF, although AVA_{echo} and AVA_{CT} were larger than in high-gradient severe AS.

In this study, we used cut-off value of $AVA_{CT}<1.2$ cm^2 as this value was suggested for severe AS in a previous study.[14] However, in classic LF-LG AS group, approximately one third of the patients exhibited $AVA_{CT} \geq 1.2$ cm^2. AVC was lower in the $AVA_{CT} \geq 1.2$ cm^2 compared to that of $AVA_{CT}<1.2 cm^2$ group, and in this group, moderate AS patients might be misclassified as severe AS and vice versa. This can also be applied to paradoxical LF-LG patients, despite 14.5% of these patients presenting $AVA_{CT} \geq 1.2$ cm^2. Although we could not derive the role of AVA_{CT} in diagnosing LF-LG AS patients, further studies whether AVA_{CT} could be used to discriminate true LF-LG AS are would be of value.

The outcome of AS after AVR was associated with preoperative high BNP levels, AF, classic LF-LG AS, and small aortic root. The plasma BNP level was associated with LV dysfunction in AS, and was a well-known predictor of poor outcome in patients with AS overall and after AVR.[17–19] AF is also a dominant predictor in both asymptomatic and symptomatic patients with moderate to severe AS, and after AVR.[20–22] Classic LF-LG AS was associated with worse outcomes after AVR compared those observed in high-gradient AS patients, although LF-LG AS patients have displayed survival benefits with AVR.[3] Finally, small aortic root measured on CT was an independent prognostic factor. This finding should be interpreted cautiously. When AS severity progresses, the increased LV cavity volume may increase the size of the aortic annulus and sinus of Valsalva. However, a small aortic root has also been associated with increased ischemic cardiovascular events and mortality in patients with AS,[23] possibly reflecting impaired root remodelling process and atherosclerotic changes.

Our study has several limitations. Because this is a retrospective study using a patient cohort that underwent AVR, patients not indicated for surgery due to poor general conditions or comorbidities or who declined operation were not included. The selection bias may affect the outcome assessment, and AVR itself was not used as an outcome parameter. Instead, we used MACCE after AVR. Therefore, the outcomes of this study may not directly infer the outcomes of AS population managed with diverse treatment options. Further studies with AS managed by conservative treatment, surgical AVR, and transcatheter AVR could be of value to evaluate overall outcomes of AS patients. Second, because the small number of LF-LG AS patients, we could not observe the role of AVA_{CT} for reclassification of LF-LG AS. However, we showed the CT characteristics of LF-LG AS: AVA_{CT} and aortic annulus were larger in classic LF-LG AS compared to those in high-gradient severe AS. This finding may be explained by the aortic root remodelling which is associated with the dilated LV. Third, although classic LF-LG patients showed higher overall mortality and a large aortic annulus, a small aortic root was one of the factors associated with MACCE. Both decreased LV function in classic LF-LG AS and impaired aortic root remodelling may contribute to the outcome, respectively, but further studies are necessary to provide more evidences.

In conclusion, classic LF-LG AS presented larger AVA_{CT} and aortic annulus than high-gradient severe AS. Old age, high BNP, AF, classic LF-LG AS and small aortic root on CT were associated with MACCE after AVR. These findings suggest the potential role of cardiac CT in classification and outcome assessment of severe AS.

Methods

Patients

This retrospective study was approved by the institutional review board committee of the Asan Medical Center, University of Ulsan College of Medicine (approval number: 2018-0233) and informed consent was waived by the institutional review board committee of the Asan Medical Center, University of Ulsan College of Medicine due to the retrospective nature of observational study. This study was performed in accordance with the Helsinki Declaration. Between June 2011 and Mar 2016, 781 patients underwent surgical AVR. The use of CT was determined mainly by clinician's decision, but in our hospital, cardiac CT examination is generally performed in most of the patients who have performed planned surgical AVR for evaluation of AV and root morphology based on the guidelines for the appropriate use of cardiac CT[24–27]. After excluding patients with moderate AS (n=24), moderate degree of concomitant aortic regurgitation or other valvular heart disease (n=177), patients not subjected to preoperative cardiac CT (n=47) or CT without multiphase data (n=21), and a patient with quadricuspid AV (n=1), 511 patients were included. High-gradient severe AS was defined as AVA_{echo}<1 cm^2 and a mean trans-valvular gradient ≥40 mmHg with LVEF < 50%. Classic LF-LG severe AS was defined as AVA_{echo}<1 cm^2, but with a low-gradient (<40 mmHg). Low-gradient severe AS with preserved LVEF was defined as paradoxical LF-LG AS. We classified patients with AS into three groups: 1) high-gradient severe; 2) classic LF-LG; and 3) paradoxical LF-LG AS. Clinical findings including age, body surface area (BSA), hypertension, atrial fibrillation (AF), B-type natriuretic peptide (BNP), echocardiography parameters, and cardiac CT data were collected. Postoperative echocardiography findings and reported clinical outcomes were comprehensively reviewed. Clinical outcomes included all-cause mortality and MACCE (composite of cardiac death, cerebrovascular accident or stroke, coronary artery revascularization or myocardial infarction, and redo-AVR) were evaluated.

Echocardiography

Preoperatively, all patients underwent transthoracic echocardiography using commercially available ultrasound machines with 3–5 MHz real-time transducers (iE33, EPIC; Philips Medical Systems, Andover, MA; Vivid 7, E9, General Electric Healthcare, Waukesha, WI, USA). Comprehensive two-dimensional and Doppler images were obtained by expert cardiologists according to American Society of Echocardiography recommendations.[28] End-systolic volume, end-diastolic volume, and LVEF were obtained with the biplane Simpson method. The maximal aortic jet velocity was recorded with the apical, right parasternal, or suprasternal window that yielded the highest-velocity signal. The maximal and mean PG across the AV were estimated using a modified Bernoulli equation, and the AVA was calculated from the continuity equation. LV mass and LV mass indexed to body surface area calculated by LV cavity dimension and LV wall thickness at end-diastole. Systemic arterial compliance (SAC) was calculated as the ratio of SV index (SVI)/pulse pressure,[29] and valvulo-arterial impedance (Zva), which is a parameter for global LV load, was defined as (systolic blood pressure + mean net aortic gradient)/SVI.[30]

Cardiac CT protocol and image analysis

Preoperative cardiac CT was performed using a second-generation dual-source CT scanner (Somatom Definition Flash; Siemens Medical Solutions, Forchheim, Germany). Detailed CT protocol is described in supplementary file 1. Post-processing was conducted using an external workstation (AquariusNet; TeraRecon, Foster City, CA, USA) using multiphase CT data sets reconstructed by a 10% R-R interval. CT analysis methods are described in supplementary figure 1. CT characteristics such as AV morphology (tricuspid, bicuspid with raphe, and bicuspid without raphe), AVA_{CT}, AVA obtained by planimetry (AVA_{plani}), aortic annulus diameter, perimeter, and area, circularity (minimum annulus diameter/maximum annulus diameter×100), and diameters of sinus of Valsalva, sinotubular (ST) junction, and ascending aorta tubular portion were measured by two experienced radiologists in consensus (BLINDED). AVA_{CT} was calculated by using the LV outflow tract (LVOT) area measured on CT in the continuity equation with velocity time integrals (VTI) at LVOT and transaortic flow: $AVA_{CT}=LVOT_{CT}\times VTI_{LVOT}/VTI_{Ao}$.

AVC was defined as a CT density of 130 Hounsfield units or greater confined to AV on non-enhanced cardiac gated images and measured using the methods suggested by Agatston et al. The AVC was measured using a commercially available software (Syngo.via Siemens Healthcare, Berlin, Germany).[31]

Systolic phase with largest AVA (20~30% RR) was selected and thick multiplanar reconstruction images were used to demarcate the tips of the aortic cusps for measuring AVA_{plani}. To evaluate reliability of CT measurements, a third experienced radiologist (BLINDED) measured CT parameters in 100 randomly selected cases and interobserver agreement was determined. Observers were blinded to clinical data including echocardiography findings and operation records.

Statistics

Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR) and categorical variables are presented as numbers and percentages. Interobserver agreement of CT findings was determined using a two-way random model intra-class correlation coefficient (ICC) with consistency assumption. Comparison of AVA measured on echocardiography (AVA_{echo}) and CT including AVA_{CT} and AVA_{plani} was performed using Pearson correlations and Bland-Altman plots were graphed. One way ANOVA with post-hoc (Tukey) test or Kruskall-Wallis test and Chi-square test were used to compare baseline clinical and radiological findings among high-gradient severe AS, classic LF-LG AS, paradoxical LF-LG AS, and moderate AS groups. Bonferroni correction was applied to control the type I error for multiple comparison, and P-value 0.05/4=0.0125 was used for comparing the three groups. Student t-test and Chi-square test were performed to compare two subgroups among the three groups. In LF-LG AS patients, clinical and CT findings for AVA_{CT}<1.2 cm^2 and AVA_{CT}≥1.2 cm^2 were compared using the Student t-test and Chi-square test or Fisher's exact test. For the stratification of risk factors for MACCE after AVR, cox proportional hazard models were used. Kaplan-Meier survival curves were drawn for statistically significant factors to predict MACCE. The 95% confidence intervals (CIs) were calculated and factors with P<0.10 were included for multivariable cox regression analysis with enter method. To avoid multicollinearity, one of the aortic root parameters was included in the multivariable analysis among the CT parameters significantly associated with MACCE in univariate analysis. For BNP analysis, a continuous parameter was used and a cut-off of 700 pg/mL[32] was set for outcome analysis using Kaplan-Meier curves.[19] P<0.05 was considered statistically significant, except for multiple dependant variable analyses. Statistical analysis was performed using commercial software (SPSS, version 20; SPSS, Chicago, IL, USA).

Declarations

Data availability

All data used during the current study are included in this published article or are available from the corresponding author upon reasonable request.

Contributions

Conception: H.J.K. and D.K., Data curation: H.J.K., S.L., J.B.K. J-M.S. D-K.K, J-K. S., J-W. K., D.H.Y., Statistical analyses, H.J.K., and H.J.K, Manuscript writing: S.J.C., Y.A., H.J.K., Revising the manuscript: H.J.K. and D.K. All authors approved the final version of this manuscript.

Funding

This study was supported by a grant (2021IT0006) from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea.

Competing interests

The authors declare no competing interests.

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Figures

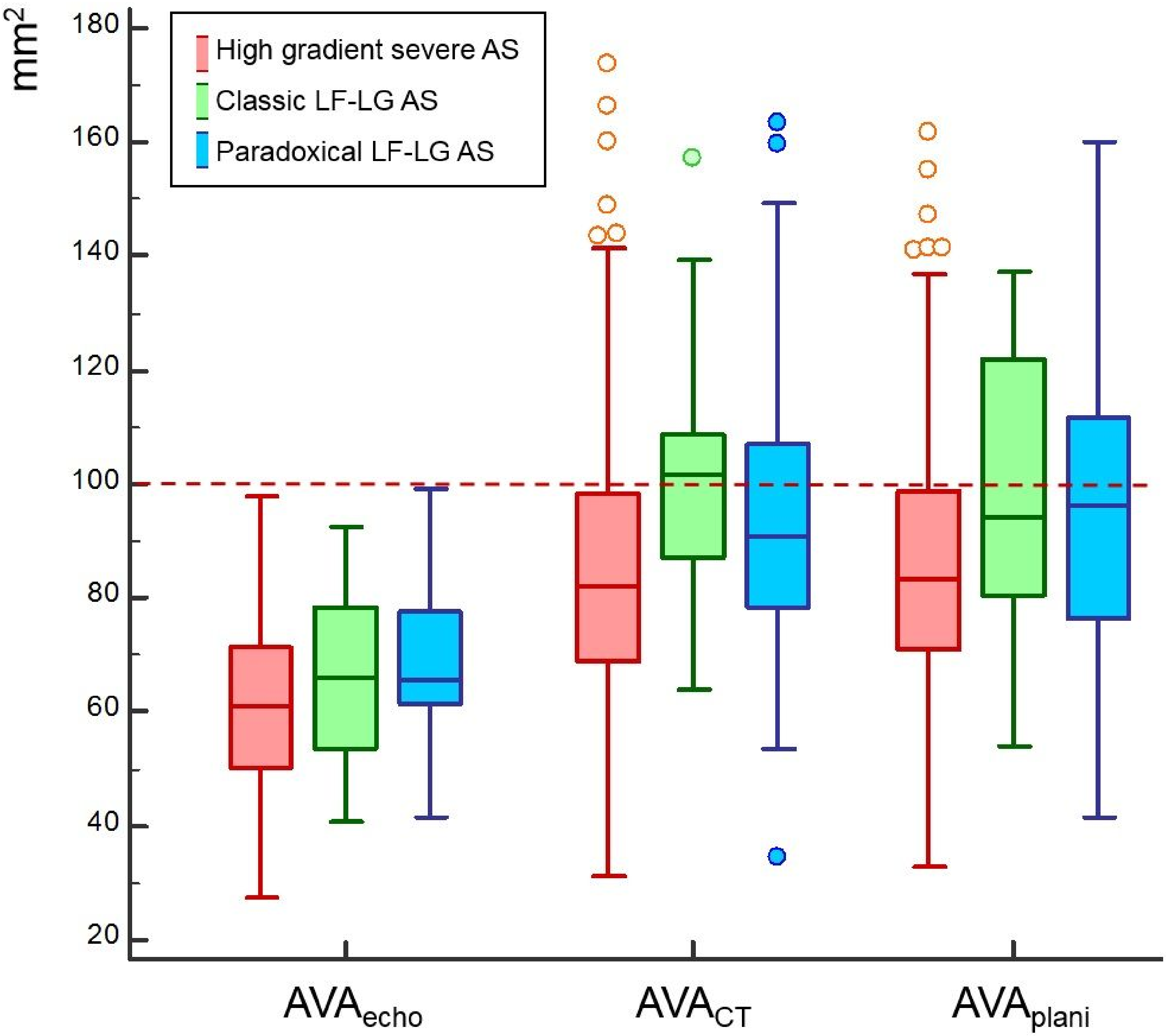

Figure 1

Box plot to demonstrate the distribution of AVA$_{echo}$, AVA$_{CT}$, and AVA$_{plani}$ according to categories of aortic stenosis

AS, aortic stenosis; AVA, aortic valve area; LF-LG, low-flow and low-gradient

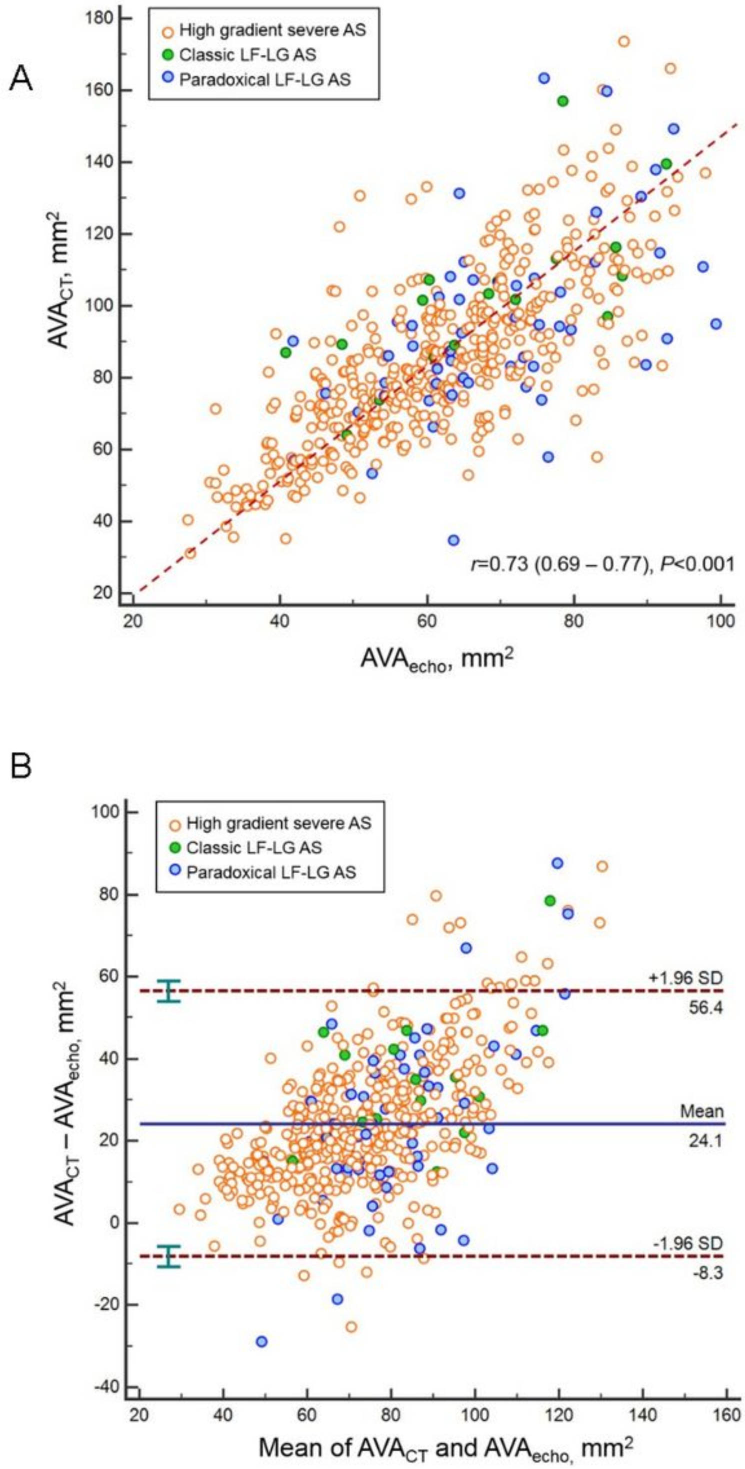

Figure 2

(a) Pearson correlation analysis result and (b) Bland–Altman plot to comparison of AVA_{CT} and AVA_{echo}

AS, aortic stenosis; AVA, aortic valve area; LF-LG, low-flow and low-gradient

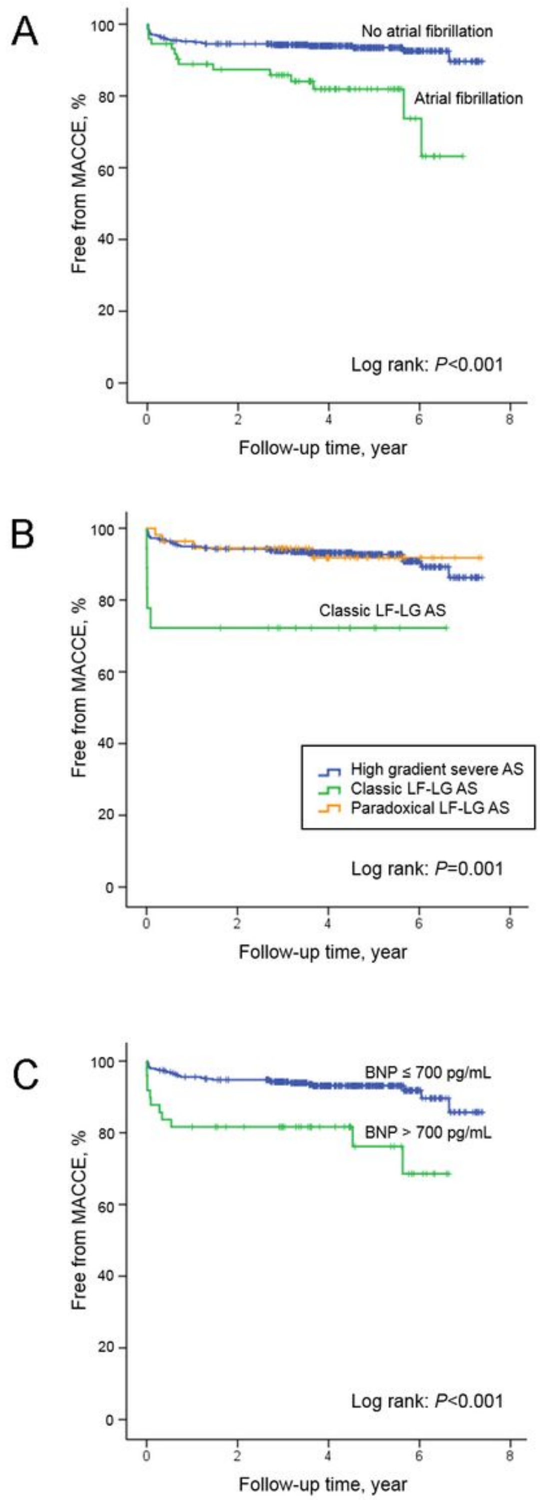

Figure 3

Survival according to (a) B-type natriuretic peptide, (b) presence of atrial fibrillation, and (c) categories of aortic stenosis

AS, aortic stenosis; LF-LG, low-flow and low-gradient

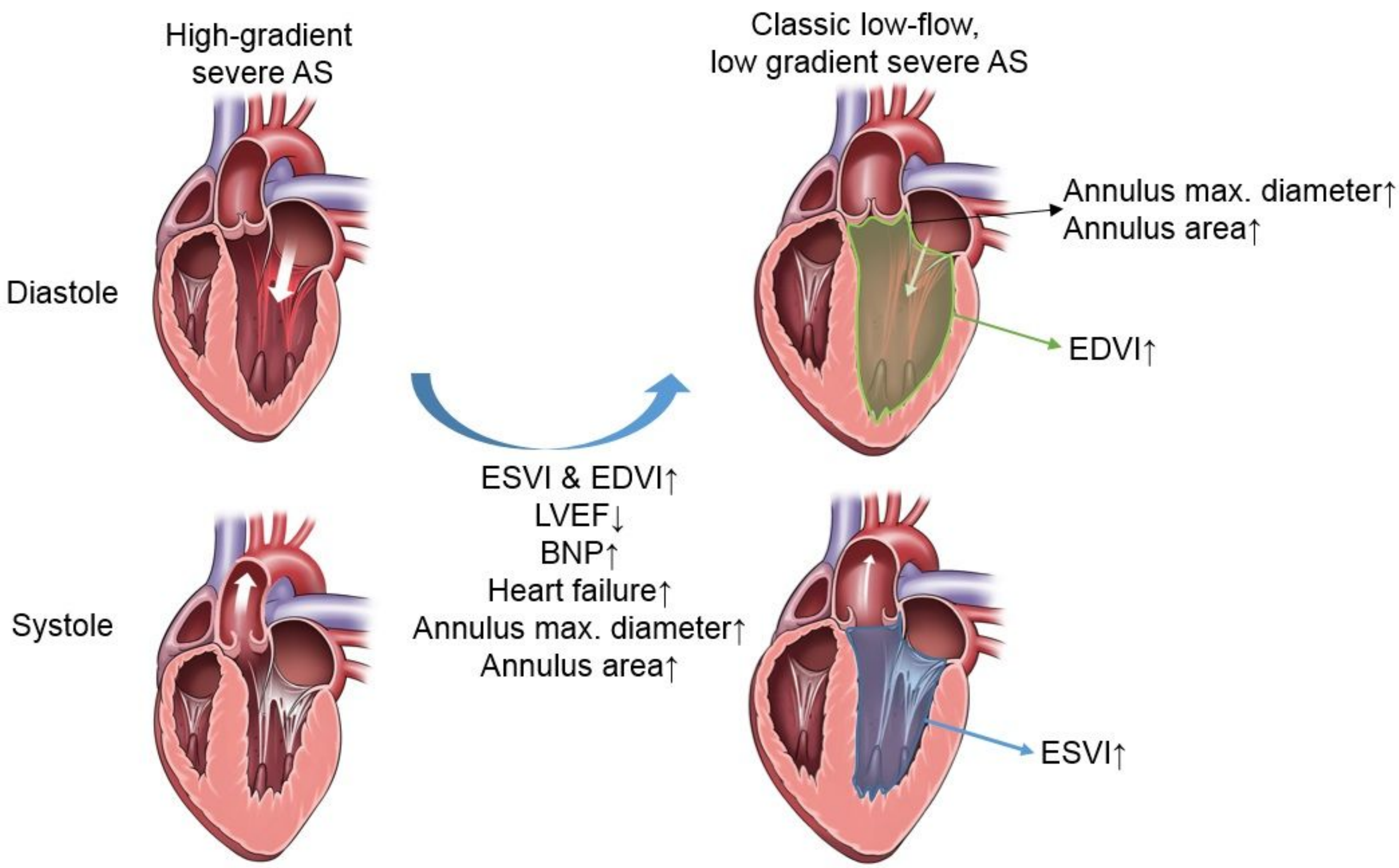

Figure 4

Characteristics of classic LF-LG AS

AS, aortic stenosis; BNP, B-type natriuretic peptide; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LVEF, left ventricular ejection fraction;

Supplementary Files

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- LFLGSupplementaryFile.docx