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ORIGINAL RESEARCH

Diffuse Interstitial Fibrosis of the Myocardium Predicts Outcome in Moderate and Asymptomatic Severe Aortic Stenosis

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ABSTRACT

BACKGROUND Patients with moderate or asymptomatic severe aortic stenosis (AS) are at risk of cardiovascular events.

OBJECTIVES The authors investigated the utility of cardiac magnetic resonance (CMR) to identify drivers of outcome in patients with moderate or asymptomatic severe AS.

METHODS A prospective, international, multicenter cohort (n = 457) of patients with moderate (aortic valve area [AVA]: 1.0-1.5 cm^2) or asymptomatic severe AS (AVA ≤1.0 cm^2 and NYHA functional class I-II) patients underwent CMR. Diffuse interstitial fibrosis and scar in the myocardium were analyzed with extracellular volume fraction (ECV%) and late gadolinium enhancement (LGE). The outcome was a composite of mortality and heart failure admission.

RESULTS Median ECV% was 26.6% (IQR: 24.4%-29.9%), and LGE was present in 31.5% (median 0.8%; IQR: 0.1%-1.7%). Greater AS severity was associated with greater left ventricular mass and diastolic dysfunction, but not with ECV% or LGE. During a median 5.7 years of follow-up, 83 events occurred. Patients with events had higher ECV% (median ECV % 26.3% vs 28.2%; $P = 0.003$). Patients in the highest ECV% tertiles (ECV% >28.6%) had worse outcomes both in the entire cohort and in those with NYHA functional class I moderate or severe AS, and ECV% was independently associated with outcome (adjusted HR: 1.05; $P = 0.039$). The ECV% had significant incremental prognostic value when added to parameters of AS severity and cardiac function, comorbidities, aortic valve replacement, and LGE ($P < 0.05$).

CONCLUSIONS Increased diffuse interstitial fibrosis of the myocardium is associated with poor outcomes in patients with moderate and asymptomatic severe AS and can help identify those who require closer surveillance for adverse outcomes. (JACC Cardiovasc Imaging. 2025;18:180-191) © 2025 by the American College of Cardiology Foundation.

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Although patients with severe aortic stenosis (AS) experience a downhill clinical course when symptoms develop,[1,2] recent data suggest that even patients with asymptomatic severe or moderate AS are at high risk of adverse events.[3,4] Current guidelines recommend aortic valve replacement (AVR) for patients with severe AS who have symptoms or left ventricular (LV) systolic dysfunction and watchful surveillance for those with moderate AS;[5,6] however, recent trials have shown benefits of early AVR in patients with asymptomatic severe AS.[7,8] Recent decrease of periprocedural risks associated with AVR,[9] especially transcatheter AVR, has led to an expansion of indications for intervention in severe AS. With this, trials are ongoing to investigate the benefit of transcatheter AVR in selected patients with moderate AS.

Despite these improvements, AVR still carries an inevitable risk of complications, and it is unclear whether all patients with asymptomatic severe or moderate AS would benefit from early intervention. In the pressure-overloaded heart, myocardial fibrosis is a key marker of myocardial damage and a pathologic driver of the progression from compensated hypertrophy to decompensated heart failure.[10-12] Myocardial fibrosis is observed in 2 forms, diffuse interstitial fibrosis and focal replacement scar, both of which can be noninvasively imaged with cardiac magnetic resonance (CMR). Increased myocardial fibrosis on CMR is associated with worse prognosis in patients with severe AS undergoing AVR.[13-15] In moderate or asymptomatic severe AS, the degree of extravalvular cardiac damage by echocardiography is associated with worse outcome;[16,17] however, there is a lack of data on the extent and prognostic value of myocardial fibrosis in these patients. Although guidelines state that AVR can be considered in patients with asymptomatic severe AS who have a low surgical risk and in those with certain indicators of adverse prognosis,[5,6] there is no mention of myocardial fibrosis to identify those at increased risk in this population.

In this prospective study, we hypothesized that the degree of myocardial fibrosis on CMR may help identify those at high risk of adverse events among patients with moderate or asymptomatic severe AS—a group of patients without established markers to guide intervention. The aim of this study was to investigate the drivers of outcome in patients with moderate or asymptomatic severe AS and, in particular, the prognostic implications of myocardial fibrosis detected by CMR.

METHODS

The study complied with the Declaration of Helsinki, and the local institutional review boards approved the study protocol. All participants provided written informed consent.

STUDY POPULATION. Patients with moderate or asymptomatic severe AS were prospectively recruited from 5 international sites and underwent CMR. Moderate AS was defined as aortic valve area (AVA) >1.0 and ≤1.5 cm^2, and severe AS AVA ≤1.0 cm^2 on echocardiography, based on the guidelines and previous papers.[5,6,17,18] Patients with severe AS who had significant exertional dyspnea, angina, and syncope were excluded from analysis; however, patients with severe AS in NYHA functional class II were included, considering that the NYHA functional class grading is subjective. Details are available in Supplemental Methods.

CARDIAC MAGNETIC RESONANCE. Patients underwent CMR at a median interval of 5 days (IQR: 0-29 days) from their echocardiography. The details of the CMR acquisition and analyses are presented in Supplemental Table 1 and Supplemental Methods. Chamber sizes, ventricular mass, and myocardial scar/fibrosis were measured according to standardized protocols.[14] The degree of diffuse interstitial fibrosis in the myocardium was estimated by calculating the relative extracellular volume fraction (ECV%) or absolute indexed extracellular volume (iECV) of the myocardium, using pregadolinium and postgadolinium T1 values measured at the short-axis midventricular septum and blood pool, hematocrit from blood samples at the time of CMR, and LV mass derived from CMR. The degree of replacement myocardial scar was analyzed first by visually assessing the presence and pattern of LGE as either "absent," "infarct (subendocardial)," or "noninfarct (LGE in areas other than the subendocardium, such as the midwall or right ventricular insertion point)" (Supplemental Figure 1), and second, by quantification of the LGE percentage of the entire LV myocardium (LGE%). Patients with mixed infarct and noninfarct patterns of LGE were included in the noninfarct group, considering that they had myocardial scar resulting from their valve disease. The myocardial area with noninfarct LGE was included in the ECV% assessment, and that with infarct-related LGE was excluded.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

CMR = cardiac magnetic resonance

ECV% = extracellular volume fraction

LGE = late gadolinium enhancement

LV = left ventricular

NT-proBNP = N-terminal pro brain natriuretic peptide

CLINICAL OUTCOMES. The primary outcome was a composite of all-cause mortality and unplanned admission for heart failure. Admission for heart failure was defined as symptoms and/or signs of congestion or low cardiac output requiring admission and use of intravenous diuretic agents or inotropic agents. Events were assessed by review of medical records, reports from family members, and official death certificates when available. AVR was performed at the discretion of the attending physician. Patients were followed up from the date of CMR to the last clinical visit or death.

STATISTICAL ANALYSIS. Details are available in Supplemental Methods. Clinical, echocardiographic, and CMR variables were compared between groups by AS severity and clinical events. Predictors of outcome were determined using univariable and multivariable Cox regression analysis. AVR was analyzed and adjusted for as a time-varying covariate in the Cox regression analysis[19] and was not considered as a censoring event. Tests for interaction were conducted to evaluate subgroup differences in the prognostic utility of myocardial fibrosis. Kaplan-Meier survival curves with log-rank tests were used to compare event-free survival according to the ECV% tertiles. For sensitivity analysis, the study cohort was defined using alternative criteria for AS severity with aortic peak velocity and mean pressure gradient[5,6] and then analyzed similarly. The incremental prognostic value of ECV% and LGE% over clinically important prognosticators, such as parameters of AS severity and cardiac function, AVR, comorbidities, and N-terminal pro brain natriuretic peptide (NT-proBNP), was assessed with net reclassification improvement analysis. Two-sided value of $P < 0.05$ was considered statistically significant. Analyses were conducted using R version 4.0 and SPSS version 25.

RESULTS

COMPARISON OF MYOCARDIAL REMODELING AND FIBROSIS ACCORDING TO THE SEVERITY OF AS. A total of 457 patients were included in the study (moderate AS, n = 176; asymptomatic severe AS, n = 281) (Supplemental Figure 2). The baseline clinical, echocardiographic, and CMR data of the population are presented in **Table 1** and Supplemental Table 2. The mean age was 68.5 ± 11.1 years, and 67.0% were men. There were 119 patients (26.0%) with low-gradient severe AS (aortic peak velocity <4 m/s and mean pressure gradient <40 mm Hg). The median ECV% was 26.6%; LGE was present in 31.5% but in minimal amounts. The distributions of both parameters are shown in Supplemental Figure 3. During follow-up, 311 patients (68.1%) received AVR at a median interval of 363 days (range 1-2,843 days; IQR: 25-1,028 days) after CMR, of whom 281 underwent surgical AVR and 30 transcatheter AVR; 156 (34.1%) received AVR within 1 year of the CMR.

Compared to patients with asymptomatic severe AS patients with moderate AS had a greater proportion of men and subjects with NYHA functional class I, and they less frequently underwent AVR (51.1% vs 78.6%, respectively). Compared to patients with asymptomatic severe AS, patients with moderate AS tended to have a lesser degree of LV diastolic dysfunction (E/e′ ratio 12.4 vs 14.2; $P < 0.001$) and lower LV mass (LV mass index 77.0 vs 81.1 g/m^2; $P = 0.034$) (**Figure 1**, **Table 1**). However, despite the differences in AS severity, there was no significant difference in the extent of diffuse interstitial fibrosis or replacement myocardial scar between the 2 groups (median ECV% 26.3% vs 27.0%; $P = 0.154$; presence of LGE 31.0% vs 31.8%; $P = 0.949$; for patients with moderate vs asymptomatic severe AS, respectively). To note, there was no difference in the proportion of diffuse fibrosis (ECV%), but the total volume (iECV) of diffuse fibrosis was higher in patients with severe AS, related to higher LV mass.

PREDICTORS OF CLINICAL OUTCOME IN MODERATE OR ASYMPTOMATIC SEVERE AS PATIENTS. During a median 5.7-years of follow-up (IQR: 4.5-6.7 years), there were 83 (18.2%) clinical events (all-cause mortality, n = 67; unplanned admission for heart failure, n = 23) (Supplemental Table 3). Compared with patients without events, those with events had smaller AVA, greater LV diastolic dysfunction (E/e′ ratio 13.2 vs 15.1; $P = 0.001$), smaller right ventricular volumes ($P < 0.001$), and increased diffuse interstitial fibrosis (ECV% 28.2% vs. 26.3%; $P = 0.003$) (Supplemental Figure 4, Supplemental Table 4).

Univariable Cox regression analysis showed positive associations between ECV% and clinical outcome (HR: 1.06 [95% CI: 1.02-1.11]; $P = 0.004$). Other univariable predictors of outcome included age, NYHA functional class, diabetes, hypertension, prior hospitalization for heart failure, atrial fibrillation, peripheral arterial disease, chronic lung disease, lower estimated glomerular filtration rate, higher NT-proBNP level, use of β-blockers, smaller AVA, greater E/e′ ratio, smaller stroke volume index, and smaller right ventricular size (Supplemental Table 5). iECV was not a significant predictor of outcome (HR: 1.01 [95% CI: 0.98-1.04]; $P = 0.570$). The presence or pattern of LGE was not a predictor of outcome, although the amount of LGE (ie, LGE% of the entire

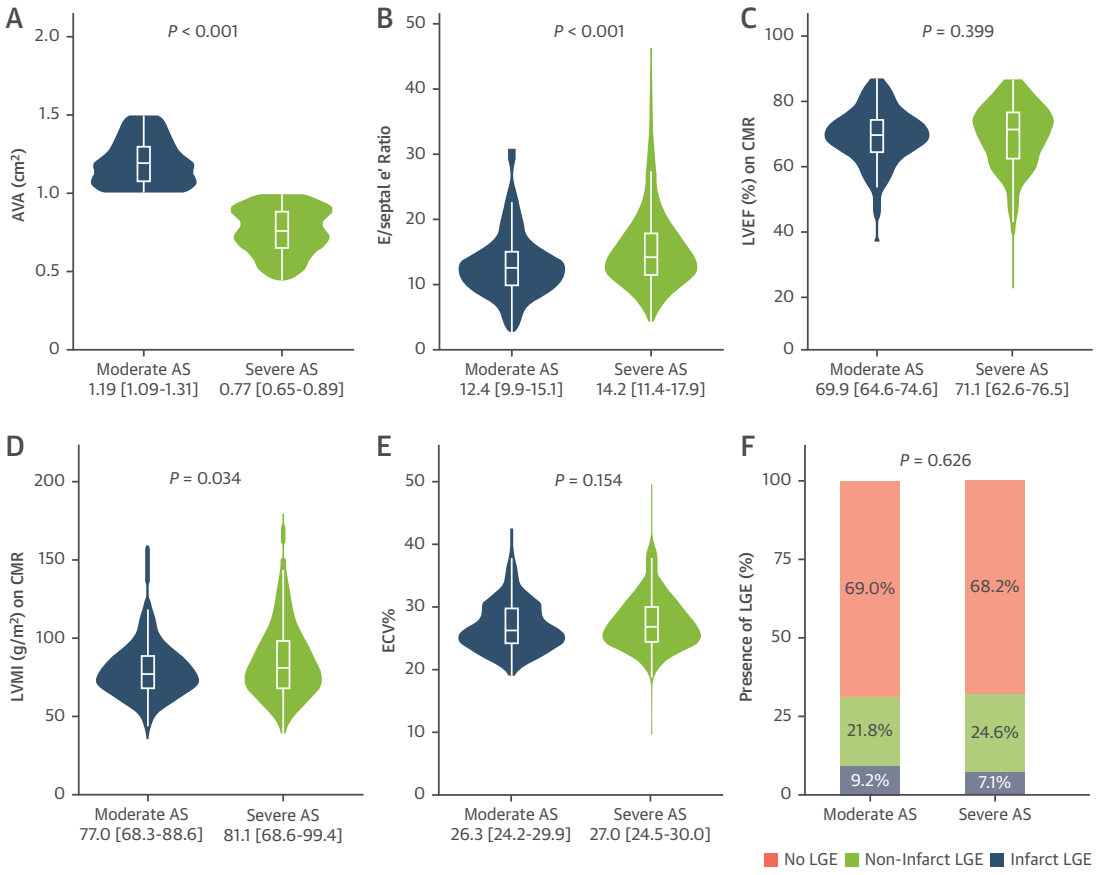
TABLE 1 Comparison of Clinical and Myocardial Remodeling Parameters by Severity of Aortic Stenosis

	Total (N = 457)	Moderate AS (n = 176)	Asymptomatic Severe AS (n = 281)	*P* Value
Age, y	70 (63-76)	69.5 (62-75)	71 (64-77)	0.171
Male	306 (67.0)	132 (75.0)	174 (61.9)	0.005
BMI, kg/m^2	26.9 (24.1-29.7)	27.7 (24.7-30.8)	26.5 (23.9-29.3)	0.010
BSA, m^2	1.84 ± 0.20	1.90 ± 0.20	1.81 ± 0.19	<0.001
Bicuspid AV[a]	147 (32.2)	56 (31.8)	91 (32.4)	0.981
NYHA functional class				<0.001
I	256 (56.0)	122 (69.3)	134 (47.7)	
II	186 (40.7)	39 (22.2)	147 (52.3)	
III-IV	15 (3.3)	15 (8.5)	0	
Diabetes mellitus	73 (16.0)	32 (18.2)	41 (14.6)	0.374
Hypertension	285 (62.4)	115 (65.3)	170 (60.5)	0.347
Prior hospitalization for HF	4 (0.9)	2 (1.1)	2 (0.7)	0.999
Significant CAD	131 (28.7)	54 (30.7)	77 (27.4)	0.517
Atrial fibrillation	48 (10.5)	16 (9.1)	32 (11.4)	0.534
Stroke	18 (3.9)	9 (5.1)	9 (3.2)	0.438
Peripheral arterial disease	6 (1.3)	3 (1.7)	3 (1.1)	0.873
Chronic lung disease[b]	26 (5.7)	7 (4.0)	19 (6.8)	0.297
eGFR, mL/min/1.73 m^2[c]	79.1 ± 18.5	79.6 ± 18.2	78.8 ± 18.6	0.634
Hematocrit, %	40.7 ± 4.1	41.2 ± 4.3	40.4 ± 4.0	0.057
NT-proBNP, pg/mL (n = 209)	108.4 (39.9-303.0)	94.4 (29.3-243.4)	115.4 (44.1-343.0)	0.065
BNP, pg/mL (n = 112)	26.8 (12.9-56.3)	23.2 (9.1-53.4)	29.4 (15.0-63.4)	0.195
ACE inhibitor/ARB	213 (46.6)	93 (52.8)	120 (42.7)	0.044
Beta-blocker	160 (35.0)	60 (34.1)	100 (35.6)	0.822
AVR during study period	311 (68.1)	90 (51.1)	221 (78.6)	<0.001
Echocardiography				
AV peak velocity, m/s	3.8 (3.3-4.4)	3.4 (2.9-3.8)	4.1 (3.7-4.7)	<0.001
AV mean PG, mm Hg	33.4 (24.0-44.0)	24.0 (20.0-33.0)	39.6 (30.1-52.3)	<0.001
AV area, cm^2	0.91 (0.72-1.13)	1.19 (1.09-1.31)	0.77 (0.65-0.89)	<0.001
E/septal e′ ratio	13.5 (10.7-17.3)	12.4 (9.9-15.1)	14.2 (11.4-17.9)	<0.001
CMR				
LV EDV index, mL/m^2	62.2 (52.4-72.9)	61.4 (52.6-71.8)	63.1 (52.4-73.2)	0.581
LV ESV index, mL/m^2	17.7 (13.4-23.9)	17.4 (13.7-23.6)	17.8 (13.3-24.3)	0.888
LV SV index, mL/m^2	43.7 (36.1-52.1)	43.8 (36.8-51.4)	43.7 (35.7-52.4)	0.843
LV cardiac index, L/m^2	2.8 (2.4-3.4)	2.7 (2.3-3.3)	2.9 (2.4-3.5)	0.193
LV ejection fraction, %	70.4 (63.4-76.1)	69.9 (64.6-74.6)	71.1 (62.6-76.5)	0.399
LV mass index, g/m^2	79.8 (68.4-95.1)	77.0 (68.3-88.6)	81.1 (68.6-99.4)	0.034
Maximum LV wall thickness, mm	16.4 (14.4-19.0)	16.3 (14.0-18.3)	16.5 (14.8-19.3)	0.059
RV EDV index, mL/m^2	68.0 (55.9-78.9)	71.7 (59.9-83.1)	65.2 (54.2-74.9)	<0.001
RV ESV index, mL/m^2	30.9 (25.4-38.8)	33.2 (27.6-42.2)	29.3 (22.6-35.4)	<0.001
RV ejection fraction, %	53.1 (45.7-60.6)	51.6 (44.3-58.3)	54.2 (47.7-61.2)	0.003
LAVI, mL/m^2	38.4 (29.4-47.8)	38.3 (29.6-47.8)	38.7 (29.4-48.1)	0.956
ECV, %	26.6 (24.4-29.9)	26.3 (24.2-29.9)	27.0 (24.5-30.0)	0.154
iECV, mL/m^2	20.3 (17.1-25.0)	19.4 (16.7-22.7)	21.2 (17.5-26.0)	0.004
Presence of LGE	143 (31.5)	54 (31.0)	89 (31.8)	0.949
LGE pattern				0.626
Absent	311 (68.5)	120 (69.0)	191 (68.2)	
Noninfarct	107 (23.6)	38 (21.8)	69 (24.6)	
Infarct	36 (7.9)	16 (9.2)	20 (7.1)	
LGE%, %	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.887
LGE, % in patients with LGE	0.8 (0.1-1.7)	0.6 (0.1- 1.3)	0.9 (0.2-2.2)	0.319

Values are median (IQR), mean ± SD, or n (%), unless otherwise indicated. [a]Including unicuspid or quadricuspid aortic valve. [b]Treatment for chronic obstructive pulmonary disease, asthma, or interstitial lung disease. [c]Calculated with the Modification of Diet in Renal Disease (MDRD) equation.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; AS = aortic stenosis; AV = aortic valve; AVR = aortic valve replacement; BMI = body mass, index; BNP = brain natriuretic peptide; BSA = body surface area; CAD = coronary artery disease; CMR = cardiac magnetic resonance; E = early mitral inflow velocity; e′ = early diastolic mitral annular velocity; ECV% = extracellular volume fraction; EDV = end-diastolic volume; ESV = end-systolic volume; eGFR = estimated glomerular filtration rate; HF = heart failure; iECV = indexed extracellular volume; LAVI = left atrial volume index; LGE% = percentage of late gadolinium enhancement of the total myocardium; LV = left ventricular; NT-proBNP = N-terminal pro brain natriuretic peptide; PG = pressure gradient; RV = right ventricular; SV = stroke volume.

FIGURE 1 Comparison of Myocardial Remodeling/Fibrosis by Severity of Aortic Stenosis



The following parameters were compared between the moderate vs asymptomatic severe AS patients: aortic valve area (A), E/septal e′ ratio (B), LVEF by CMR (C), LVMI by CMR (D), ECV% (E), and proportion of participants with LGE (F). The numbers below each column denotes the median (IQR). AS = aortic stenosis; AVA = aortic valve area; CMR = cardiac magnetic resonance; ECV% = extracellular volume fraction; LGE % = percentage of late gadolinium enhancement of the total myocardium; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index.

myocardium) was associated with outcome (HR: 1.11 [95% CI: 1.02-1.21]; $P = 0.016$). ECV% (adjusted HR: 1.05 [95% CI: 1.02-1.10]; $P = 0.017$) and LGE% (adjusted HR: 1.08 [95% CI: 1.01-1.17]; $P = 0.034$) were both significantly associated with the clinical outcome after adjustment for age, sex, AV area, LV ejection fraction, and AVR as a time-dependent covariate (**Table 2**, Model 1). Even after further adjustment for important comorbidities, ECV% remained an independent predictor of outcome (**Table 2**, Model 2). Net reclassification improvement analysis demonstrated that ECV% had a significant incremental prognostic value over parameters of AS severity, LV systolic and diastolic function, AVR, comorbidities, and also LGE% (Supplemental Table 6).

Sensitivity analysis was performed in the study population of patients with moderate or asymptomatic severe AS using the alternative definition by aortic peak velocity and mean pressure gradient (n = 426) (Supplemental Figure 5). There were 121 patients (28.4%) with discordant echocardiography measurements (AVA ≤1.0 cm^2 with aortic peak velocity <4 m/s and mean pressure gradient <40 mm Hg); patients with either LV ejection fraction <50% (n = 6) or stroke volume index <35 mL/m^2 (n = 39) were categorized as having classic

TABLE 2 Multivariable Analysis of Predictors of the Composite Outcome of All-Cause Mortality and Admission for Heart Failure

	Multivariable Model 1[a]		Multivariable Model 2[b]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
ECV%	1.05 (1.02-1.10)	0.017	1.05 (1.00-1.10)	0.039
LGE%	1.08 (1.01-1.17)	0.034	1.05 (0.96-1.14)	0.300
Age, per 10 y	1.99 (1.54-2.57)	<0.001	1.90 (1.45-2.50)	<0.001
Male	0.81 (0.51-1.26)	0.346	0.73 (0.46-1.17)	0.192
AV area, per 0.10 cm^2	0.89 (0.80-0.98)	0.016	0.88 (0.80-0.97)	0.009
LV ejection fraction, per 10%	0.87 (0.73-1.04)	0.122	0.89 (0.75-1.06)	0.192
AV replacement[c]	0.65 (0.37-1.14)	0.132	0.62 (0.36-1.10)	0.101
Prior hospitalization for HF			4.11 (1.35-12.5)	0.013
Significant CAD			1.32 (0.82-2.11)	0.249
Atrial fibrillation			1.84 (1.04-3.26)	0.036

[a]Including demographics and imaging parameters. [b]Including demographics, imaging parameters, and major comorbidities. [c]Analyzed as a time-dependent covariate.
Abbreviations as in Table 1.

or paradoxical low-flow low-gradient severe AS, whereas the rest of the patients with normal flow state and aortic peak velocity 3-3.9 m/s or mean pressure gradient 20-39 mm Hg (n = 76) were categorized as having moderate AS. Again, analysis of this study population demonstrated that ECV% was an independent predictor of the clinical outcome (adjusted HR: 1.05 [95% CI: 1.00-1.10]; $P = 0.030$) (Supplemental Table 7).

ASSOCIATION OF DIFFUSE INTERSTITIAL FIBROSIS WITH CLINICAL OUTCOME IN MODERATE OR ASYMPTOMATIC SEVERE AS PATIENTS. The association between ECV% and clinical outcome was consistent in subgroups of patients with moderate AS, those with NYHA functional class I severe AS, and those with NYHA functional class II severe AS (*P* for interaction = 0.878) (**Figure 2**). The associations between ECV% and clinical outcome was also consistent across subgroups by AVA, aortic peak velocity or mean pressure gradient, and LV ejection fraction, and after excluding patients with bicuspid aortic valve or low-flow, low-gradient severe AS.

The study cohort was divided into tertiles of ECV% to explore the associations between diffuse interstitial fibrosis and clinical outcome (Supplemental Table 8). Patients in the highest ECV% tertile (ECV% >28.6%) had a higher proportion of women and atrial fibrillation, fewer patients in NYHA functional class I, lower estimated glomerular filtration rate, higher NT-proBNP levels, greater E/e′ ratio, smaller right ventricular size, and more presence of LGE. However, there was no significant difference in AS severity between the 3 groups.

There were 17 (11.3%), 26 (17.1%), and 40 (25.8%) events in the low, mid, and high ECV% tertile groups, respectively (Supplemental Table 3). Spline regression analysis showed a higher risk for events with increasing ECV% (**Figure 3A**). The patients in the highest ECV% tertile (>28.6%) had significantly worse outcomes (**Figure 3B**) (log-rank $P = 0.009$; estimated 5-year event rate for those in the low-, mid-, and high ECV% tertile, 9.9% vs 13.8% vs 19.3%), with a 2-fold increase of risk for clinical events than did those in the lowest ECV% tertile (HR: 2.30 [95% CI: 1.30-4.05]; $P = 0.004$) (Supplemental Table 5). The trend of worse outcome for patients in the highest ECV% tertile was also observed in the analysis of individual outcomes, such as all-cause mortality (Supplemental Figure 6A) (log-rank $P = 0.030$) or admission for heart failure (Supplemental Figure 6B) (log-rank $P = 0.020$). The trend of worse outcome for patients in the highest ECV% tertile was also consistent in the subpopulations limited to entirely asymptomatic patients (NYHA functional class I) with moderate or severe AS (**Figure 3C**) (log-rank $P = 0.050$), patients with moderate AS only (Supplemental Figure 6C) (log-rank $P = 0.080$), and patients with asymptomatic severe AS (NYHA functional class I-II) (Supplemental Figure 6D) (log-rank $P = 0.020$). Even after AVR, worse outcomes were observed in patients with increased ECV% (**Figure 3D**) (log-rank $P = 0.030$).

Spline regression analysis showed a weak tendency for increased risk of clinical events with higher LGE% (Supplemental Figure 7A). Outcomes did not differ by the presence or pattern of LGE (log-rank $P = 0.600$ and $P = 0.700$, respectively) (Supplemental Figures 7B and 7C).

DISCUSSION

In this international multicenter cohort of patients with moderate or asymptomatic severe AS, diffuse interstitial fibrosis of the myocardium quantified by

FIGURE 2 Degree of Association Between ECV% and Clinical Outcome According to Various Subgroups of the Study Population

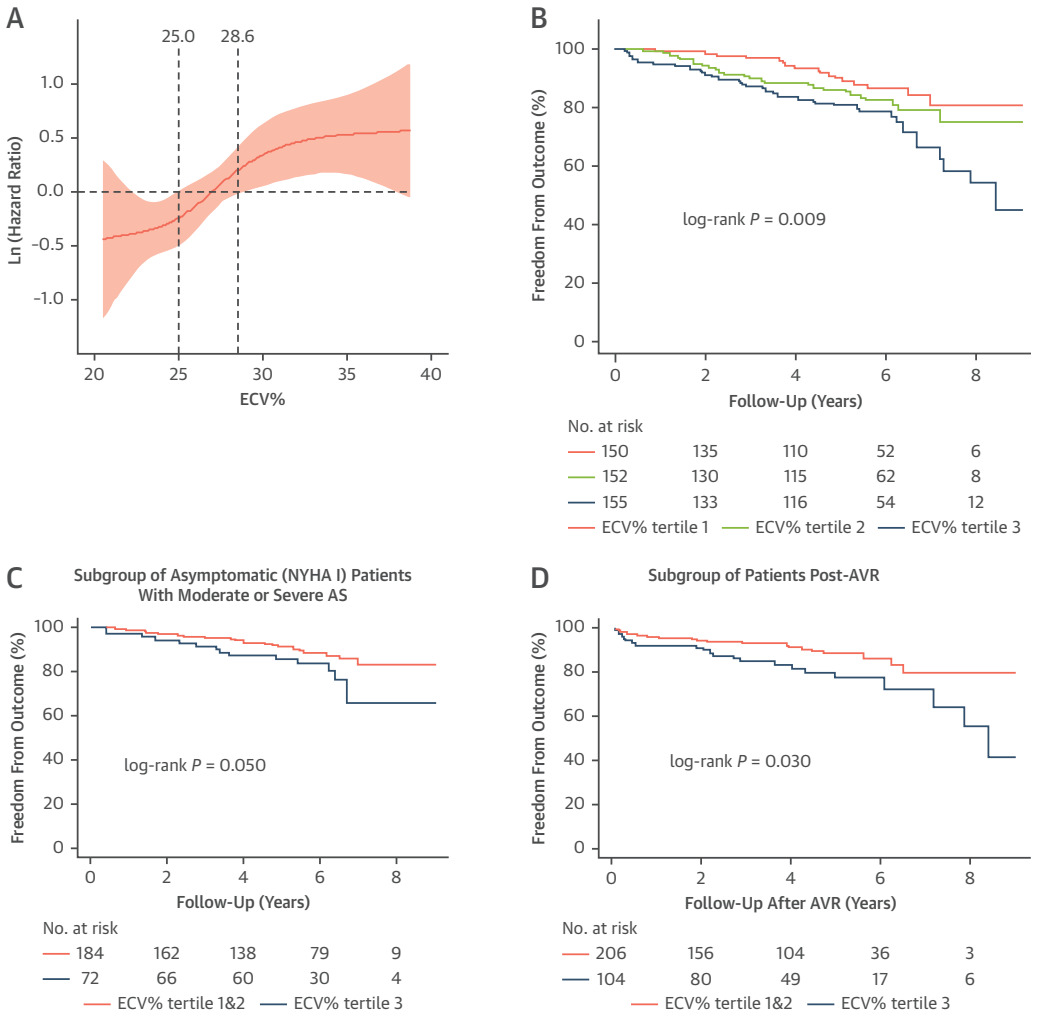
Subgroups	N	Events	HR (95% CI) for ECV%	*P*-Value	*P*-for-Interaction
Entire study population	457	83	1.06 (1.02-1.1 1)	0.004	
AS severity and symptoms					
Moderate AS	176	21	1.06 (0.96-1.17)	0.241	0.878
Severe AS, NYHA I	134	28	1.05 (0.97-1.12)	0.217	
Severe AS, NYHA II	147	34	1.06 (1.00-1.13)	0.047	
AV area					
AV area >1.0 and ≤l.5 cm^2	176	21	1.06 (0.96-1.17)	0.241	0.965
AV area ≤l.0 cm^2	281	62	1.06 (1.01-1.11)	0.014	
AV peak velocity					
AV Vmax <4.0 m/s	265	47	1.07 (1.02-1.13)	0.007	0.449
AV Vmax ≥4.0 and <5.0 m/s	142	27	1.06 (0.98-1.15)	0.146	
AV Vmax ≥5.0 m/s	50	9	0.94 (0.77-1.15)	0.539	
AV mean PG					
AV mean PG <40 mm Hg	303	53	1.07 (1.02-1.12)	0.007	0.793
AV mean PG ≥40 mm Hg	154	30	1.05 (0.96-1.15)	0.268	
LVEF					
LVEF ≥50%	437	77	1.06 (1.01-1.1 1)	0.015	0.290
LVEF <50%	20	6	1.12 (0.97-1.28)	0.127	
Bicuspid AV					
Tricuspid AV	310	67	1.07 (1.02-1.12)	0.015	0.816
Bicuspid AV [a]	147	16	1.05 (0.95-1.17)	0.352	
Discordant AS					
Excluding LF LG severe AS	412	72	1.06 (1.01-1.11)	0.015	0.391
LF LG severe AS	45	11	1.10 (0.97-1.25)	0.129	

Horizontal bars show HRs with 95% CIs for clinical events per 1% increase in ECV%. [a]Including unicuspid or quadricuspid aortic valve. AV = aortic valve; ECV% = extracellular volume fraction; LF LG = low-flow low-gradient; PG = pressure gradient; Vmax = peak velocity; other abbreviations as in Figure 1.

ECV% on CMR was significantly associated with the composite outcome of all-cause mortality and unplanned admission for heart failure (**Central Illustration**). The main findings can be summarized as follows. First, greater severity of AS was associated with greater LV mass and diastolic dysfunction, but not necessarily with greater extent of myocardial fibrosis/scar, in patients with moderate or asymptomatic severe AS. Second, increased diffuse interstitial fibrosis was a significant predictor of outcome, independent of AS severity or AVR in these patients, with 1% increase in ECV% resulting in 5% increase in risk for clinical events. The association with outcome was stronger for diffuse interstitial fibrosis (ECV%) than for focal myocardial scar (LGE). Third, increased diffuse interstitial fibrosis was associated with female sex, atrial fibrillation, lower estimated glomerular filtration rate, and worse LV diastolic dysfunction and symptoms.

Whereas recent clinical trials have shown the clinical benefit of early AVR in patients with asymptomatic severe AS,[7,8] it remains to be determined whether AS severity parameters such as peak aortic velocity are the optimal parameters to guide valve intervention in this population. Additionally, although retrospective data have suggested that AVR may be beneficial in patients with moderate AS and LV systolic dysfunction,[20,21] it is uncertain in whom AVR may be beneficial among those with moderate AS. Currently, there is no indication for AVR in patients with moderate AS unless they have another

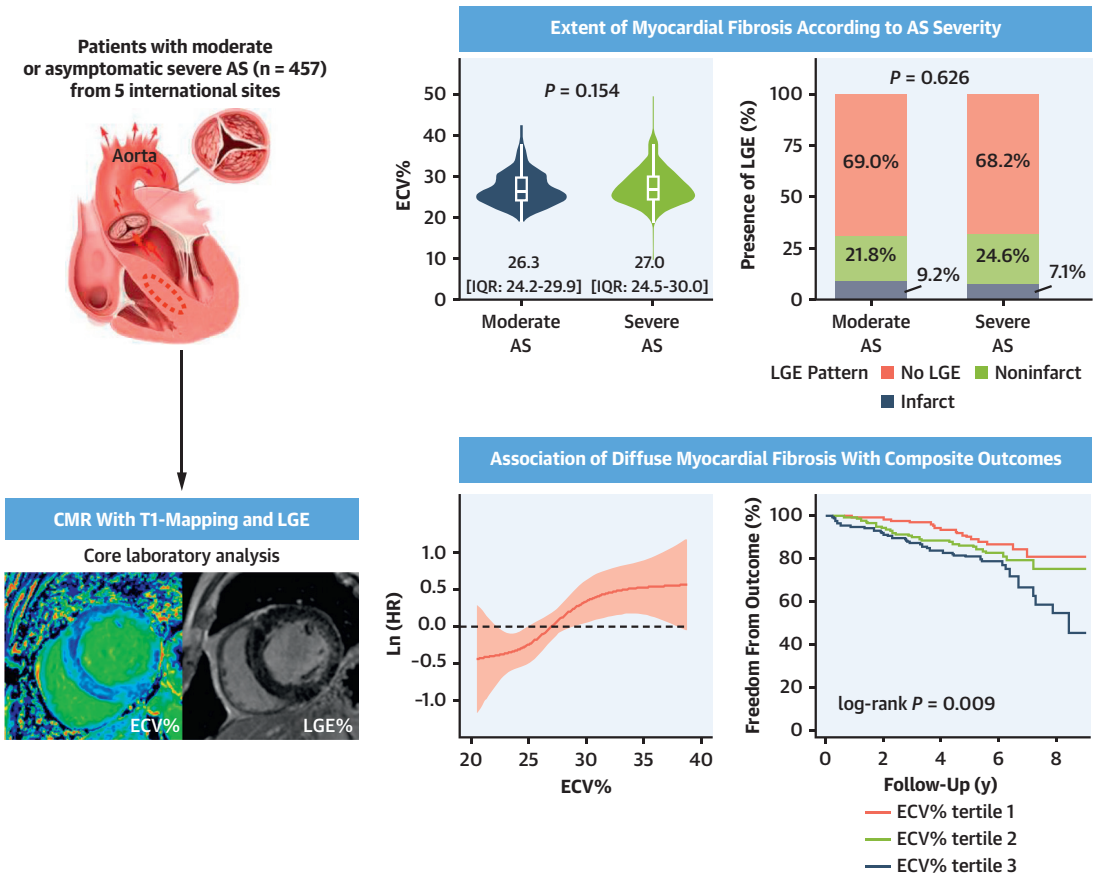
FIGURE 3 **Comparison of Event-Free Survival by Tertiles of Diffuse Interstitial Fibrosis**



(A) Spline regression analysis showing the association of ECV% with the composite clinical outcome of all-cause mortality and unplanned admission for heart failure. Dotted lines indicate the cutoffs for the ECV% tertiles. (B) Event-free survival in the entire population. (C) Event-free survival in patients with entirely asymptomatic (NYHA functional class I) moderate or severe AS. (D) Post-AVR event-free survival in patients who underwent AVR. AVR = aortic valve replacement; other abbreviations as in Figure 1.

indication for cardiac surgery (NYHA functional class IIb).[5] Besides overt LV systolic dysfunction, other studies have suggested that symptoms, NT-proBNP levels, LV global longitudinal strain, E/e′ ratio, and LV hypertrophy are associated with clinical outcomes in moderate AS,[18,22-27] some of which are inclusion criteria in trials currently investigating the benefit of pressure unloading with early transcatheter AVR in patients with moderate AS who have symptoms or signs of cardiac damage (NCT02661451, NCT04889872, and NCT05149755). On a closer look, all these parameters represent the myocardial health in AS. Myocardial tissue characterization with CMR assessing the degree of LV fibrosis has been strongly associated with poor survival in previous multicenter studies of patients with severe AS;[13,14] however, these findings were

CENTRAL ILLUSTRATION Study Overview



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The extent of myocardial fibrosis and its prognostic significance was evaluated using CMR in a multicenter cohort of patients with moderate or asymptomatic severe AS. AS severity was not the main determinant of the degree of myocardial fibrosis. Increased diffuse interstitial fibrosis, quantified by ECV% on CMR, was independently associated with the composite outcome of death and admission for heart failure.
AS = aortic stenosis; CMR = cardiac magnetic resonance;
ECV% = extracellular volume fraction; LGE = late gadolinium enhancement.

confined to patients with severe AS undergoing AVR, mostly symptomatic, and data on the role of CMR in moderate AS are scarce.[28] Until now, it has been largely unknown whether the extent of interstitial fibrosis/scar is also a reliable prognosticator in patients with significant AS and without an NYHA functional class I indication for intervention.

Our study showed that fewer than one-third of patients with moderate or asymptomatic severe AS had myocardial scar, and even in those patients, LGE % was minimal; meanwhile, patients with moderate or asymptomatic severe AS had ECV% (mean 27.4% ± 4.6%) higher than healthy individuals of similar age and sex (mean 26.0% ± 2.3%)[11] and mildly lower than patients with severe AS undergoing AVR (27.7% ± 3.6%).[14] In patients with AS, interstitial myocardial fibrosis measured by ECV% is reversible after AVR, whereas myocardial scar assessed by LGE is irreversible.[29,30] In a small study, the progression of myocardial scarring increased significantly at the stage of severe AS, although some patients already had nonischemic myocardial scars even at the stage

of moderate AS.[31] This suggests that myocardial damage is not yet extensive and that the degree of diffuse interstitial fibrosis may be a more sensitive marker of myocardial health than the irreversible scar in patients with moderate or asymptomatic AS. Interestingly, we observed that greater AS severity was not necessarily associated with the degree of myocardial fibrosis/scar at this stage of AS. Parameters of AS severity were similar among the subgroups by ECV% tertile. Indeed, the degree of extravalvular cardiac damage assessed by echocardiography was not closely associated with peak aortic velocity or mean pressure gradient in previous cohorts of asymptomatic moderate to severe AS,[16] demonstrating that patients show various degrees of myocardial remodeling that may not be entirely determined by AS severity.

Importantly, we found that increased diffuse interstitial fibrosis was independently predictive of clinical events in patients with moderate or asymptomatic AS, even after adjustment for AS severity, AVR, and other comorbidities. Patients in the highest ECV% tertile (>28.6%) had a more than 2-fold increase in risk for outcomes compared with those in the lowest ECV% tertile. The prognostic value of ECV% was consistent after stratification into subgroups of moderate and severe AS. In total, our results suggest that the degree of diffuse interstitial fibrosis can better identify high-risk AS patients who warrant closer surveillance at an earlier stage of significant AS. Although there is a continuous increase in risk for adverse outcomes with higher ECV%, a threshold of approximately >29% can be considered a high-risk feature. The association between LGE and clinical events was not strong in the present study, in contrast to findings observed in severe AS,[13] probably related to the minimal degree of LGE in the study cohort. The lack of association of iECV with outcomes is consistent with the previous study demonstrating the prognostic value of ECV% in patients with severe AS with indications for AVR, and is likely related to female patients or low-gradient phenotypes with lower LV mass but worse outcomes.[14]

To note, the progression of myocardial fibrosis can be affected not only by AS but also by comorbidities such as hypertension or diabetes,[32-34] and these comorbidities can also affect the outcome. However, in the current study, there was no significant difference in comorbidities among patients by ECV% tertiles except for more women, lower estimated glomerular filtration rate, and more atrial fibrillation in the highest ECV% tertile. Furthermore, ECV% was an independent predictor of the outcome in multivariable analyses, and it had incremental prognostic value even if major comorbidities were considered in the net reclassification improvement analysis. These observations support our suggestions that increased interstitial fibrosis is independently associated with worse outcomes in patients with moderate or asymptomatic AS. Although the interstitial fibrosis of the myocardium may partially be explained by comorbidities, our series of analyses certainly demonstrates that the worse outcome in those with increased ECV% is not a mere reflection of the comorbidities.

Our study is the first to provide evidence that increased myocardial fibrosis evaluated with noninvasive imaging can identify those at high risk of clinical events in patients with moderate or asymptomatic severe AS who have no or mixed recommendations for intervention. This study expands on the previous study demonstrating that increased ECV % is an independent predictor of mortality in patients with severe AS who are scheduled for AVR under the contemporary guidelines.[14] It also corroborates the previous study in which machine learning techniques identified myocardial fibrosis parameters as one of the strongest predictors of survival in patients with severe AS awaiting AVR.[15] Lee et al[11] also reported in 191 patients with moderate or severe AS that increased ECV% was associated with worse LV diastolic dysfunction and could identify patients with worse symptoms and outcome. Although there is a substantial overlap in ECV% between patients with AS and healthy control individuals, our current results along with the previous results demonstrate that increased ECV% portends a poor prognosis in AS.[11,14,15] Our results imply that CMR with T1 mapping and LGE may be recommended to patients with moderate AS or asymptomatic severe AS considered for early AVR, for prognostication of, and decision for, intervention. However, how measures of myocardial fibrosis can be used to optimize the timing of AVR needs to be established by further studies, with randomized trials that will provide the ultimate answer. An ongoing trial is expected to answer whether earlier AVR guided by the presence of myocardial scar (LGE) on CMR may be beneficial in patients with asymptomatic severe AS (NCT03094143), thus providing a precision approach in this population. To date, noninvasive measures of myocardial fibrosis have not been considered as inclusion criteria in the trials investigating the benefit of early AVR in patients with moderate AS. Considering the results of our study, future clinical trials should investigate whether patients with asymptomatic severe or moderate AS with apparent cardiac

damage on CMR in the form of increased ECV% would benefit from pressure unloading with early AVR. Further research should also elucidate factors increasing myocardial susceptibility to pressure overload, inasmuch as the modification of these factors may be beneficial in patients with significant AS.

STUDY STRENGTHS AND LIMITATIONS. Certain strengths of the current study are worth noting. First, an international multicenter prospective cohort was established from key institutions investigating the utility of CMR in AS, making our findings more generalizable. Second, the CMR images were analyzed at a centralized core laboratory, minimizing possible measurement variabilities between the institutions.

There are some limitations as well. First, although the results provide evidence for the association between ECV% and clinical events, further studies are needed to determine the optimal ECV% cutoff for identifying LV decompensation and to what degree increases in ECV% are due to valve disease or other comorbidities in this population. Furthermore, because this study cannot provide a direct answer to whether and how to treat these patients according to the ECV%, randomized trials will be required to determine whether early AVR would be beneficial in those with increased ECV% vs watchful waiting in those with normal ECV%. Second, although ECV% potentially adjust for scanner or sequence differences that makes it relatively ideal for multicenter research,[14,35] there may be some center-to-center differences not fully accounted for. Likewise, the decision of AVR was at the discretion of the attending physician, not by standardized protocols, which may differ among the participating centers. Thus, we did not include AVR in the outcome. Third, the sample size of the current study (n = 457) may have insufficient power for extensive multivariable adjustment and subgroup analyses. However, this is the largest study with CMR data for the population of moderate or asymptomatic severe AS. Last, exercise testing to assess symptom status in patients with asymptomatic severe AS was not uniformly done at all centers, which reflects the current real-world clinical usage status of exercise testing for AS.[36]

CONCLUSIONS

Whereas current guidelines mainly focus on the hemodynamic status of the valve to stage and to consider intervention in AS, our findings emphasize that the health of the myocardium is also an important factor that should be considered in the evaluation and treatment of patients with AS treated expectantly. In an international multicenter prospective cohort of patients with moderate or asymptomatic severe AS, those with increased diffuse interstitial fibrosis, especially those in the highest ECV% tertile, were at higher risk of death and admission for heart failure. The noninvasive assessment of myocardial damage by CMR in these patients can identify high-risk patients who warrant closer surveillance for possible adverse outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Increased diffuse interstitial fibrosis of the myocardium measured by CMR is an independent predictor of mortality and heart failure admission in patients with moderate or asymptomatic severe aortic stenosis.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In this aortic stenosis population at increased risk of clinical events, the degree of diffuse interstitial fibrosis by noninvasive imaging can help identify high-risk patients who require closer surveillance and possibly earlier intervention.

TRANSLATIONAL OUTLOOK: Future studies assessing the benefit of early intervention in patients with moderate or asymptomatic severe aortic stenosis should consider measures of myocardial fibrosis when planning the trials or interpreting the results.

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KEY WORDS aortic valve stenosis, cardiac magnetic resonance, fibrosis, myocardium, outcome

APPENDIX For an expanded Methods section as well as supplemental figures, tables, and references, please see the online version of this paper.