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Original Article

Prevalence and prognostic significance of left ventricular myocardial late gadolinium enhancement in severe aortic stenosis☆

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ABSTRACT

Background: Myocardial fibrosis occurs in aortic stenosis (AS) as part of the hypertrophic response. It can be detected by LGE, which is associated with an adverse prognosis in the form of increased mortality and morbidity.
Objectives: To assess the prevalence of LGE patterns using cardiac magnetic resonance (CMR) in severe AS patients and to study its prognostic significance.
Methods: Patients enrolled into the study from June 2012 to November 2014. All the patients underwent CMR and various patterns of LGE studied. These patients if symptomatic were advised AVR and others were managed conservatively. All patients were followed up and watched for outcomes like mortality, heart failure/hospitalization for cardiovascular cause, fall in left ventricular ejection fraction (LVEF) $\geq$20% and arrhythmia.
Results: A total of 109 patients (mean age-57.7 $\pm$ 12.5yrs) underwent CMR with 63 males. These patients were followed up for a mean of 13 months. Among 38 patients who underwent AVR, 6 died (5–cardiovascular cause, 1–non cardiovascular). 71 patients were managed conservatively out of which 18 died (17-cardiovascular cause, 1-non cardiovascular cause). LGE patterns were seen in 46 patients (43%); mid myocardial enhancement was seen in 31.1% of cases (33 patients). No LGE pattern was seen in 57%(63 patients). Basal and mid regions were maximally involved with mid myocardial enhancement in 66% & 68.3% respectively. LV ejection fraction ($p = 0.002$), peak aortic systolic velocity ($p = 0.01$) and peak aortic systolic gradient ($p = 0.02$) were the main predictors of LGE. Main predictors of primary outcome were NYHA class [OR- 13.4(2.8–26.1), $p \leq 0.001$], age- 62 $\pm$ 9.6yrs($p = 0.001$), EF simpson-50.9 $\pm$ 13%($p \leq 0.001$), LGE[OR 2.8 (1.27–6.47),$p = 0.01$], number of segments involved [2.37 $\pm$ 2.1,$P \leq 0.001$] & CMR LV mass (151.73 $\pm$ 32 gms, $p = 0.007$). LGE predicted heart failure/hospitalization for cardiovascular cause [OR- 3.8(1.2–11.9), $p = 0.01$] and fall in LVEF [OR- 5.8(1.5–22.5), $p = 0.005$]. Patients with LGE had 2.87 times risk of adverse outcomes and patients with more than 3 segment LGE involvement had again increased chances for adverse outcomes.
Conclusions: LGE was detected by CMR in 43% of patients with severe AS. It predicted recurrent heart

Abbreviations: ACC, American College of cardiology; AHA, American heart association; AR, aortic regurgitation; AS, aortic stenosis; ASE, American society for echocardiography; AVR, aortic valve replacement; CI, confidence interval; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; CW, continuous wave; EHA, European heart association; FIESTA, fast imaging employing steady state acquisition; GFR, glomerular filtration rate; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricle ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; OR, odds ratio; PW, pulse wave; SD, standard deviation; Zva, valvulo-arterial impedance.

☆ Need for publishing this article- Asymptomatic severe aortic stenosis cases are increasing in number mainly in the elderly. At present conservative management is being followed for a great lot. There are many risk markers and if detected early, patients can be subjected to early surgery and reduce mortality. One such risk marker is myocardial LGE. Multiple large studies are required to prove its effect as it is a novel upcoming tool. Ours is one such study which may contribute to the existing two large studies published. Earlier studies focussed on the Western population and our study is the first of its kind done in South Asia showing a different subset population with different etiology for aortic stenosis. Hence it is worth publishing.

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failure, hospitalization for cardiovascular cause and fall in LV ejection fraction. Our study has laid a path to larger prospective studies with long term follow up to assess the prognostic impact of CMR in patients with severe AS.

1. Introduction

Aortic stenosis (AS) has become a serious problem both in the developed and the developing countries.[1] Its prevalence is increasing with age. It is a progressive disease with a long, indolent asymptomatic phase followed by a shorter symptomatic stage.[2] The onset of symptoms is associated with increased morbidity and high mortality even after AVR.[2] Hence the various factors that determine adverse prognosis have to be detected in the asymptomatic phase so that such patients can be subjected to early AVR and avert complication.

AS results in pressure overload and ventricular wall stress, thereby stimulating LVH. Initially, increased wall thickness maintains normal wall stress and contraction but ultimately this becomes maladaptive.[3,4] Studies have demonstrated fibrosis in the left ventricle of patients with aortic stenosis. It has been postulated that increasing myocyte size eventually leads to myocyte apoptosis and subsequently replacement fibrosis, and that this sequence is responsible for the progression from LVH to heart failure.[5] Myocardial fibrosis (Fig. 1B) has also been linked to the development of arrhythmia and sudden cardiac death in post operative AS patients as well. CMR is able to detect replacement myocardial fibrosis noninvasively by using LGE (Fig. 1B).6 The greater the amount of LGE, greater is the number of adverse outcomes.[7,8] There are studies which correlates left ventricular myocardial fibrosis in histopathology versus CMR.[9,10]

Studies have proven that myocardial enhancement has adverse outcomes in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy and coronary artery disease.11–14 More recent studies have demonstrated various patterns of myocardial enhancement in patients with aortic stenosis in the absence of coronary artery disease especially midwall enhancement pattern (Figs. 2 B, F, 1 B) and these patterns have also shown to have adverse outcomes.[7,15] There are no studies from the Indian subcontinent studying this matter. Hence the goal of this study is to determine the prevalence and prognostic implications of left ventricular myocardial fibrosis by LGE in severe AS patients.

2. Methods

2.1. Hypothesis

LGE by CMR can be useful for risk stratification of patients with severe AS. It could predict outcomes like mortality, heart failure/hospitalization, arrhythmia and fall in LVEF. LVH with the same septal and posterior wall thickness may have varying amounts of LGE which may have varying outcomes like heart failure, arrhythmia, sudden death or may be asymptomatic throughout. The first objective was to assess the prevalence of LGE and its various patterns in severe AS patients and the second objective was to study its prognostic significance.

2.2. Design

It was a single centre prospective observational study conducted in the department of Cardiology, Government Medical College, Kozhikode, Kerala, India from August 2012 to July 2015. Study was approved by the 'Institutional Research Committee' and 'The Ethics Committee' of Government Medical College, Kozhikode. Informed consent was taken from all patients enrolled in the study.

The study included all adult patients with severe AS defined as indexed aortic valve area $\leq 0.6\,cm^2/m^2$ detected by echocardiogram. Severe asymptomatic aortic stenosis was defined as a patient with no symptoms of heart failure, angina or syncope with severe aortic leaflet calcification or congenital stenosis with severely reduced leaflet opening or indexed aortic valve area $\leq 0.6\,cm^2/m^2$ whereas severe symptomatic aortic stenosis patients are those with symptoms of heart failure, angina or syncope with severe aortic leaflet calcification or congenital stenosis with severely reduced leaflet opening i.e. aortic valve area $\leq 1.0\,cm^2$ (or indexed aortic valve area $\leq 0.6\,cm^2/m^2$).[16]

It excludes patients with severe AR, greater than mild involvement of other valves, cardiomyopathy, previous myocardial infarction, any contraindications to contrast CMR especially

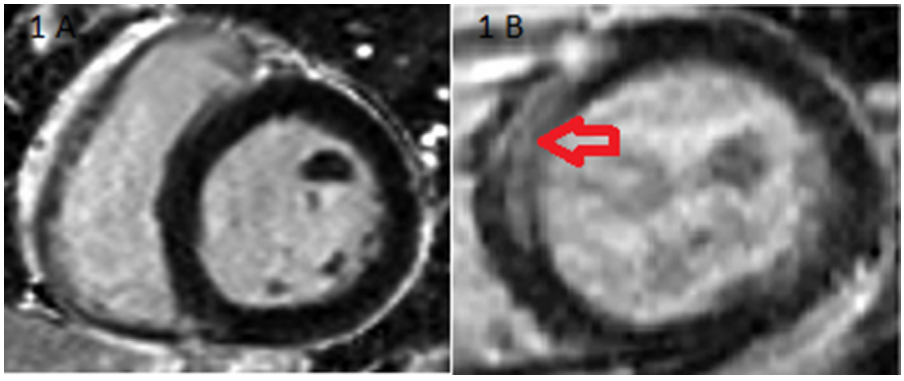


Fig. 1. A- Normal myocardium. B- Myocardium showing enhancement.

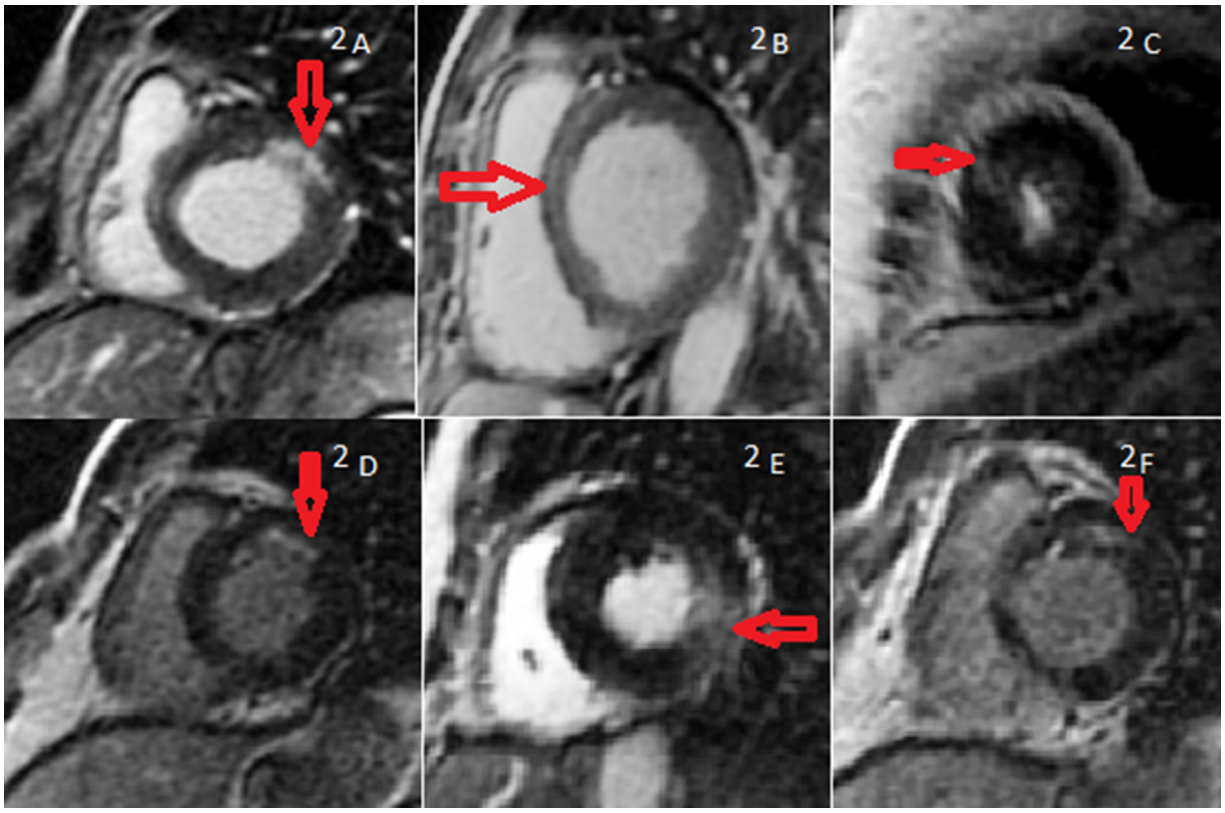


Fig. 2. A- Transmural hyper-enhancement in the basal antero-lateral region. B- Mid myocardial fibrosis in the basal antero-septum, septum & infero-septal regions. C- Patchy enhancement in the apical septum and apical lateral walls. D- Mid anterior wall sub-endocardial hyper-enhancement. E- Mid lateral wall transmural hyper-enhancement. F- Mid myocardial hyper-enhancement in the mid anterior wall.

estimated GFR (Cockcroft- Gault equation) of ≤30 mL/min and finally refusal to consent.

Largest international trial till date had sample size n = 154 and sample calculation was also done to get a power of 80% to assess LGE as a prognostic marker. Keeping the prevalence of LV fibrosis as 33% a sample size of 203 was assumed.

2.3. Study plan

Baseline clinical examination, electrocardiogram, chest x-ray, treadmill test (for asymptomatic only) was done along with routine blood investigations. Comprehensive echo and CMR done thereafter. Coronary angiogram was done before proceeding to AVR. Asymptomatic severe aortic stenosis patients did not undergo angiogram due to objection from institution ethics committee.

2.4. Outcomes: primary outcomes

Composite of mortality, LV EF fall >20%, new onset heart failure or hospitalization for cardiovascular causes and new onset arrhythmia.

2.5. Secondary outcomes

Individual components of primary outcomes.

2.6. Echocardiographic protocol

Philips HD11 XE Ultrasound machine was used. AS was assessed using peak velocity and mean gradient. Continuity equation was applied to detect valve area. LV systolic function was assessed by modified Simpson's method averaging 3 samples. Patients with atrial fibrillation, 5 samples were assessed and average taken.

2.6.1. Peak velocity

Adjustment of transducer position and angle was crucial as velocity measurement assumes a parallel intercept angle between the ultrasound beam and direction of blood flow. CW transducer was used. Wall filters were set at high level and gain minimized. Gray scale was used to trace aortic stenosis signal. A smooth velocity curve with a dense outer edge and clear maximum velocity was recorded. The maximum velocity was measured at the outer edge of the dark signal. Multiple acoustic windows were taken to determine the highest gradient.

2.6.2. Mean gradient

Calculated from the traced velocity curve from where maximum velocity was obtained.

2.6.3. Valve area

Calculated using the continuity equation.

2.6.4. LVOT diameter

Measured in the parasternal long-axis zoomed view in mid-systole from the white–black interface of the septal endocardium to the anterior mitral leaflet, parallel to the aortic valve plane and within 0.5–1.0 cm of the valve orifice.

2.6.5. Valvulo arterial impedance (Zva)

Calculated using Mean gradient + Systolic bood pressure/ indexed stroke volume. The systolic blood pressure was taken using Omaron BP apparatus at the time of echocardiogram.

2.6.6. Left ventricular systolic function

Modified Simpson's method was used to assess the LV volumes. Severe AS was defined as in accordance with Valvular heart disease guidelines-ACC/AHA/ASE.[16]

Inter-observer and intra-observer variability were assessed in 10% of study population and good correlation was obtained. Observers were blinded to clinical and CMR data.

2.7. CMR protocol

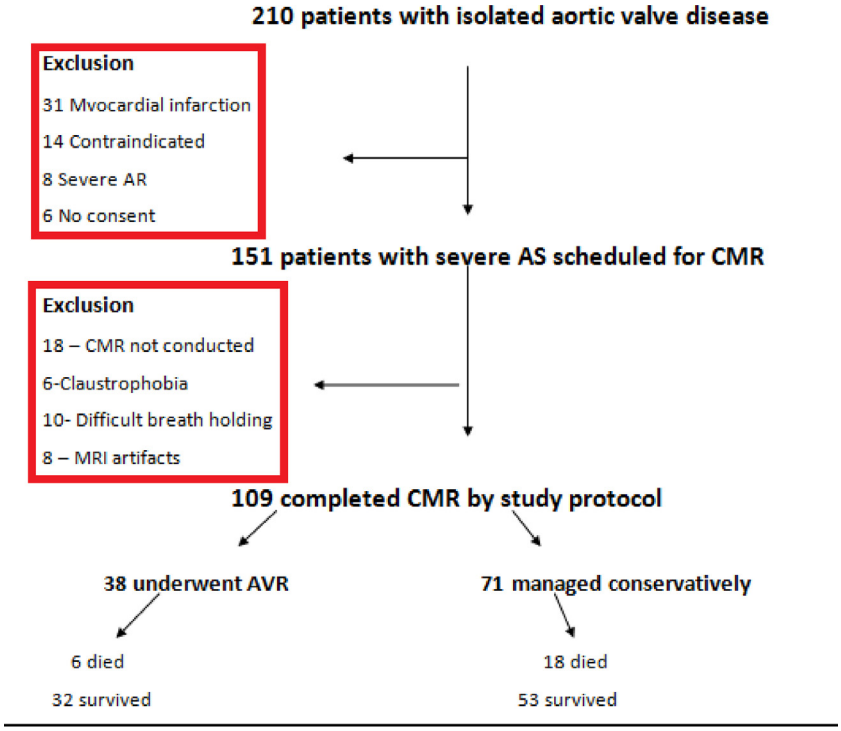
CMR was performed using a 1.5 T Signa HDXt Echospeed 16 channel, General Electric scanner with a standardized protocol. LGE was first acquired in gradient echo sequence FIESTA for static imaging. Steady state free precession was used for cine imaging. Fifteen minutes after injection of 0.2 mmol/kg of gadolinium contrast agent, images were acquired in standard 2 chamber, 4 chamber and short axis views and LGE analysed.[15] For quantification of LV function and volumes, the endocardial and epicardial contours were semi automatically applied in end-systole and end-diastole using a dedicated software. LV mass was calculated from the total end-diastolic myocardial volume multiplied by the specific gravity of the myocardium (1.05g/ml). All values indexed to body surface area and was considered abnormal if they were outside the 95th percentile. The region with the lowest mean signal intensity is considered "remote" myocardium, and LGE regions are considered >2.4 SD of remote.

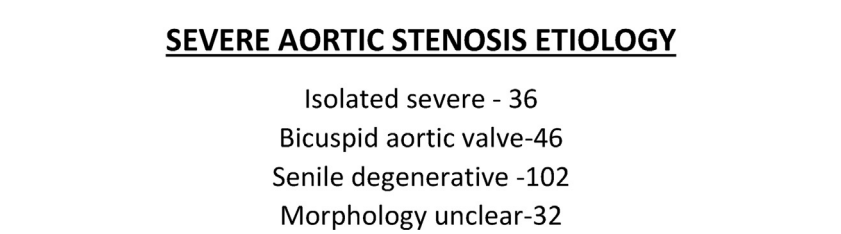
Left ventricle was divided into 17 segments. Fibrosis patterns were recorded and amount of fibrosis was determined by counting the number of segments in which the fibrosis was present. Fibrosis is said to be present if the LGE is present in at least 10% of the segment by area. If fibrosis was present in a segment it was counted as' one'. Anything less than 10% was excluded.

LGE patterns were divided into 3 groups – 1) No LGE (Fig. 1A) 2) Localized Enhancement consistent with prior myocardial infarction (infarct LGE group) (Fig. 1B) a) Transmural enhancement – myocardial enhancement extending the entire thickness of a particular segment (Fig. 2A,E). b) Sub endocardial enhancement-myocardial enhancement seen in the inner layers of myocardium (Fig. 2D) 3) Mid myocardial pattern of enhancement (mid myocardial LGE group) – myocardial enhancement in mid region of left ventricular wall and not extending to endocardial or epicardial regions of a particular segment (Fig. 2B,F). Patchy type (Fig. 2C). These patterns were correlated with clinical endpoints.

Inter-observer and intra-observer variability were assessed in 10% of study population by two observers and good correlation was obtained. The observers were blinded to clinical and echocardiographic data.

Table 1
Severe aortic stenosis etiology.





2.8. Follow up

After a detailed echocardiographic and CMR evaluation, symptomatic patients were referred for AVR. Meanwhile these patients were followed up for outcomes like number of hospitalization for cardiovascular cause, heart failure, arrhythmia, fall in left ventricular ejection fraction ≥20% and death. Symptomatic patients were followed up for events before surgery and after AVR during the study period. There was a group of symptomatic patients who refused surgery due to personal reasons and they were also followed with the asymptomatic group during the study period.

2.9. Statistical methods

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as percentages and analysed using the chi-square test. Mean with the 95% confidence intervals (CIs) were reported. Hazard ratios (HR) were expressed

please continue as one sentence i e, were expressed as mean.as mean (95% CI). Univariate was followed by multivariate regression analyses using Cox & Snell R square model. The 'Goodness of fit ' level for this study was 30.3%. A 2-sided p value <0.05 was regarded as statistically significant. All analyses were performed using SPSS 18.0 (IBM Corporation, Armonk, New York) software. Primary outcome was composite of death, arrhythmia, heart failure/hospitalization for cardiovascular cause and LV ejection fraction fall ≥20%. Secondary outcomes were individual primary outcomes.

3. Results

Patients were recruited from July 2012 to November 2014. Mean follow up was 13 months (Range: 6 m–17 m). Initially 210 patients were enrolled and after exclusion 109 patients underwent CMR (Table 1). Baseline characteristics of these patients are given in (Table 5). It was found that, out of 109 patients, there were 63 (57.8%) males. There were 91 patients with NYHA class I/II symptoms and 18 patients with NYHA class III/IV symptoms. Mean age was 57.3 ± 12.5 years, mean ejection fraction was 56.5 ± 12.4% and the mean LV mass was 141.1 ± 30.2 g. Among echocardiographic parameters analysed, the mean of peak velocity was 4.2 ± 0.6 m/s, mean peak systolic gradient was 73.5 ± 23 mm Hg; mean of mean gradient was 44.7 ± 13.6 mmHg. The mean valvulo-arterial impedance was 4.1 ± 1.1 mm Hg ml^{-1} m^2.

3.1. Prevalence & patterns of myocardial fibrosis

(Tables 2 and 3) No LGE pattern was seen in 63 patients (57%). LGE was seen in the remaining 43% patients (46 patients). Mid myocardial LGE was the most common pattern of fibrosis seen in 33 (31%) patients. Whereas subendocardial and transmural patterns were seen in 4(3.7%) and 8(7.3%) patients respectively. Mixed variety was seen in 1 patient (0.9%).

3.2. Extent of myocardial involvement

(Table 3) 14 patients (12.9%) had at least 2 segment involvement. 3–5 segment involvement was seen in 28(25.6%) patients. 4 patients had 6 or more segment involvement. No patients had greater than 8 segment involvement.

3.3. Region of involvement

(Table 4) Maximum involvement was seen in the basal region followed by mid region and then the apical region. 59 of the 85 basal LV segments of all patients taken together with fibrosis had mid myocardial LGE pattern. 41 out of 60 LV segments with fibrosis had mid myocardial LGE pattern in the mid region. Only 2 out of 15 apical segments with fibrosis had mid myocardial fibrosis. So mid myocardial pattern was more seen in the basal and mid regions.

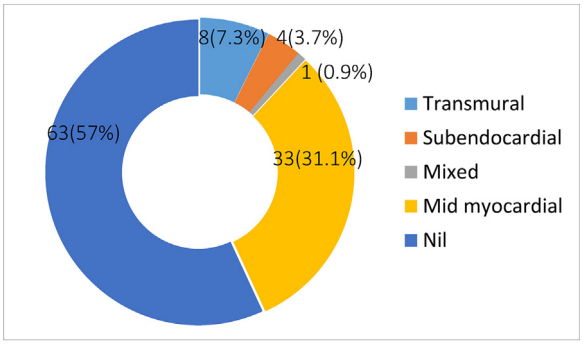
3.4. Mortality data

Out of the 109 patients, there were 24 deaths. 6 patients died post operatively and 18 died in the non surgical group. Among the six who died post operatively, 5 died due to cardiovascular cause and one died of bleeding. 3 patients had LGE and had at least more than two segment LGE involvement. Among the 18 patients who died without AVR. 10 had some form of LGE pattern and all the 10 patients had more than 2 segment involvement. (Table 1)

Considering the predictors of myocardial LGE (Table 5), no categorical variable showed prediction but among the continuous variables- modified Simpsons ejection fraction less than 52.8 ± 12.4%, aortic VTI more than 93.6 ± 10.2cms, peak aortic systolic velocity more than 4 ± 0.5 m/s and peak gradient more than 67.4 ± 20.1 mmHg were predictors of fibrosis in severe AS.

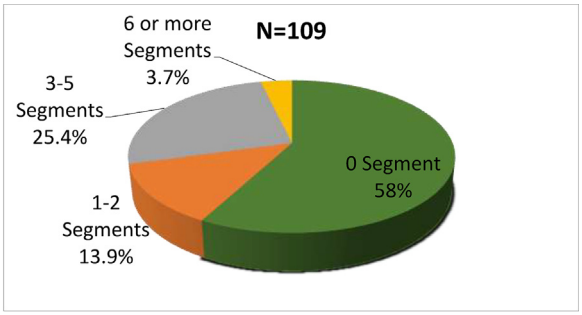
Univariate analysis (Table 6) for primary outcomes showed that higher NYHA class, dyspnea [odds ratio 3.9(1.6–9.4) p value = 0.002], current smoking [odds ratio 2.18(CI-1.1–18.8), p value-0.037] and CMR LGE fibrosis [odds ratio 2.28(2.27–6.47), p value = 0.01] influenced the primary outcome.

Table 2
Patterns of lge involvement.



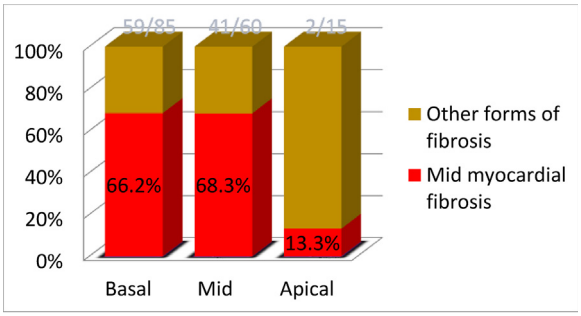
Total number of patterns -5

Table 3
Extent of lge involvement.



Total number of segments- 17

Table 4
Region of lge involvement.



Total- 160 segments had some form of fibrosis; Mid myocardial fibrosis seen in 102 segments

Table 5
Baseline characteristics.

Parameter	N = 109	Myocardial Fibrosis present N = 46 n(%)	Myocardial Fibrosis absent N = 63 n(%)	OR (95%CI)	P Value
Categorical variables					
Age in yrs (Age mean)		58.7 (12.2)	56.3 (12.7)		0.33
Males	63	27 (58.7)	36 (57.1)	1.1 (0.53–2.5)	0.7
NYHA I/II	91	34 (73.9)	57 (90.4)	2.65 (0.9–7.4)	0.06
NYHA III/IV	18	11 (26.1)	7 (9.6)		
Smoker	9	6 (13)	3 (4.7)	3.1(0.73–13.2)	0.1
COPD	18	9 (19.5)	9 (14.2)	1.5(0.55–4.2)	0.41
Angiographic CAD	38	20 (43.4)	18 (28.5)	1.1(0.5–2.3)	0.81
Chronic kidney disease	12	3(6.5)	9 (14.2)	0.43(0.11–1.7)	0.22
Diabetes mellitus	11	5 (10.8)	6 (9.5)	1.2(0.3–4.2)	0.7
Hypertension	55	24(52.1)	31(49.2)	1.2(0.5–2.61)	0.6
Continuous variables					
EF Simpsons(%)		**52.8 (12.4)**	**59.1 (8.5)**		**0.002**
CMR LV mass(g)		149.2(28.4)	135.4 (30.3)		0.18
Ao VTI(cms)		93.6(10.2)	97.8 (12.3)		0.06
Peak aortic velocity(m/s)		**4.0 (0.5)**	**4.3 (0.6)**		**0.01**
Peak sys gradient(mmHg)		**67.4 (20.1)**	**77.7 (24.1)**		**0.02**
Mean gradient(mmHg)		42.4 (13.2)	46.3 (13.8)		0.14
Valvulo-arterial impedance (Z_{va}) (mmHg m^2 ml^{-1})		4.36 (1.5)	4.0 (0.8)		0.13
Indexed EDV(ml/m^2)		84 (20.4)	82 (15.1)		0.67

*bold indicates significant P-value.

Age >62yrs (p value <0.001), lower ejection fraction (50.9 ± 13%) (p value <0.001), more than two segment involvement of LGE in CMR (p value <0.001), higher LV mass >151.73 ± 32 g (p value = 0.007) indicated worse outcomes.

The individual outcomes were separately analysed and found that the myocardial LGE chiefly influenced the primary outcomes by affecting the heart failure/hospitalization for cardio vascular cause [odds ratio 3.8(CI-1.2–11.9)] and fall in LV ejection fraction

Table 6
Univariate analysis- predictors of primary otcome.

Parameter	Primary outcome (N = 38) n (%)	No primary outcome (N = 71) n (%)	Odds ratio (95% CI)	P Value
Categorical variables				
NYHA Class III/IV	**13 (34.2)**	**5 (7)**	**13.4(2.8–26.1)**	**<0.001**
Angina	14 (36.8)	16 (22.5)	2 (0.84–4.7)	0.11
Syncope	9 (23.6)	7 (9.8)	2.84 (0.9–8.3)	0.05
Dyspnea	**29 (76.3)**	**32 (45)**	**3.9 (1.62–9.4)**	**0.002**
Smoker	**6 (15.7)**	**3 (4.2)**	**2.18 (1.1–18.86)**	**0.03**
COPD	9 (23.6)	9 (12.6)	2.13 (0.76–5.9)	0.14
Angiographic CAD	13 (34.2)	25 (35.2)	0.56 (0.25–1.29)	0.16
Chronic kidney disease	4 (10.5)	8 (11.2)	0.92 (0.26–3.3)	0.90
Diabetes mellitus	5 (13.1)	6 (8.4)	1.64 (0.46–5.7)	0.43
Hypertension	21(53.5)	34 (47.8)	1.34 (0.6–2.9)	0.46
MRI Fibrosis	**22(57.8)**	**23 (32.3)**	**2.8 (1.27–6.47)**	**0.01**
Continuous variables				
Age(yrs)	**62(9.6)**	**54.3(12.9)**		**0.001**
EF Simpson(%)	**50.9(13)**	**59.5(7.9)**		**<0.001**
Segments involved [SI](n)	**2.37(2.1)**	**0.9(1.7)**		**<0.001**
CMR LV Mass(g)	**151.73(32)**	**135.4(27.8)**		**0.007**
Ao VTI(cms)	93.97(9.9)	97.2(12.3)		0.16
Peak Velocity(m/s)	**3.9(0.57)**	**4.3(0.5)**		**0.003**
PSG(mmHg)	**65(19.41)**	**78.0(23.7**		**0.005**
MG(mmHg)	**46.93(13.49)**	**40(13)**		**0.03**
Z_{va} (mm Hg ml^{-1} m^2)	**4.5(1.5)**	**3.9(0.8)**		**0.025**
Indexed EDV(ml/m^2)	85.32(20)	82.0(15.7)		0.35

Table 7
Secondary outcomes analysed separately.

Categorical variables								
Parameter	Mortality		Arrhythmia		HF/Hospitalization		LVEF fall ≥20%	
	OR(95%CI)	P	OR(95%CI)	P	OR(95%CI)	P	OR(95%CI)	P
MRI Fibrosis	1.42(0.6–3.5)	0.43	1.78(0.6–5.7)	0.32	**3.8(1.2–11.9)**	**0.01**	**5.8(1.5–22.5)**	**0.005**
Sex	0.6(0.2–1.5)	0.26	0.8(0.3–2.7)	0.75	1.2(0.4–3.8)	0.68	0.8(0.3–2.7)	0.75
NYHA Class	**4.6(1.6–13.7)**	**0.003**	**6(1.7–20.9)**	**0.002**	**8.3(2.6–27)**	**0.001**	**13.7(3.8–50.2)**	**<0.001**
Smoker	1.73(0.4–7.6)	0.42	**4.5(1–20.9)**	**0.04**	1.7(0.3–9.3)	0.5	2.3(0.4–12.5)	0.12

Continuous variables Parameter	Primary outcome (n = 38) Mean(SD)	Free of primary outcome (n = 71)Mean(SD)	P Value
Age(yrs)	**62(9.6)**	**54.3(12.9)**	**0.001**
EF Simpson(%)	**50.9(13)**	**59.5(7.9)**	**<0.001**
Segments involved [SI](n)	**2.37(2.1)**	**0.9(1.7)**	**<0.001**
CMR LV Mass(g)	**151.73(32)**	**135.4(27.8)**	**0.007**
Ao VTI(cms)	93.97(9.9)	97.2(12.3)	0.16
Peak Velocity(m/s)	**3.9(0.57)**	**4.3(0.5)**	**0.003**
PSG(mmHg)	**65(19.41)**	**78.0(23.7**	**0.005**
MG(mmHg)	**46.93(13.49)**	**40(13)**	**0.03**
Z_{va} (mm Hg ml^{-1} m^2)	**4.5(1.5)**	**3.9(0.8)**	**0.025**
Indexed EDV(ml/m^2)	85.32(20)	82.0(15.7)	0.35

Table 8
Multivariate analysis of predictors of primary outcome.

Parameter	Odds ratio(95% CI)	P Value
Age >62yrs (YRS)	**2.9(1.3–4.6)**	**0.004**
MRI Fibrosis	1.68 (0.6–4.6)	0.30
NYHA Class III/IV	**5.7(1.2–26.6)**	**0.024**
Current smoker	2(0.3–12.3)	0.42
EF Simpson(%)	1(0.99–1.1)	0.09
CMR LV Mass (g)	1(0.99–1.01)	0.72
Peak Velocity (m/s)	1.4(0.5–3.7)	0.48
Z_{VA} (mm Hg ml^{-1} m^2)	1(0.6–1.6)	0.94

≥20% [odds ratio 5.8(CI-1.5–22.5)]. Mortality and arrhythmia were not affected by LGE. (Table 7)

Multivariate analysis showed that age >62 years [odds ratio 2.9 (CI 1.3–4.6), p value = 0.004] and higher NYHA class [odds ratio 5.7 (CI 1.2–26.6), p value = 0.024] were the only predictors of primary outcomes. (Table 8)

4. Discussion

Our study is one of the first studies done from the Indian sub continent with the highest number of patients that has looked into the prevalence and predictive value of LGE. Mean age of the population with myocardial LGE in our study was 58.7 ± 12years. Baron's study showed a mean age of LGE as 79 ± 4 years. The

present study has comparatively younger population with LGE. This study showed a prevalence of LGE in 43% (N = 47) and mid myocardial involvement in 31.1% (N = 34). Similar study by Dweck et al.[7] showed the prevalence of LGE among 143 AS patients to be 66% and mid myocardial LGE was the most common pattern seen in 38% of patients. Another study by Baron et al.[15] (N = 154) showed a prevalence of LGE in 29%. Mid myocardial LGE involvement was almost similar when compared with other studies. Region of involvement of LGE –most studies showed anterior/septal segments of basal and mid region showed maximum involvement. Our study showed similar results. A Korean study showed mid myocardial fibrosis is the most common type of LGE in their study which was similar to the present study.[18]

Predictors of fibrosis in the present study were – NYHA class, Ejection fraction, LV mass & peak aortic velocity which were comparable to other studies.[7,15] Predictors of primary outcome by univariate analysis were – NYHA class, presence of LGE, number of segments with LGE, CMR LV mass, age, valvulo-arterial impedance (Zva) and LV ejection fraction. Predictors after multivariate regression were NYHA class and age >62yrs. LGE appeared to predict HF/hospitalization and fall in LVEF.

The Dweck's study[7] showed that the presence of myocardial fibrosis was associated with a 6–8 times all cause mortality. Dweck's & Baron's study both showed that LGE predicted all cause mortality but not sufficient to predict cardiovascular mortality. The present study was not able to show that LGE could predict mortality as the study is underpowered and probably has a short follow up. LGE has influenced the primary outcome in our study by showing correlation with fall in LV EF (p = 0.005) and heart failure/hospitalization rates (p = 0.016) similar to other large studies. Patients with LGE had 2.87 times chance for primary outcome and patients with more than 3 segment involvement had increased chance for primary outcomes. This was consistent with Dweck's[7] and Baron's study[15]. Patients with no LGE had relatively good prognosis which was consistent with many international studies.[7,15]

4.1. Clinical implications

Currently AVR is done based on symptoms and various echocardiographic parameters. Other investigative modalities are not used. This study definitely shows a trend towards worse outcomes in patients with LGE and it could be a marker to stratify patients into high risk and low risk groups. Patients with LGE may be planned early AVR as there is decreased morbidity and mortality when surgery is planned early in these patients.[17]

5. Limitations

1. The study was underpowered to show prognostic impact of LGE on mortality by multivariate analysis.
2. Limited follow up period may have affected results.
3. CMR –LGE mass could not be quantified and hence its actual impact could not be deciphered.

6. Conclusion

Myocardial LGE (especially mid-myocardial pattern) detected by CMR is present in ~41% of patients with severe aortic stenosis.

Myocardial LGE predicted heart failure, hospitalization for cardiovascular causes and decrease in LV ejection fraction.

Larger prospective studies are required to assess the prognostic impact of CMR in patients with severe AS.

Conflict of interest

All authors have thoroughly studied the article and approve of it. Each author has no conflicts of interest and nothing to disclose.

Disclosure

No conflict of interest to report

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Definitions

Severe asymptomatic aortic stenosis – A patient with no symptoms of heart failure, angina or syncope with severe aortic leaflet calcification or congenital stenosis with severely reduced leaflet opening or indexed aortic valve area $\leq 0.6\,cm^2/m^2$.

Severe symptomatic aortic stenosis – Patients with symptoms of heart failure, angina or syncope with severe aortic leaflet calcification or congenital stenosis with severely reduced leaflet opening i.e. aortic valve area $\leq 1.0\,cm^2$ (or indexed aortic valve area $\leq 0.6\,cm^2/m^2$).

Severe aortic regurgitation – Patients with aortic regurgitation jet vena contracta > 6 mm. If vena contracta is between 3 mm and 6 mm, multiple parameters like effective regurgitant orifice area $\geq 30\,mm^2$ or regurgitant volume ≥ 60 mL, holodiastolic flow reversal in descending thoracic aorta, AR pressure half time < 250msec is also considered as severe AR.

Diabetes mellitus (DM) - Patient is said to have diabetes if he/she is documented to take medications like oral hypoglycemic agents/insulin or has criteria for diagnosis of diabetes (Fasting blood sugar ≥ 126 mg/dl, post-prandial blood sugar ≥ 200 mg/dl or HbA1c ≥ 6.5gm% any one of the three present)

Hypertension - A patient is said to have hypertension if he has systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg or he is on medications for the same.

Chronic kidney disease (CKD) - Defined as kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73 m(2) for 3 months or more, irrespective of cause. Kidney damage in many kidney diseases can be ascertained by the presence of albuminuria, defined as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens.

Angiographic coronary artery disease (CAD) - Patient had coronary artery disease (CAD) if there was >50% stenosis in coronary vessels ≥ 1.5 mm in diameter.

Current Smoker – Adult who have smoked 100 cigarettes in their lifetime and currently smoke cigarettes every day (daily) or some days (nondaily).

Chronic Obstructive Pulmonary Disease - Characterized by airflow obstruction that is not fully reversible. Airflow obstruction is defined as a reduced FEV1/FVC ratio (where FEV1 is the forced expired volume in one second and FVC is the forced vital capacity), such that FEV1/FVC is less than 0.7.

NYHA Class I - Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.

NYHA Class II - Mild symptoms (dyspnoea, angina, palpitation, syncope) and slight limitation during ordinary activity.

NYHA Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity,e.g.walking short distances (20–100 m).Comfortable only at rest.

NYHA Class IV - Severe limitations in physical activity. Experiences symptoms even while at rest. Mostly bedbound patients.

Syncope – Sudden brief loss of consciousness and postural tone, characterized by a fast onset, short duration, and spontaneous recovery. It is due to cerebral hypoperfusion.

Good LV function - Left ventricular ejection fraction by Modified Simpson's method ≥ 55%.

Mild LV systolic dysfunction - Left ventricular ejection fraction by Modified Simpson's method between 40 and 54%.

Moderate LV systolic dysfunction - Left ventricular ejection fraction by Modified Simpson's method between 30 and 39%.

Severe LV systolic dysfunction - Left ventricular ejection fraction by Modified Simpson's method <30%.

Valvulo arterial impedance (ZVA) – Calculated by measuring the systolic blood pressure at the time of echocardiogram. Then the mean gradient was measured. The following formula was applied- Zva = Mean gradient + Systolic bood pressure/indexed stroke volume where stroke volume derived from modified Simpsons method is indexed to body surface area.

Cardiovascular Mortality - Mortality pertaining to a cardiac cause. It also includes perioperative death in AVR patients and also sudden cardiac death.

Sudden cardiac death – Unexpected natural death from a cardiac cause within a short time period, generally <1 h from the onset of symptoms, in a person without any prior condition that would appear fatal.

LV EF fall by ≥ 20% – Fall in left ventricular ejection fraction ≥ detected by modified Simpsons method in echocardiography during follow up.

Heart Failure/Hospitalization - Includes events with any hospital admission for features of heart failure, arrhythmia or any cardiovascular cause necessitating admission.

Arrhythmia – Includes any event with heart rate ≥ 100/min other than sinus tachycardia and events with heart rate ≤60/min other than sinus bradycardia.

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