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Prognostic Significance of CMR Findings in Patients with Known Coronary Artery Disease – Experience from a South Asian Country

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ABSTRACT

Objectives: South Asians (SA) have a higher burden of coronary artery disease (CAD) and are known to have a worse prognosis compared to other ethnicities. Therefore, it is imperative to improve the risk stratification of SA patient with CAD and to seek out newer prognostic markers beyond the conventional echocardiography.The aim of this study was to investigate whether variables obtained by cardiac magnetic resonance (CMR) improve risk stratification of South Asian patients with known CAD.

Material and Methods: We retrospectively analyzed 147 patients with evidence of CAD that had a CMR at our center between January 2011 and January 2019. LV volumes and regional wall motions were acquired by cine images, while infarct size (IS) was measured by late gadolinium enhancement. At a mean follow-up of 3.36 ± 2.22 years, cardiac events (non-fatal myocardial infarction, hospitalization due to heart failure, life-threatening arrhythmia, or cardiac death) occurred in 49 patients. An IS ≥35%, left ventricular ejection fraction (LVEF) ≤31%, and a wall motion score index (WMSI) ≥1.9 were strongly associated with follow-up cardiac events (P < 0.001). Patients that had none or less than 3 of these factors, showed a lower risk of cardiac events (HR 0.22 CI [0.11–0.44] P < 0.001 and HR 0.12 CI [0.04–0.32] P < 0.001, respectively) compared to those with all three factors.

Conclusion: Integration of CMR derived factors such as IS and WMSI with LVEF can improve the prognostication of the SA population with CAD. Better risk stratification of patients can lead to improved and cost-effective therapeutic strategies to ameliorate the prognosis of these patients.

Keywords: Cardiac MRI, Coronary artery disease, Infarct size, Late gadolinium enhancement, South Asians, Wall motion score index

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of mortality and morbidity worldwide. Despite advances in prevention, detection, and treatment of CAD in the last decades, most patients with significant CAD die of sudden cardiac death (SCD) or congestive heart failure (CHF).[1] Non-invasive imaging modalities, such as echocardiography, SPECT imaging, cardiac computed tomography, and cardiac magnetic resonance (CMR) imaging, have been increasingly used to diagnose and identify different predictors of major adverse cardiac events (MACE) and cardiac death in patients with known CAD.[2-4]

CMR is a comprehensive and accurate imaging modality that combines anatomic information with dynamic assessment of cardiac function. CMR imaging has high spatial and temporal resolution, and a lack of geometric assumptions, which makes CMR measurement of LV volumes both accurate and reproducible.[5] Late gadolinium enhancement (LGE) by CMR accurately delineates irreversible myocardial injury with extraordinary spatial resolution, which enables CMR to discriminate easily between sub-endocardial and transmural scar. Hence, LGE by CMR is considered the standard for myocardial infarction (MI) size quantification and myocardial viability.[6]

Studies have shown that CMR is capable of providing independent prognostic information that allows for risk stratification in patients after recent MI, as well as in patients with suspected or known CAD.[7,8] CMR derived parameters such as the extent of infarct size (IS), presence or absence of myocardial viability, wall motion score index (WMSI), and left ventricular ejection fraction (LVEF) have been implicated as predictors of mortality and MACE in patients with known CAD and acute MI.[9] Therefore, the determination of these parameters on CMR is valuable for the prognostication of patients with CAD.

CMR imaging has been available in South Asia as a diagnostic tool for at least a decade but its exact utilization is largely unknown. Echocardiography has been the favored non-invasive imaging modality largely due to its wider availability and lower cost as compared to CMR. Hence, information derived from echo is mostly employed for prognostication of our patients with CAD and history of MI.

Our center has been the pioneer of cardiac imaging in the country. At present, it serves as the only center offering CMR facility to a large area of population and hence has been a frequent referral center for CMR imaging in patients with known or suspected CAD. Through this study, we aim to assess the prognostic stratification power of the individual as well as combined assessment of different parameters detected by CMR in South Asian patients that have evidence of CAD. We believe that the integration of the parameters, together with conventional risk factors, could improve the prognostic stratification of these patients, especially the ones with a history of MI.

MATERIAL AND METHODS

All consecutive patients who had evidence of CAD and were referred to our center for CMR during the period January 2011 to January 2019 were included in our study. Evidence of CAD was defined by (a) history of MI as documented in clinical records or q waves in 12 lead ECG recording, (b) history of prior revascularization (percutaneous coronary intervention or coronary artery bypass surgery, and (c) ≥50% stenosis of a major epicardial coronary artery on invasive coronary angiogram. The major exclusion criteria were patients with acute MI of ≤2 weeks, patients with severe valvular heart disease, hypertrophic cardiomyopathy, myocarditis, sarcoidosis, or other infiltrative cardiomyopathies. The study was exempted from ethical approval by the ethics committee at the Aga Khan University Hospital, Karachi.

CMR data acquisition

CMR was performed using a 1.5T Siemens Avanto scanner. A breath-hold steady-state free-precession ECG-triggered sequence was used to evaluate global LV function. In each patient, two long-axis views (one vertical and one horizontal) were acquired and a set of contiguous short-axis views were acquired from the mitral plane to the apex with the following parameters: Slice thickness 7 mm, distance factor 25%, field of view 34 cm, matrix 192 × 192, flip angle 80, TR/TE 58.74/1.12, and bandwidth 930 hz/px. LGE images were obtained 8–10 min after bolus injection of gadolinium derivates. Images were acquired in the same short-axis and long-axis slices as used for cine CMR. The inversion time was optimized to null signal from the normal myocardium.

CMR analysis

All the cine and LGE images were analyzed by a single reader with a >10-year experience in cardiovascular imaging. The analysis of CMR images was performed on a third party software – Media Q mass. The endocardial and epicardial borders were drawn manually on the series of short-axis cine slices of the LV at end-diastole and end-systole to obtain end-diastolic volume (LVEDV) and end-systolic volume (LVESV), respectively. The LVEF was calculated from the LVEDV and LVESV and presented as percentages to LVEDV. The LV was analyzed in the standard 17 segments model including six basal, six middle, four distal segments, and the apex.

Wall motion of each segment was graded according to a four-point scale where 1 is normal, 2 is hypokinetic, 3 is akinetic, and 4 is dyskinetic. WMSI was derived by the equation:[10]

$$\text{WMSI} = \frac{\text{Total wall motion score}}{17} \tag{1}$$

LGE images were analyzed visually using the similar 17 segments model. The trans-mural extent of the LGE was graded comparing the myocardial area to that in the segment: Grade 1 = 1–25%; Grade 2 = 26–50% [Figure 1]; Grade 3 = 51–75% [Figure 2]; and Grade 4 = 76–100% [Figures 2 and 3]. The IS was calculated as a percentage of the whole LV using the following equation[11]:
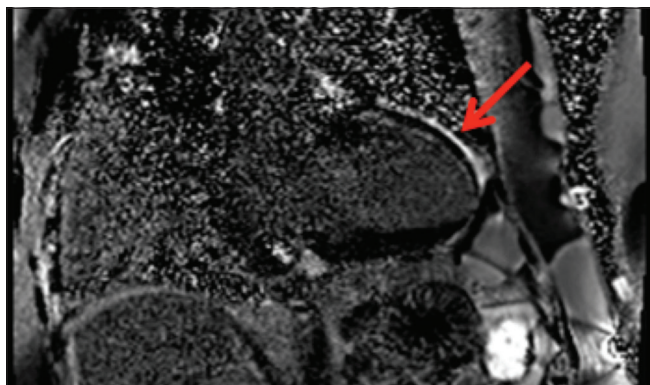
Figure 1: A 64-year-old male with a history of anterior wall myocardial infarction. Cardiac magnetic resonance images with late gadolinium enhancement in two-chamber orientation showing sub-endocardial hyper-enhancement involving <50% of wall thickness (Grade 2) in the anterior wall (red arrow).
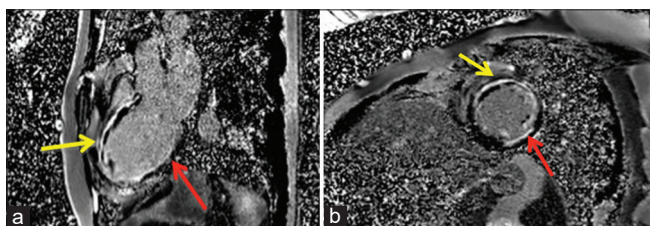

Figure 2: A 60-year-old male with a history of anterior wall myocardial infarction. (a) Cardiac magnetic resonance imaging with late gadolinium enhancement in three chamber orientation showing sub-endocardial hyper-enhancement of 50–75% of wall thickness (Grade 3) in the inferolateral segments (red arrow) and transmural hyperenhancement (Grade 4) in the anteroseptal segments with the evidence of microvascular obstruction (yellow arrow). (b) Cardiac magnetic resonance imaging with late gadolinium enhancement in short axis view showing Grade 3 hyper-enhancement in the lateral and inferolateral segments (red arrow) and Grade 4 hyperenhancement in the anterior and anteroseptal segments with the evidence of microvascular obstruction (yellow arrow).

$$\frac{\begin{array}{c}\text{Sum of all trans}-\text{mural extent of LGE scores}\\ \text{throughout LV }\left(\text{range, }0-4\right)\end{array}}{\left(\text{Total Number of segments }\times 4\right)} \quad (2)$$

Microvascular obstruction (MVO) was defined as any hypo-enhanced area present within the hyper-enhanced infarcted region on LGE images.

Follow-up

Follow-up clinical events were recorded by review of hospital records for clinical visits, hospital admissions, and telephonic interviews with the patient or family member, where the patient was unavailable. The clinical events considered were all-cause mortality, cardiac death, hospital admissions due to MI, hospital admissions due to heart failure (CHF), and
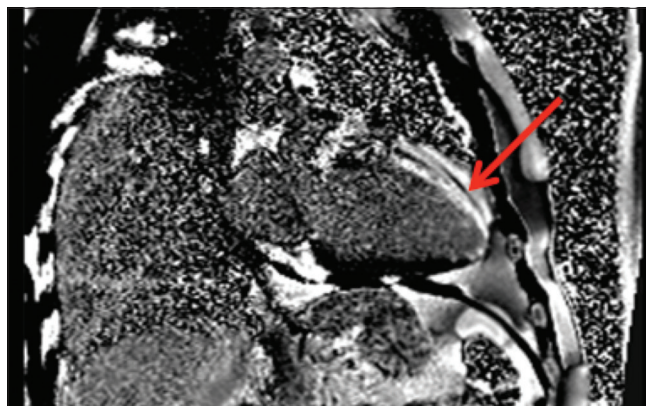

Figure 3: A 42-year-old female with a history of anterior wall myocardial infarction. Cardiac magnetic resonance imaging with late gadolinium enhancement in two-chamber orientation showing trans-mural hyperenhancement (Grade 4) in the apex and anterior wall (red arrow).

life-threatening arrhythmias. All deaths were presumed to be cardiac death unless a clear non-cardiac cause could be established. MI was defined by typical clinical symptoms, relevant ECG changes, and/or elevated troponin I. Life-threatening arrhythmia was defined as documented ventricular tachycardia or ventricular fibrillation by ECG strips or ICD interrogation. The primary outcome was the occurrence of a cardiac event (MACE) which was composite of cardiac death, follow up MI, CHF, and life-threatening arrhythmia, during follow-up.

Statistical analysis

Statistical analysis was performed with the use of the Statistical Package for the Social Sciences, version 24.0, IBM, Chicago, IL, USA. Quantitative variables were expressed as mean and standard deviations or medians (interquartile ranges), as appropriate. The study cohort was analyzed both as a whole and according to the presence or absence of cardiac events. Qualitative variables were expressed as absolute frequencies and percentages and were compared using the Chi-square test or Fisher's exact test, as appropriate. Continuous data were compared using an independent-samples t-test or the Mann–Whitney U-test, depending on their distribution. Follow-up variables were analyzed and the Hazard ratios (HRs) of cardiac events for individual factors were calculated. In addition, the median values of LVEF, WMSI, and IS were obtained which were 31% for LVEF, 1.9 for WMSI, and 35% for LGE extent These factors were then dichotomized according to their median values and also included in the analysis as a categorical variable, that is, LVEF > or ≤31, WMSI < or ≥1.9, and LGE extent < or ≥35%. The HRs for cardiac events and cardiac mortality according to the presence or absence of the combination of the three factors were also calculated (LVEF ≤31%, WMSI ≥1.9, and

LGE extent ≥35%). A two-sided *P* < 0.05 was considered statistically significant for all tests by univariate binary logistic regression for predictors of cardiac events. Nelson–Aalen cumulative hazard of mortality at different follow-up time was estimated in STATA.

RESULTS

A total of 150 patients with known CAD had a CMR at our center. Three patients had incomplete data and were not included in the analysis. Hence, a total of 147 patients with known CAD were part of our analysis. All patients had completed at least 6 months of follow-up (except those

with mortality). At a mean follow-up of 3.37 ± 2.22 years post-CMR, 49 patients (33.3%) had a cardiac event while 98 patients remained free of any cardiac event. During the follow-up 23 patients (15.6%) died, of which 16 (10.9%) were cardiac deaths. The MACE were mainly driven by hospitalization due to CHF (35 patients), while 24 patients had a life-threatening arrhythmia and eight patients had MI. During follow-up, 28 patients (19%) underwent an implantable cardioverter/defibrillator (ICD) implantation, and 32 patients had PCI while 20 patients had CABG.

Patients were subsequently divided into two groups, with and without cardiac events on follow-up, for further analysis.

Table 1: Baseline characteristics of patients according to follow-up cardiac events.

	Total patients $n=147$ (%)	Patients with cardiac events $n=49$	Patients with no cardiac events $n=98$	*P*-value*
Age	57.89±9.97	58.71±9.30	57.48±10.32	0.48
Male	138 (93.9)	47 (95.9)	91 (92.9)	0.47
DM	77 (52.4)	28 (57.1)	49 (50)	0.41
HTN	82 (55.8)	32 (65.3)	50 (51)	0.1
Dyslipidemia	75 (51)	28 (57.1)	47 (48)	0.38
Smoker	38 (25.9)	12 (24.5)	26 (26.5)	0.79
Angiographic evidence of CAD	117 (79.6)	36 (73.5)	81 (82.7)	0.19
SVCAD	24 (16.3)	6 (12.2)	18 (18.4)	0.46
DVCAD	26 (17.7)	7 (14.3)	19 (19.4)	
TVCAD	67 (45.6)	23 (46.9)	44 (44.9)	
MI >1	32 (21.8)	13- 26.5	19-19.4	0.32
Prior CABG	11 (7.5)	4 (8.2)	7 (7.1)	0.83
Prior PCI	17 (11.6)	7 (14.3)	10 (10.2)	0.47

*Pearson chi-square test or Fisher's exact test for categorical data as appropriate; Student's t-test or Mann–Whitney for continuous data as appropriate.
DM- Diabetes Mellitus, HTN- Hypertension, SVCAD -Single vessel coronary artery disease, DVCAD- Double vessel coronary artery disease,
TVCAD- Three vessel coronary artery disease, MI > 1- More than 1 myocardial infarction, PCI - Percutaneous coronary intervention.

Table 2: CMR findings of patients according to the cardiac events.

	Total patients $n=147$	Patients with cardiac events $n=49$	Patients with no cardiac events $n=98$	*P*-value*
EDV	216.39±66.30	243.46±58.79	203±66.0	<0.001
ESV	152.06±58.34	180.44±53.76	138±55.56	<0.001
SV	64.94±17.39	62.81±17.93	66.0±17.11	0.30
LVEF	31.21±8.58	26.37±7.40	33.66±8.11	<0.001
WMSI	1.93±0.32	2.11±0.26	1.84±0.32	<0.001
MVO	31 (21.2)	13 (26.5)	18 (18.6)	0.27
Aneurysmal segment	10 (6.9)	6 (12.5)	4 (4.2)	0.06
LV thrombus	17 (11.6)	8 (16.3)	9 (9.3)	0.21
Infarct size/transmularity	36.20±15.27	45.59±11.38	31.36±14.79	<0.001
LGE transmural extent Grade I (number of segments)	0.22±1.07	0.27±1.01	0.20±1.10	0.75
LGE transmural extent II (number of segments)	1.42±2.33	1.49±2.1	1.39±2.45	0.80
LGE transmural extent III (number of segments)	3.16±3.36	3.35±3.87	3.07±3.09	0.64
LGE transmural extent IV (number of segments)	3.01±3.50	4.43±3.69	2.30±3.20	<0.001

*Pearson chi-square test or Fisher's exact test for categorical data as appropriate; Student's *t*-test or Mann–Whitney for continuous data as appropriate.
EDV - End-diastolic volume, ESV- End systolic volume, SV- Stroke volume, LVEF - Left ventricular ejection fraction, WMSI- Wall motion score index,
MVO - Micro-vascular obstruction, LGE- Late gadolinium enhancement.

Table 1 shows the baseline characteristics of the study population and the two groups. The mean age of the total study population was 57.89+/- 9.97 year. There was great disparity in the gender of the study population with 93.9% being male. The majority of the patients had an angiographic evidence of CAD (79.6%).

Table 2 shows the CMR findings in the study population and among the two groups. As evident from the table EDV, ESV, WMSI, IS, and transmural extent of LGE were significantly higher ($P < 0.001$) in patients who had cardiac events on follow-up, compared to those who had no cardiac events. Similarly, LVEF was significantly lower (p < 0.001) in those with cardiac events. There was no significant difference in SV, LV thrombus, and MVO between the cardiac event group and no cardiac event group.

Table 3 shows the HRs for cardiac events by CMR variables. CMR variables of LVEDV, LVESV, LVEF, IS, and WMSI were associated with increased risk of cardiac events at univariate Cox regression analysis. Moreover, after adjusting for age, LVEF ≤ 31% (HR 4.37, CI [2.22–8.59]; $P < 0.001$), WMSI ≥1.9 (HR 3.52, CI [1.87–6.64]; $P < 0.001$), and IS ≥35 (HR 3.80, CI [1.83–7.87]; $P < 0.001$) showed the highest association with risk of cardiac events during follow-up.

Patients were divided into three subgroups based on the presence of the above variables associated with cardiac events (i.e., LVEF <31%, WMSI >1.9 and IS >35): Three markers (52 patients; 32 cardiac events, 61.5%); one to two markers (50 patients, 12 cardiac events, 24%); and none of the three markers (45 patients, 5 cardiac events, 11.1%). Patients that had none or only one to two of these markers had a lower risk of a worse outcome (HR 0.22, $P < 0.001$ and HR 0.12, $P < 0.001$, respectively) than patients having all three markers [Table 4].

DISCUSSION

Through this study, we aimed to assess the prognostic significance of the different factors detected by CMR in South Asian patients that are known to have CAD. Our results showed that IS, LVEF, and WMSI derived by CMR are independent predictors of MACE. This, in essence, means that the extent of scar tissue, the global LV function and regional wall motion abnormalities are some of the important factors that determine the prognosis of a patient with known CAD. Furthermore, when these three cardiac indices were evaluated in combination, specifically as IS ≥35%, LVEF ≤31, and WMSI ≥1.9, they fine-tuned the prognostic stratification of these patients. These finding can be explained by the pathophysiological changes in a patient with previous MI. The viable myocardium after an MI is replaced by scar tissue. The extent of the scar tissue stabilizes in few weeks after an acute MI.[12] As a result of the scarred myocardium, the LV

Table 3: Hazard ratios for cardiac events by cardiac magnetic resonance variables both before and after adjustment for age.

	Hazard ratio (95% CI); p value	Adjusted Hazard ratio with age (95% CI) *P*-value
Age, years	1.02 (0.99–1.05)	
LVEDV	1.007 (1.003–1.01) **	1.007 (1.003–1.01)*
LVEDV >209	2.20 (1.21–4.01) **	2.12 (1.16–3.86)**
LVESV	1.009 (1.004–1.01) ***	1.009 (1.004–1.01)***
LVEF	0.91 (0.88–0.95) ***	0.91 (0.88–0.95)***
LVEF ≤31	4.47 (2.28–8.78)***	4.37 (2.22–8.59)***
WMSI	13.01 (4.78–35.39)***	11.68 (4.21–32.40)***
WMSI ≥1.9	3.68 (1.96–6.92)***	3.52 (1.87–6.64)***
Infarct size	1.05 (1.03–1.07)***	1.05 (1.03–1.07)***
Infarct size ≥35	3.58 (1.73–7.40)**	3.80 (1.83–7.87)***
Stroke volume	0.99 (0.97–1.01)	0.99 (0.98–1.01)
MVO Yes versus No	0.99 (0.52–1.89)	1.12 (0.57–2.17)
LV thrombus	1.63 (0.76–3.48)	1.91 (0.88–4.13)
Aneurysmal segment	1.74 (0.74–4.12)	1.78 (0.75–4.20)

*$P<0.05$, **$P<0.01$, ***$P<0.001$

Table 4: Hazard ratios for cardiac events according to LVEF ≥ or <31%, WMSI ≥or <1.9, LGE extent ≥ or <35%.

	Cardiac events; *n*=49 (%)	HR (95% CI)
Three markers	32 (61.5)	1.0 (Ref.)
One to two markers	12 (24)	0.12 (0.04–0.32)*
No marker	5 (11.1)	0.22 (0.11–0.44)*

*$P<0.001$. Three markers: Infarct size ≥35% and WMSI ≥1.9 and LVEF ≤31%. One to two markers: One or two of the Infarct size ≥35%, WMSI ≥1.9%, LVEF ≤31%. No markers: Infarct size <35% and WMSI <1.9 and LVEF <31%

regional wall motion abnormalities develop.[13] These, in turn, cause a reduction in the global LV function that is expressed by LVEF.

Reduced LVEF is a known risk factor of SCD and is used to guide medical therapy in patients with CAD.[14,15] However, the use of LVEF as standalone risk stratification marker has some limitations. Post-MI patients with moderate to preserved LV function despite having a lower relative risk also experience a large number of SCD events.[16] Moreover, not all patients with low LVEF experience arrhythmic death.[17] Thus, guiding therapy only based on depressed ejection fraction may not be cost-effective. Therefore, other variables to optimize the risk stratification of patients with known CAD are required.

In literature, IS on CMR, derived either by quantitative or semi-quantitative techniques, has been described as an important predictor of mortality and MACE in patients

with known CAD.[18] Some studies have found that IS was a stronger predictor of mortality than LVEF.[10,19-20] Studies have also shown that the IS also correlates with the risk of ventricular arrhythmias and can find its application to guide device placements. A meta-analysis found that a greater extent of LV scar was associated with over a four-fold increase in the relative risk of a ventricular arrhythmic event compared with patients with less scar.[21]

However, our results were similar to those studies that found IS to be complementary to the prognostic value of LVEF.[22] Bello *et al.* demonstrated that the likelihood of death in patients with IS of >24% (of LV mass) increased with an HR of 2.4.[23] Kwon *et al.* used a total scar score expressed as the number of segments with LGE divided by 17 (total number of AHA segments), in patients with ischemic cardiomyopathy, which was associated with a 38% (95% CI, 1.07–1.79) increase in the hazards for adverse cardiac events.[14] Catalano *et al.* described that IS derived using a technique similar to our study, added to the prognostic value of LVEF.[22] It is worth mentioning here that in comparison to their study, the IS in our study was larger (36.2 0 ±15.27% vs. 13 ± 15%) and the LVEF was lower (31.21 ± 8.58% vs. 51 ± 13%).

WMSI is another CMR variable that has been implicated in risk stratification of post-MI patients. Mahenthiran *et al.* demonstrated that a WMSI >1.5 was associated with higher ICD events.[24] Similar to our study Di Bella *et al.* found that WMSI was a predictor of cardiac events when evaluated individually as well as in combination with other parameters.[20]

In our study, we also evaluated the multiparametric approach for further prognostic stratification of patients. We used an approach similar to that described by Di Bella *et al.*[20] Similar to their study, our results of the combined evaluation of cardiac indices enhanced the prognostic stratification of CMR. Both studies show that patients with three cardiac markers derived from CMR had a higher risk of cardiac events and lower survival. However, there were some differences in our study. We used LVEF as one of the variables in combined evaluation while in Di Bella *et al.*'s study LVEF did not emerge as a prognostic factor and was not evaluated in combination with other variables. This could be explained by the lower mean LVEF in our study compared to their (31.21 ± 8.58% vs. 39.7 ± 16%).

The importance of the results of this study lies in the fact that the SA population have a higher burden of cardiovascular disease and are known to have a worse prognosis compared to other ethnicities.[25] There is an extreme need to develop improved and cost-effective methods for better prognostication of the SA population going beyond the use of LVEF by echocardiography. CMR in the modern era has emerged as an important non-invasive tool for assessing patients. Unfortunately, CMR is underutilized in the South Asian countries mainly due to limited resources and expertise.

This study provides the stepping stone for identifying the high-risk patients and thereby strategizing steps to improve their survival. These strategies may include incorporating those patients in to short- and long-term follow-up programs to ensure optimal medical therapy, ICD/CRT implantations, and avoidance of revascularization where the risks potentially outweigh the benefit.

Limitation

This study has several limitations. First, this is a retrospective study done in a single center. Hence, the results from this study need to be confirmed by a larger prospective multicenter study in the South Asian population. Second, the females in the study population were underrepresented. Moreover, the small number of patients and cardiac events occurring during follow-up did not allow performing a multivariate analysis.

CONCLUSION

Although embedded in the limitation of a retrospective analysis, our study is a significant effort to bridge the literature gap of CMR studies in SA population. Our results demonstrate that larger IS, lower LVEF, and higher WMSI are associated with significantly worse outcomes. Hence, CMR could aid in further identification and risk-stratification of this high-risk population in SA. Although further studies are warranted to assess the usefulness of IS and WMSI as a selection criterion for a major therapeutic decision, findings of the present study promote the inclusion of CMR into the current clinical management of SA patients with known CAD, especially of those with reduced LVEF at echocardiography.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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