



Original Article

Incremental value of Late Gadolinium Enhancement by Cardiac MRI in risk stratification of heart failure patients with moderate and severe LV dysfunction

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ABSTRACT

Objective: This is a prospective study of patients with LVEF $\leq 40\%$, with the objective of correlating CV events to LGE detected and quantified by CMRI.

Methods: Heart Failure (HF) patients with LVEF $< 40\%$ who underwent CMRI were included. LGE volume of $\geq 6\%$ of the myocardial volume was considered significant. Data of appropriate ICD shocks, CV hospitalizations and mortality were recorded.

Results: There were 133 HF (72 ICM & 62 NIDCM) patients with a mean age of 54 ± 12 years, mean LVEF of $34 \pm 6\%$ and a follow up of 24 ± 3 months. Totally 46 CV events were recorded in 30 patients, 44 in LGE +ve & 2 in LGE -ve groups (HR 17.8, 95% CI-8.03-39.3, $P = 0.000095$). All the 7 deaths were in LGE +ve group. CV events were 22 (30.5%) in ICM group and 8 (13.1%) in NIDCM group ($p = 0.03$). All the 22 ICM patients and 6 of the 8 NIDCM with CV events were LGE +ve. The distribution of CV events amongst LGE +ve and LGE -ve were 35 vs 0 (ICM) and 9 vs 2 (NIDCM); $p < 0.005$. CV events in LVEF $< 30\%$ group, were seen in 19 (47.5%) vs 1 (5.8%) in LGE +ve vs LGE -ve and no of events were 29 vs 1 ($p = 0.003$). In those with LVEF $> 30\%$ the corresponding figures were 9 (22.5%) vs 1 (2.8%) and 15 vs 1 respectively ($p = 0.02$).

Conclusion: Demonstration of significant LGE by CMRI indicates high risk occurrence of CV events (CV hospitalization, appropriate shocks and total mortality) in NIDCM & ICM patients with LVEF $< 40\%$.

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1. Introduction

Risk stratification of Heart Failure (HF) patients has traditionally centered around assessment of LV function. This is based on the fact that LV Dysfunction is an established indicator of poor prognosis and it continues to be a robust marker of increased mortality and arrhythmic death.^{1,2} Understandably, design of all the major randomized clinical trials on which the current HF guidelines are based, have severe LV dysfunction as a mandatory inclusion criterion.^{3–6} However, subsequent real-world clinical practice has found this parameter lacking in adequate sensitivity and specificity in predicting cardiovascular (CV) outcomes. Cardiac Magnetic

Resonance Imaging (CMRI) is being increasingly used to fill this lacuna and has proven to be a reliable tool in providing risk stratification of HF patients beyond LV EF. Several studies have shown the detection of Late Gadolinium enhancement (LGE) in patients with Ischemic, Non - Ischemic Dilated and Hypertrophic cardiomyopathy (NIDCM, ICM and HCM) correlating with occurrence of ventricular arrhythmias and mortality. In these cohorts, CMRI - LGE has extended the benefit of prognostication to patients with LV dysfunction of varying severity and has contributed to evaluating patients presenting with ventricular arrhythmias.^{7–12} However, there has been no uniformity in methodologies employed concerning the quantification of myocardial scar, and no existing consensus on the threshold cut off for LGE to serve as a guide to therapy. Further, studies are scarce which have analyzed the influence of interaction of different substrates and varying degrees of LV dysfunction with CV events. We designed a prospective follow-

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up study including both ICM & NIDCM, HF patients with severe and moderate LV dysfunction to detect and quantify LGE by CMRI. We hypothesized that a threshold cut-off of LGE of 6% by volume would predict CV events in this population.

2. Methods

Consecutive consenting HF patients attending our Institution from January 2018 to December 2019, with Left Ventricular Ejection Fraction (LVEF) by 2D echocardiogram $\leq 40\%$ who underwent CMRI were included in this study. All patients underwent at least 2 echocardiograms before being included in the study, the latest being within 2 ± 1 days of CMRI. The LV end-diastolic & end-systolic volumes and LVEF were assessed by biplane Simpson's equation using the apical four and two chambered views. LV dysfunction was categorized using LVEF as severe ($\leq 30\%$) and moderate (31–40%). Majority of the patients (126/133) underwent coronary angiogram. The diagnosis of ICM and NIDCM was made by standard diagnostic criteria.^{13,14} NIDCM was diagnosed when there was ventricular dilation and impairment of cardiac function in the absence of significant coronary artery disease.

All patients received Guideline Directed Medical Therapy (GDMT) for HF and were recruited in the study after being on stable medications for at least 3 months. Patients who were excluded were those who were not willing or could not be subjected to CMRI, who were clinically diagnosed as myocarditis, whose expected survival as assessed by the treating physicians was less than 6 months and those who could not be relied upon to have regular follow-up. The basic clinical data of all the patients recruited in this study was collected. Implantation of ICD/CRT/CRT-D devices was at the discretion of the treating physician after discussion with patients and their families. Follow-up was by monthly telephonic contact, and device interrogation, if relevant, every three months. Patients were also scheduled for device interrogation within the next 48 h if they experienced a shock. Telephonic follow-up was done by one of the investigators (LK). Information on symptoms, medication usage, interim hospitalization, ICD shocks and survival was collected. In the case of mortality, details were collected from one of the family members, death summary was reviewed and the cause of death was ascertained. During device interrogation, therapies if any, were analyzed and data recorded. Cardiovascular Events (CV) events analyzed in this study were - CV hospitalization, mortality or appropriate Shocks/Aborted or Resuscitated sudden cardiac death (SCD). Appropriate ICD shocks were considered synonymous with aborted/resuscitated SCD. The protocol was approved by local institutional ethics committee.

2.1. CMR protocol

Patients were imaged on 3.0 TMR scanning machine (Achieva TX, Philips Medical Systems, Netherlands) using a 16 channel Torso PA coil with ECG gating and breath-holding and patient in supine position.

2.2. Pre-contrast

Cardiac MR imaging was performed using a custom made protocol in the following sequence.

- 1 Axial images of thorax BB-SSh (Black blood single shot, respiratory sequence)
2. Long axis 2D cine B-TFE (Balanced Turbo Field Echo)
3. Short axis 2D cine B-TFE and 4-Chamber 2d cine B-TFE.

4. STFE-Grid-BH (Sense TFE Tagging sequence with breath hold) which was acquired in short axis at three levels, at base, mid cavity and apical region.

2.3. Post-contrast

During intravenous injection of 10 mL 0.5 mmol/mL Meglumine gadoterate DynSTFE (Dynamic Sensitivity encoded Turbo Field Echo) perfusion scan was performed in short axis. Followed by PSIR-TFE-BH (Phase sensitive Inversion recovery TFE with breath hold) scan at 7 min & 15 min after contrast injection.

2.4. Post processing technique

After the contrast study, the Short axis 2D cine B-TFE sequence was used to calculate the cardiac parameters using the commercially available workstation (EWS, Philips Medical systems) using MR Cardiac Explorer Analysis function software. All short-axis slices were divided according to their relationship to the papillary muscles. The mid ventricular slices at the level of the papillary muscles and the basal and apical slices above and below the papillary muscles respectively. Using the semi-automated quantitative analysis software endocardial and epicardial borders were defined. Spoke-wheel was then drawn over all the slices and phases dividing the myocardium into segments, 6 at base and mid-cavity and 4 at apical cavity (in accordance with the American Heart Association standardized segmentation model). Apex was the 17th segment.

The post contrast Short Axis PSIR-TFE sequence was used to quantify the scar. Here too, the epicardial and endocardial borders were traced at all the slices from base to apex. LGE was considered present only if confirmed on both short-axis and matching long-axis myocardial locations. The distribution of LGE was characterized as either transmural, sub endocardial, mid wall, epicardial, focal/involving the right ventricular insertion points, or diffuse. If more than one pattern was present, the distribution was characterized on the basis of the predominant pattern.

Using the myocardial segment showing complete wash-out as a reference, the delayed enhancing areas were highlighted based on signal intensity using computer software.

(Fig. 1A) We used 2.5–3.0 SD as the cut-off to define hyper enhanced segments.

The total myocardial volume and contrast-enhanced volume were calculated automatically. The extent of contrast enhancement was expressed as

Percentage of total enhanced myocardial volume

$$= \frac{\text{Volume of enhanced myocardium}}{\text{Total LV Myocardial volume}} \times 100$$

Report generated gave a detailed analysis of the scar at every slice and at all the segments. The advantage of the above described analysis is that it helped to determine the transmural index of the scar in ambiguous segments (Fig. 1 B). Scar volume was calculated in all the patients and a cut off of $\geq 6\%$ of the myocardial volume was taken as a significant scar as it represents the volume of least 1 myocardial segment to minimize the misregistration artifacts and partial volume effects.¹⁵ Patients were categorized to 2 groups- LGE +ve ($\geq 6\%$) and LGE -ve ($< 6\%$).

2.5. Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (IBM SPSS, Armonk, NY, USA). A p -value < 0.05 was considered

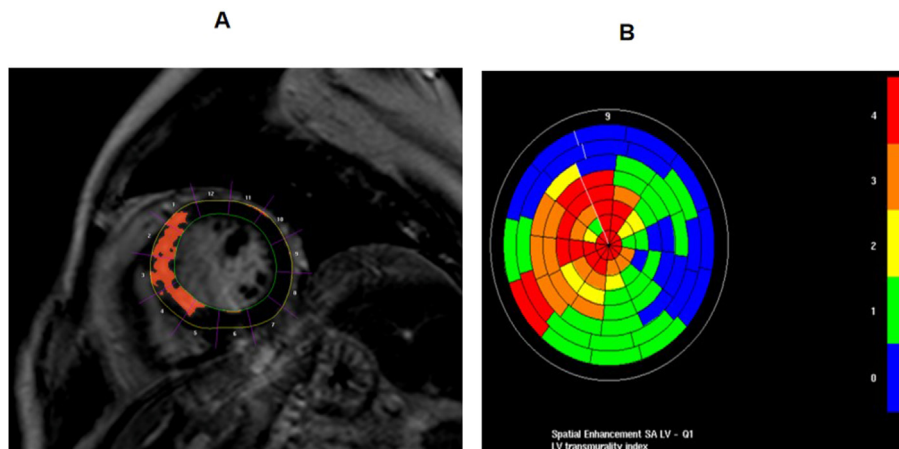


Fig. 1. A: Figure showing Late Gadolinium enhancement. The delayed enhancing areas are highlighted based on signal intensity using computer software. **B:** Detailed analysis of the scar at every slice and at all the segments and also to determine the transmural index of the scar.

statistically significant. Discrete variables were presented and compared in percentage and continuous variables as mean \pm Standard deviation. Student's *t*-test was done to compare continuous variables. Two sample *t* tests were used to compare mean values of continuous data between two groups. Chi square tests were used to compare discrete data between groups, in those cases where the expected cell count was <5 , Fisher's exact test was used. Cumulative event rates by time in months were calculated according to the Kaplan–Meier method. Differences in event rates between groups were assessed with the log-rank test without adjustment for multiple comparisons. Event times for all patients were measured from the time of undergoing CMRI. The hazard ratio for the prediction of the events was calculated for MACE using Cox proportional-hazards model.

3. Results

There were 145 HF patients considered for the study, 12 patients were excluded as they did not consent for CMRI or procedure could not be done due to technical limitations. Totally 133 (72 ICM & 61 NIDCM) patients were included for analysis. No patient was lost to follow-up. The follow-up period was 2–28 months (mean 24 ± 3 months). ECG analysis showed wide QRS (Mean duration = 156 ± 22 m s) in 93 patients (LBBB in 55, RBBB in 24 & 14 had IVCD) and narrow QRS (mean duration 95 ± 26 m s) in 40 patients. Among the 72 ICM patients, 16 underwent CABG and 50 underwent PCI and the rest were on medical follow-up. Defibrillators were implanted in 20 patients (14 ICD & 6 CRT-D), majority of these (15/20) being for secondary prevention. Patients who underwent defibrillator implantation for secondary prevention were: Resuscitated SCD-3, Documented VT -8, Inducible Monomorphic VT on EP Study -4.

The demographic data of the overall study population and patients in the 2 groups (LGE +ve & LGE -ve) is shown in Table 1.

At the end of last follow-up totally 30 patients (22.6%) had 46 CV events. Of these 28 had significant scar (LGE+). The CV events recorded were 37 CV hospitalizations, 2 appropriate ICD discharges and 7 deaths. The 37 CV hospitalizations occurred in 26 patients (1–3, Mean - 1.4 ± 0.6), 5 of whom died in hospital. Number of patients who experienced CV events in the 2 groups, LGE +ve & LGE -ve were 28 vs 2 and number of CV events were 44, vs 2 (Hazard ratio 17.8, 95% CI-8.03-39.3, $P = 0.000095$). All the 7 deaths occurred in LGE +ve group, 2 of these were classified as sudden. The overall CV events correlated with substrate, LVEF, and LGE are

summarized in Fig. 2. Fig. 3, is an illustrative CMRI image of one of the patients in this study.

3.1. CV events in ICM & NIDCM

More patients in ICM group than NIDCM patients were LGE +ve, 59 (82%) vs 21 (34%) ($P < 0.0001$). All the ICM patients who were LGE +ve, the scar was transmural. In LGE + NIDCM patients, location of scar was mid-wall in 14 (67%), Epicardial in 4 (19%), sub-endocardial in 3 (14%). CV events were seen in 22 (30.5%) ICM and 8 (13.1%) NIDCM patients. CV events were noted in 22 ICM patients (30.5%) and 8 NIDCM patients (13.1%) ($p = 0.02$). All the 22 ICM patients who had CV events and 6 of the 8 NIDCM patients who had CV events were in the LGE +ve group. The distribution of CV events amongst LGE +ve and LGE -ve were 35 vs 0 in ICM Cohort and 9 vs 2 in NIDCM cohort ($p < 0.0001$). The 2 patients who had SCD in this study had ICM with large areas of transmural scar. Figs. 4 and 5 show the event free survival data in different subsets of our cohort.

3.2. CV events in severe and moderate LV dysfunction

There were 57 patients (42.8%) with LV EF $\leq 30\%$. The prevalence of LGE +ve was higher compared to the 76 patients with LVEF $>30\%$ (70.1% vs 52.6%, ($P = 0.04$). In both the groups CV events were experienced predominantly in LGE +ve patients. In the low EF group, number of patients with CV events were 19 (47.5% vs 1 (5.8%) in LGE +ve vs LGE -ve and CV events were 29 vs 1 ($p = 0.003$). In patients with LVEF $>30\%$ the corresponding figures were 9 (22.5%) vs 1 (2.8%) and 15 vs 1 respectively ($p = 0.02$).

4. Discussion

This manuscript highlights the importance of identifying and quantifying LGE in predicting the composite risk of CV events in HF patients with LVEF $\leq 40\%$.

4.1. LGE assessment and quantification in risk stratification

Myocardial scar is recognized to be the essential pathological substrate in HF population which supports macro re-entrant lethal ventricular arrhythmias responsible for arrhythmic mortality, and appropriate ICD shocks. There is demonstrated evidence that circuits of VT anchor around these scars and identification of scar is

Table 1
The demographic data of the overall study population and patients in LGE +ve & LGE -ve groups.

Parameter	Overall N = 133	LGE +ve N = 80	LGE -ve N = 53	p Value LGE +ve vs LGE -ve
Age (in years)	54 ± 13	52 ± 12	55 ± 11	P = 0.14
Gender (M/F)	105/28	70/10	35/18	P = 0.003
ICM/NIDCM (N =)	72 (54%)/61(46%)	59 (74%)/21(26%)	13(25%)/40 (75%)	P < 0.0001
LVEF (%)	33 ± 6	32 ± 8	34 ± 4	P = 0.10
Mean LVEDD (mm)	51.8 ± 12.3	53.8 ± 10.9	5.0 ± 9.8	0.1375
Mean LVESD (mm)	35.8 ± 9.6	36.2 ± 10.1	34.3 ± 9.0	0.1258
TAPSE	20 ± 7	21 ± 6	19 ± 7	0.2764
Scar Volume (%)	16 ± 14	24 ± 12	2 ± 2	P < 0.0001
NYHA Class				
I	9 (6.7%)	5 (6.2%)	4 (7.5%)	P = 0.77
II	78 (58.6%)	47 (58.5%)	31 (58.4%)	P = 0.96
III	46 (34.5%)	28 (35%)	18 (33.9%)	P = 0.90
IV	0	0	0	
Betablockers	121 (91%)	72 (90%)	49 (92%)	P = 0.70
ACEI/ARB	33 (25%)	19 (24%)	14 (26%)	P = 0.80
Sacubitril- Valsartan	84 (63%)	51 (64%)	33 (62%)	P = 0.82
Aldactone/Eplerinone	120 (90%)	72 (90%)	48 (91%)	P = 0.51
Diuretics	71 (53%)	42 (53%)	29 (55%)	P = 0.82
Ivabradine	11 (8%)	7 (9%)	4 (8%)	P = 0.84
ICD/CRTD	20 (15%)	13 (16.25%)	7 (13.2%)	P = 0.63

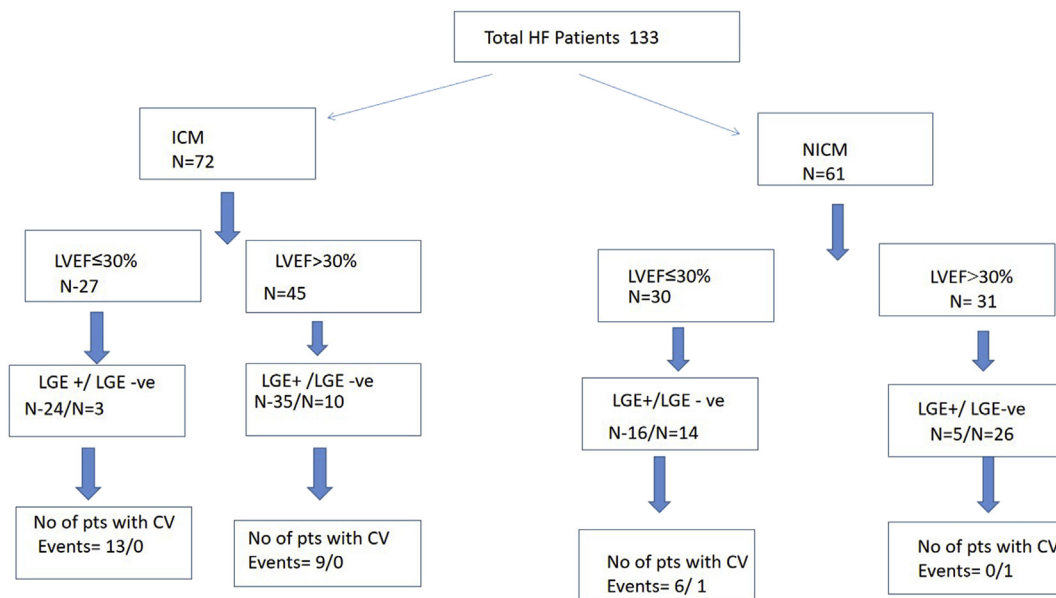


Fig. 2. Flow chart Summarizing CV events in different subgroups.

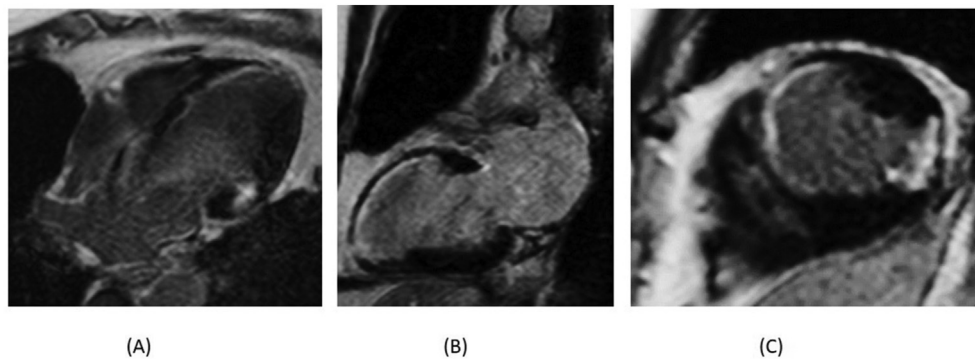


Fig. 3. Panels A, B & C: 62 yrs male with ICM and Moderate LV dysfunction (LVEF = 38%) with a Scar Transmurals enhancement of the apex, anterior, septal and lateral segments at apical level; anteroseptal, inferoseptal and inferolateral segment at the mid cavity level. Of the 17 segments, LGE is demonstrated in 7 segments - 5 in LAD territory and 2 in the Left Circumflex artery territory.

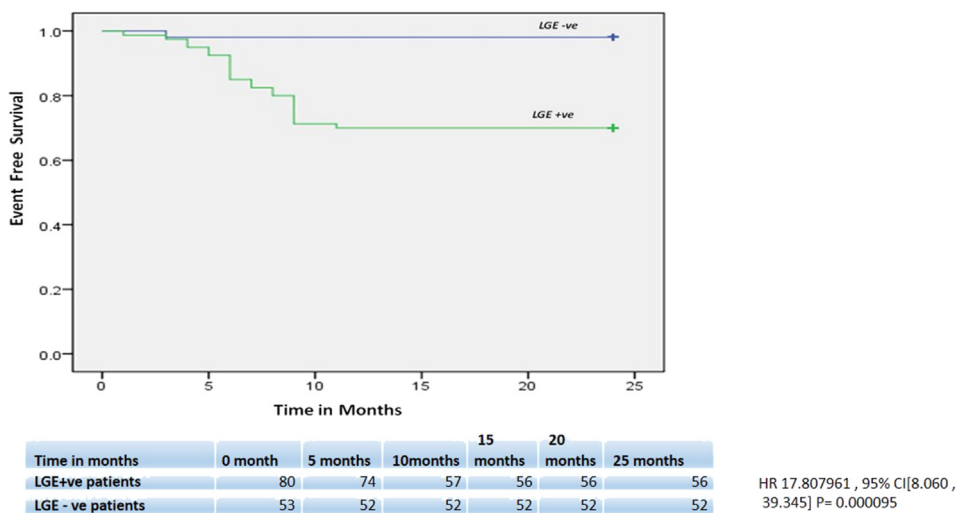


Fig. 4. Kaplan Mayer Survival curve of patients in groups showing better event free survival in patients without LGE.

also important in radio-frequency ablation of VTs. The advent of CMRI has seen the emergence of an effective non-invasive tool to identify and characterize LGE which is a reliable surrogate for myocardial scar and cardiac fibrosis.¹⁶ Apart from detection, LGE quantification has been shown to provide additional value in the prognostication of HF patients.^{8,17} The results of this study, convincingly demonstrate the ability of LGE at a threshold of 6% in identifying patients at a risk of experiencing CV events(Fig. 6). This discriminative capability unequivocally extended to patient groups with varying degrees of LV dysfunction and different HF substrates. We demonstrated that scar burden also correlates with HF hospitalization and overall mortality.

4.2. LGE detection in ICM & NIDCM patients

The clinical value of LGE assessment can be appreciated in both ICM and NIDCM substrates. The KM curve in Fig. 5, clearly shows that in both substrates, LGE strongly correlates with CV events. Most of LGE +ve in NIDCM patients were in the Low EF group (16/21, 76%) while, 35 of 59 (59%) LGE +ve ICM patients had LVEF > 30%. This observation leads to the inference that while CMRI may help in identifying high risk patients in NIDCM cohort, it may extend device indications in the ICM group. The event rates in LGE + ICM in the higher LV EF group were not inconsequential (25.7%), showing that demonstrating significant LGE is more useful in predicting events in patients with ICM than LVEF.

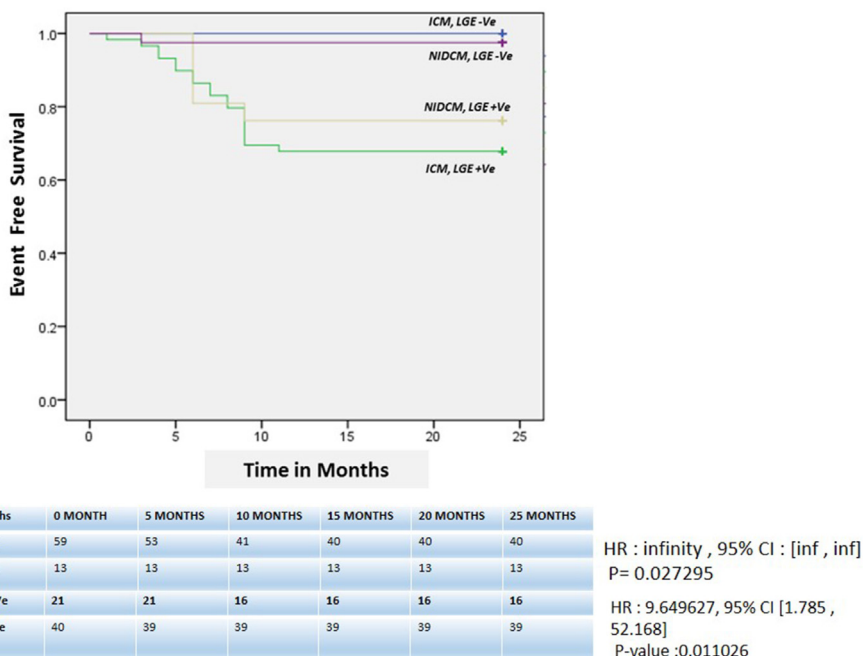


Fig. 5. Kaplan Mayer Event free survival curves comparing 4 groups ICM LGE +ve, NIDCM LGE +ve, ICM LGE -ve & NIDCM LGE-ve. This figure shows higher event free survival in both substrates without LGE.

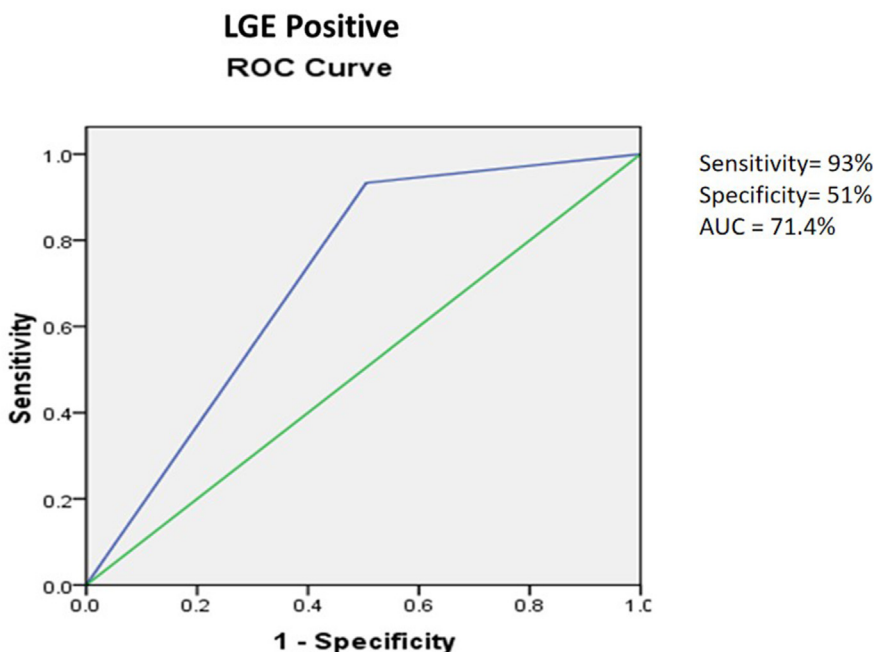


Fig. 6. ROC Curve with LGE at 6% cut off showing AUC (Area under curve) of 71.4%. Sensitivity and specificity refer to prediction of composite events of CV hospitalization, mortality or appropriate Shocks/Aborted or Resuscitated sudden cardiac death (SCD).

Results of the DANISH study call for re stratification of the currently defibrillator eligible NIDCM patients.¹⁸ Sub group analysis of this study however showed that there are nevertheless some subsets who may benefit from device implantation. Our results show that LGE qualifies as a reliable and dependable tool to identify these subsets as can be seen by the fact that in this substrate, LGE-ve patients were practically devoid of CV events irrespective of severity of LV dysfunction. A relatively lower overall incidence of CV events in our study, despite the paucity of device usage can probably be attributed to the emphasis on adherence to GDMT. Though not the objective of this study, this data supports the concept of pharmacotherapy being a very event and cost-effective strategy.

4.3. LGE and LV dysfunction

LVEF $\leq 30\%$ is currently considered the most reliable parameter in clinical practice, correlating with high incidence of SCD, and total mortality. Yet, it is a well-accepted fact that cardiovascular risk prediction by LVEF based algorithms in HF population has not met the expectations of clinical practice. On one hand many patients with severely impaired LV function do not have adverse events, on the other hand a significant number of patients with moderate LV dysfunction experience SCD.¹⁹ Clearly a reliable and dependable risk stratification tool has been an unmet clinical need. There is increasing data linking myocardial fibrosis to cardiac events in patients with heart failure of diverse etiologies.¹⁸ LGE detection by CMRI, which is a surrogate for myocardial scar/fibrosis has helped to identify the pathological substrate responsible for CV events in these patients. In this study, 20 of the 57 patients with LVEF $\leq 30\%$, had CV events, and a large proportion, 19 (95%) of them had LGE +ve. These findings were consistent irrespective of the substrate as seen by the fact that in the low EF group all the 13 ICM patients and 6 of the 7 NIDCM patients who had CV events had LGE +ve. In our study, we intentionally included patients with

moderate LV dysfunction, a population traditionally excluded by device guidelines to observe the CV events and their correlation with LGE. This inclusion enabled us to record 15 additional CV events in 9 patients with LVEF $>30\%$ with all of them demonstrating LGE.

4.4. Clinical significance

This study complements and adds strength to the current evidence to include LGE detection and quantification by CMRI in the risk stratification algorithm of HF patients. This data is clinically very relevant in certain parts of the world, where use of HF devices as per guidelines is not possible due to multitude of factors. This strategy of using LGE may be an effective solution in such geographies by developing a scientific basis on which device based therapy can be prioritized.

4.5. Limitations

This is a study with a relatively limited follow-up and events. We acknowledge that the event numbers would have been higher at a longer follow-up enabling further analysis of subgroups. Nevertheless we believe the significant trends that have been demonstrated in this study are fairly conclusive of the benefits of using LGE as a risk stratification tool. Low event rates also precluded detailed analysis of arrhythmic and non arrhythmic deaths in different subgroups.

5. Conclusion

Demonstration of significant LGE by CMRI indicates higher risk of cardiovascular events in NIDCM & ICM patients with severe and Moderate LV dysfunction. LGE should be incorporated in risk stratification algorithms in HF patients.

Contributorship statement

1. B. Hygriv Rao: Design of the study, Analysis of data, Manuscript writing, Study PI, responsible for overall content.
2. Laxman Kolluru: Patient follow up, data collection, data analysis, manuscript writing
3. Jwala Srikala: Study design, CMRI Protocols & reporting, data analysis, manuscript writing
4. H. Nagaraj Rao: Data analysis, manuscript writing
5. Sania Maheen: CMRI reporting, data collection, data analysis

Funding statement

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Ethics

The study conduct complies with the declaration of Helsinki. It has been approved by institutional ethics committee.

Declaration of competing interest

None.

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