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Could Cardiac MR Imaging with Late Gadolinium Enhancement Affect The Risk Stratification and Outcome Prediction In Non-Ischemic Cardiomyopathies?

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ABSTRACT

Background: Cardiac MR (CMR) evaluating non-ischemic cardiomyopathies (NICMs) is superior 3D imaging with non-invasiveness, more accuracy and reproducibility of measurements. It provides comprehensive structural, functional information, tissue characterization, and assesses fibrosis by LGE.

Objective: The study aimed to investigate these imaging data and their prognostic value in NICM.

Patients and methods: 46 NICM patients were assessed by echocardiography/cardiac magnetic resonance (CMR). They were divided into 3 groups: dilated, hypertrophic and miscellaneous types. Late gadolinium enhancement (LGE) presence and myocardial extent/percentage were assessed with clinical follow up for a median of 1-year for any Major adverse cardiac events (MACE). For each group, univariate analysis of clinical/imaging risk factors in the associations with LGE/MACE was performed. **Results:** Twenty-six dilated cardiomyopathy patients, 62% had LGE and 31% had MACE. Using LGE as a predictor for MACE was statistically significant ($p = 0.007$). Using univariate analysis, the presence of LGE ($p=0.00$) and the extent of LGE ($p < 0.0001$) demonstrated the strongest unadjusted association with MACE. ROC curves revealed a cutoff value of LGE > 4.5% as MACE predictor. Twelve hypertrophic cardiomyopathy patients (67%) had LGE and (50%) had MACE. Using LGE as a predictor for MACE was statistically significant ($p=0.014$). Using univariate analysis, the presence of LGE ($p=0.01$) and the extent of LGE ($p=0.01$) demonstrated the strongest unadjusted association with MACE. ROC curves revealed a cutoff value of LGE > 4.5% as MACE predictor.

Conclusion: CMR with LGE is crucial in NICM evaluation with prognostic value; changing the way that myocardial disorders will be understood and managed in the near future.

Keywords: NICM, CMR, LGE.

INTRODUCTION

NICM is a variety of structural functional myocardial disorders in the absence of hypertension, coronary artery, valvular and congenital heart diseases. Classification of cardiomyopathies is complex with many available systems such as The American Heart Association and The European Society of Cardiology classifications [1, 2]. Cardiomyopathy has a prevalence of 0.02% of the population and more common in younger individuals and women [3]. Echocardiography is the simplest first investigatory line imaging technique used for screening and diagnosis of cardiomyopathies on the basis of morphology as in multiple previous studies [4]. MRI as an imaging modality in these issues, is superior and three dimensional with non-invasiveness, high soft-tissue contrast, availability of a large FOV, multiplanar acquisition capability, accuracy and reproducibility of the measurements and without ionizing radiation [5].

There are multiple technical challenges unique to CMR as rapid complex cardiac motion, pulsations of the surrounding great vessels, respiratory motion and systolic blood velocities, which complicate cardiac imaging. These challenges are under trials to be overcome by implementation of ECG gating, navigator echo respiratory gating, breath-hold techniques, rapid high-performance gradients and advanced pulse sequences [6, 7]. CMR has the ability to assess cardiac morphology, ventricular function, edema, perfusion, viability and imaging characteristics of the surrounding vasculature [8]. Myocardial enhancement by LGE sequence in NICM has different patterns, unlike ischemic heart disease, has no particular coronary artery distribution and is often midwall rather than subendocardial or transmural. The first-pass perfusion study usually does not show any focal perfusion defect in NICM but instead may show normal results or early increased enhancement [8].

Aim of the study was to use these imaging data for prognostic determination, risk stratification and outcome prediction in NICM; aiming for better understanding and management of NICM in the near future.

PATIENTS AND METHODS

Study design and population: We performed a prospective observational (cross-sectional study) from April 2018 to April 2021.

The study included 49 adult patients of both sex and different ages with any type of clinically suspected non-ischemic cardiomyopathy or by Doppler echocardiography.

Exclusion criteria: Those with significant coronary disease by clinical history or cardiac investigations (coronary angiography and/or positive imaging stress testing), those with previous cardiac myomectomy or alcohol septal ablation and uncontrollable dysrhythmia affecting ECG-gating. Also, those with any general MRI or Gadolinium-based contrast agent-related contraindications.

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Methods:

Full family and clinical history, clinical examination, ECG, laboratory investigations including cardiac enzymes, were performed by the help of the referring physician, each patient was classified according to NYHA classification.

Echocardiographic examination was done for each patient as recommended by the American Society of Echocardiography [9].

Imaging acquisition (CMR protocol):

CMR examinations were performed (using 1.5 T super conducting MR scanner Philips Achieva, Philips Healthcare -The Netherlands and Sense cardiac coil). CMR examinations have been adjusted as directed by the clinical suspicion and continuous assessment of images during the scan**.** We obtained images with breath holding and retrospective ECG gating techniques.

CMR sequences:

FFE multi-planer localizer for planning of the imaging views, then multiple sequences are obtained:

1- Gross anatomical images in three orthogonal planes using bright blood imaging.
2- Functional cine imaging using segmented K-space balanced turbo field echo (b-TFE) sequence in short axis, tow, three and four chamber views and all obtained with repeated breath-holds.

Table (1): Parameters for (b-TFE) are summarized as flowing:

TR/TE 2.9/1.4	FOV: 320
Phases: 30	NSA: 1
Matrix 160x256	Bandwidth: 1225.5Hz
Slice thickness: 8mm	Slice number: 9-11
Flip angle: 60˚	Total scan time: 37.7

3- Non-contrast tissue characterization according to case includes: T2-weighted and STIR images for edema detection and T1-weighted images for suspected fat infiltration assessment.
4- Flow quantification CMR velocity mapping was done in selected cases as those with mitral regurgitation at aortic level in our study for accurate quantification of ejection fraction (EF%).
5- Post-contrast phases: Gadolinium-based contrast agent was injected as a bolus (0.2 mmol/kg of body weight) via an arm vein in the anti-cubital fossa by infusion pump followed by a 20–40 ml saline bolus. Three post-contrast phases have been obtained at the following times: First pass is acquired immediately to visualize inducible perfusion defects, early gadolinium enhancement (EGE) acquired at 90 –120 seconds, detects thrombi, hyperemia and microvascular obstruction post myocardial infarction and finally, LGE acquired at 10 –15 min detects delayed contrast washout in areas of infarction, fibrosis or inflammation. For LGE, inversion recovery gradient echo or phase sensitive inversion recovery (PSIR) sequences were utilized for normal myocardium nulling.

Image analysis: Using a semi-automated workstation of (Philips extended MR workspace 2.6.3.4)**:**

LV diameters and volumes in term of End Systolic Diameter (ESD), End Diastolic Diameter (EDD), End Systolic volume (ESV), End Diastolic Volume (EDV)- and wall motion, mass and EF were measured by delineation of endocardium and epicardium of LV in cine short axis images. All volume and mass measurements were indexed to body surface area. Fibrosis (LGE) was assessed by 2 CMR-trained physicians, visually by LGE compared to normal myocardium rapid washout and interpreted as absent or present only if seen in 2 orthogonal phase-encoding directions. Then, LGE was quantified in a short-axis stack images in grams then expressed as a percentage of total left ventricular mass by a semiautomatic detection using one of validated methods [10].

Outcome events and follow up: Blinded to radiological data, clinical follow up by cardiac physician for average ±12 month interval was done for end points defined as sudden cardiac death (SCD), implantable cardioverter defibrillator (ICD) therapy, ventricular arrhythmias, and heart failure.

Ethical consent:

An approval of the study was obtained from Assiut University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Using SPSS analytic system, continuous data were presented as mean ± SD. Continuous data were compared using an unpaired Student t test. Nominal data are presented as number and percentage and were compared using a chi-square test. The bivariate Pearson correlation coefficient was used for agreement between the main cardiac measurements taken by echocardiography and CMR. For each group of patients (specific type of NICM), Descriptive data were also expressed as done for all patients. We performed a multivariate analysis of the association with established clinical and imaging risk factors and myocardial fibrosis (LGE) in patients with a cardiomyopathy. The Cox regression analysis model was also used to calculate the hazard ratio (HR) for the prediction of events of the outcomes. For outcome events, we used the univariate analysis, and then considered all of the significant variables in it to the best overall multivariate models for the composite endpoint, with a probability to enter set at $p < 0.05$ and to exclude the effect from the regression at $p > 0.05$. Receiver-operator-characteristic (ROC) curves were used to calculate optimal cutoff (value with the maximal sensitivity and specificity) of LGE extent

to predict MACE. P value < 0.05 was considered significant.

RESULTS

Study population demographic data: In total, a series of 49 patients were investigated. 3 patients were excluded as they had a typical LGE infarction pattern although they show non-ischemic criteria clinically and negative stress testing prior to the CMR. When coronary angiography was subsequently performed for each of them, they had coronary disease. So, the final patient's number included in our study was 46 patients.

There are 26 males (56.5%) of the patients. The age of patients was ranging from 23 to 67 years with mean of age of 43 ± 13.9 years. The majority of patients (69.6%) were NYHA functional class II. The main symptom was dyspnea, all patients complained of it, and to lesser extent easily fatigability, palpitation and atypical chest pain in order. Then, according to CMR pathological findings, the study population was divided into 3 groups: The 1st group in our study included 26 patients with DCM, the most common type of NICM. The 2nd group included 12 patients have different types of HCM. The 3rd group included 8 miscellaneous less common types of NICM.

Group 1 (DCM patients) (Fig. 1**):** This group included 26 patients (69% were men). The mean age was 45 ± 15 years. 77% of patients were NYHA functional class II. Table (2) showed that patients with fibrosis (positive LGE) had significantly higher LV volumes compared to those without fibrosis. Also, they had a statistically significant lower LVEF than those without fibrosis. The regression analysis revealed that, the heart rate and NYHA classification as risk factors, and cardiac index, ESV, EDV and EF as imaging criteria in order, had the strongest prediction for fibrosis/LGE.

LGE was present in 62% of patients. The LGE mean in positive LGE patients is 5.25% of myocardium. The main LGE pattern was mid-myocardial in 87% and epicardial in 13% of patients. The main LGE myocardial location was septal/insertional points in 38% of patients.

MACE (Major adverse cardiac events) (outcome): occurred in 31% of the patients during a mean of 12 months of follow-up. All patients with MACE, were among those with LGE. 4 patients developed ventricular arrhythmia and the other 4 patients developed heart failure. Using LGE presence as a predictor for MACE was statistically significant in this group having a sensitivity of 100 %, specificity of 56%, PPV of 50 % and NPV of 100% (p value=0.007).

Table (2): Clinical and MRI Imaging characteristics of group 1 (DCM) and their analysis according to the presence or absence of LGE

	All patients (n=26)	**LGE Positive (n=16)**	**LGE Negative (n=10)**	**p value**
Age (years)	45 ±15	43 ±15	48 ±15	0.43
Male	18 (69)	12 (67)	6 (33)	0.42
BMI (kg/m^2)	27 ±6	27 ±6	27 ±6	0.91
HR (beat/min)	78 ±8	84 ±6	70 ±4	0.00
HTN	4 (15)	2 (50)	2 (50)	0.61
DM	6 (23)	4 (67)	2 (33)	0.77
Family history of NICM	2 (8)	2 (100)	0 (0)	0.25
NYHA II	20 (77)	10 (50)	10 (50)	0.03
CMR				
LV lat. Wall systolic th. (mm)	9±2	10±3	9±1	0.46
LV lat. Wall diastolic th. (mm)	8±2	9±2	7±2	0.04
IVS systolic th. (mm)	11±3	12±3	9±2	0.07
IVS diastolic th. (mm)	9±3	10±4	8±2	0.13
LV ESD (mm)	61±14	60±16	62±11	0.76
LV ESV (ml)	181±127	228±128	105±47	0. 01
LV EDD (mm)	73±15	71±13	77±17	0.34
LV EDV (ml)	234±129	279±145	161±44	0.02
LVEF (%)	25±10	22±10	30±9	0.04
COP, l/min	4±1	4±1	4±1	0.15
Cardiac index (l/min/m^2)	2±1	3±2	2±0	0.01
LA length in 4CH view (mm)	59±7	60±8	56±6	0.11
LA width in 4CH view (mm)	48±9	50±8	43±10	0.04
LV mass without papillary m. (g)	149±71	167±84	119±28	0.09
LV mass with papillary m., g	217±97	236±114	188±51	0.22

Values are mean ± SD. Echo= echocardiography; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; th. = thickness; LV ESD = left ventricular internal dimension in systole; LV EDD = left ventricular internal dimension in diastole; IVS=inter-ventricular septum; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVEDV = left ventricular end diastolic volume; COP= cardiac output; LA =left atrium; m. = muscle.

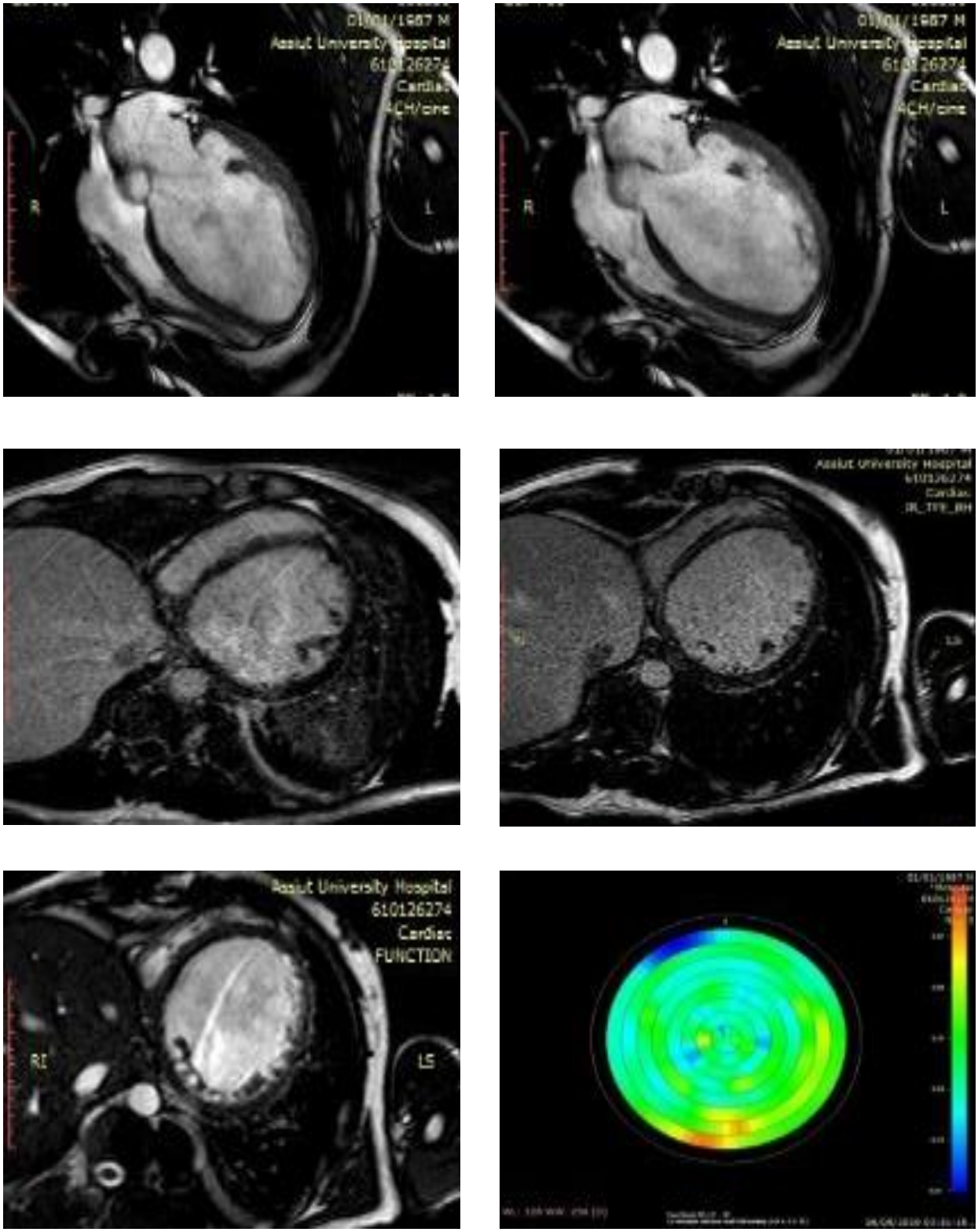

Fig. (1): CMR of DCM patient; Row A: 4CH SSFP MR images showed dilated LV with myocardial thinning in diastole at left and systole at right. B: Short-axis IR images showed LV LGE, Patchy mid-wall at junction between inferior and lateral wall at mid-ventricular level at left and linear mid-wall septal at mid-ventricular level at right. C: Short-axis 2CH SSFP view shows LV dilatation at left and colored diagram for relative LV wall thickness at right.

The Cox regression analysis revealed that the presence of LGE ($p = 0.00$) and its extent for each 1% absolute increase in LGE volume ($p < 0.0001$), demonstrated the strongest unadjusted association with MACE as seen in table (3).

Table (3): Univariate analysis for association with MACE in group 1 (DCM)

	HR Hazard ratio	59% CI	LR Chi-Square	P value
Sex	3.87	0.13-17625	7.94	0.00
HTN	3.37	0.00-189	2.61	0.11
DM	3.61	0.01-65007	4.10	0.04
Family history of NICM	2.22	0.02-0.79	4.10	0.04
NYHA	2.10	1.59-41.52	7.54	0.01
Age	0.03	o.92-1.02	1.65	0.20
BMI	0.03	0.87-1.09	0.21	0.65
HR	0.16	1.03-1.35	7.26	0.01
CMR				
LV wall systolic th.	0.13	0.89-1.46	1.09	0.30
LV wall diastolic th.	0.29	0.92-1.94	2.53	0.11
IVS systolic th.	0.00	0.08-1.26	0.00	0.98
IVS diastolic th.	0.09	0.91-1.32	0.85	0.36
ESD	0.12	1.02-1.25	8.50	0.00
ESV	0.02	1.00-1.03	16.90	0.00
EDD	0.00	0.96-1.04	0.00	0.96
EDV	0.02	1.00-1.03	15.24	0.00
EF	0.17	0.73-0.98	11.37	0.00
COP	0.16	0.59-2.32	0.21	0.64
Cardiac index	1.29	0.64-20.58	2.53	0.11
LA length	0.02	0.92-1.31	0.17	0.68
Myocardial mass	0.02	1.00-1.03	10.92	0.00
LGE presence	3.90	0.15-16805.16	8.41	0.00
LGE % (extent)	0.81	1.03-4.92	19.42	0.00

CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; NICM=non-ischemic cardiomyopathy. th. = thickness; LV ESD = left ventricular internal dimension in systole; LV EDD = left ventricular internal dimension in diastole; IVS=inter-ventricular septum; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVEDV = left ventricular end diastolic volume; COP= cardiac output; LA =left atrium.

Analysis of ROC curves revealed a percentage of LGE by volume of > 4.5% could be used as a cutoff value (area under the curve: 0.97; sensitivity: 75%; specificity: 100%) for increased risk of MACE (Fig 2).

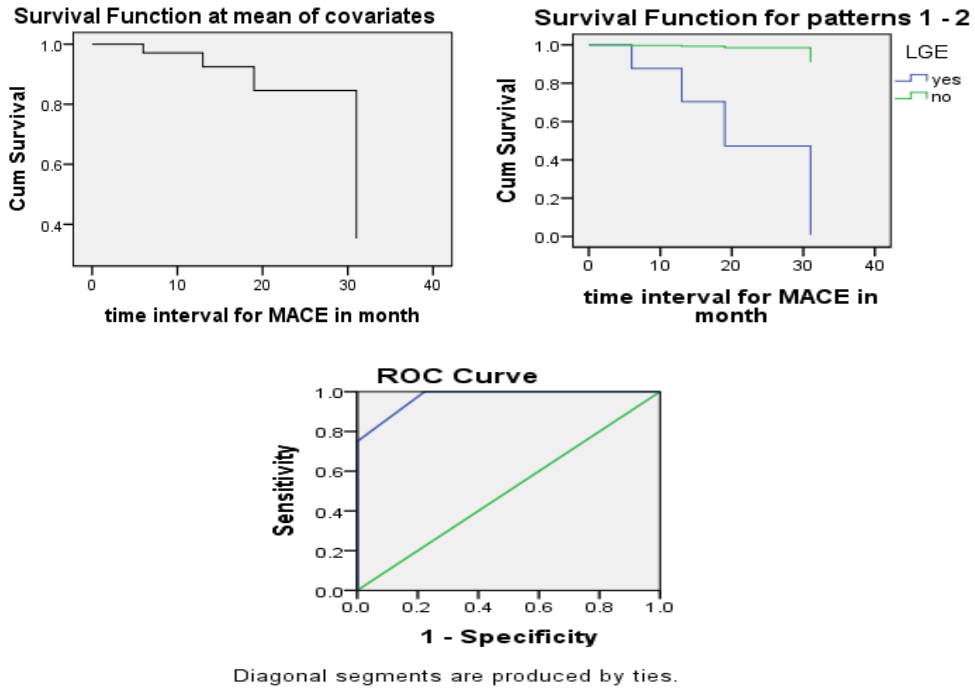

Fig. (2): The 1st row: Event-Free Survival using Kaplan-Meier curves displaying event-free survival in cohorts according to: (A) for survival function at mean of covariates (B) the dichotomous presence or absence of LGE. The 2nd row showed ROC curves for LGE extent for the association of the Composite Outcome Discharge. Analysis revealed that the percentage of LGE by volume of > 4.5% (area under the curve: 0.97; sensitivity: 75%; specificity: 100%) for prediction of events.

Group 2 (HCM patients) (Fig 3, case 2)**:** This group included 12 patients 50% were males.

The mean age = 41 ± 12 years. 67% of patients were NYHA functional class II. From table (3), patients with fibrosis (positive LGE) had more severe hypertrophy compared to those without fibrosis exhibiting significantly higher maximum diastolic LV wall, IVS thickness and LV mass. LVEF was higher in those with fibrosis than those without, but this is was not statistically significant. The regression analysis revealed that maximum LV diastolic wall thickness, IVS diastolic thickness and LV myocardial mass as imaging criteria in order, had the strongest prediction for fibrosis/LGE.

LGE was present in 67% of patients. The mean LGE percentage in positive LGE patients is 6.75% of myocardium. The LGE pattern was midwall in 75% and transmural in 25% of positive patients. LGE myocardial location was septal/insertional points in 38% and inferior in 38% of positive patients.

MACE occurred in 50% of the patients during a mean of 12 months of follow-up. All patients with MACE, were among those with LGE. 4 patients developed ventricular arrhythmia and the other 2 patients died with cardiovascular related mortality/SCD. Using LGE presence as a predictor for MACE was statistically significant in this group having a sensitivity of 100%, specificity of 67 %, PPV of 75 % and NPV of 100% (p value=0.014).

Table (4): Clinical and MRI imaging characteristics of group 2 (HCM) and their analysis according to the presence or absence of LGE

	All patients (n=12)	**LGE Positive (n=8)**	**LGE Negative (n=4)**	**p value**
Age (years)	41±12	43±14	36±6	0.36
Male	6(50)	2(33)	4(67)	0.01
BMI (kg/m^2)	28±6	27±7	29±2	0.48
HR (beat/min)	74±11	77±11	67±6	0.14
HTN	8(67)	4(50)	4(50)	0.08
DM	0	0	0	-
Family history of NICM	6(50)	5(83)	1(17)	0.22
NYHA II	8(67)	4(50)	4(50)	0.08
CMR				
LV lat. Wall systolic th. (mm)	19±4	21±4	16±1	0.05
LV lat. Wall diastolic th. (mm)	18±5	20±4	13±3	0.01
IVS systolic th. (mm)	22±6	22±5	23±9	0.80
IVS diastolic th. (mm)	20±5	23±1	14±5	0.00
LV ESD (mm)	32±12	39±12	36±14	0.44
LV ESV (ml)	53±39	43±38	74±37	0.22
LV EDD (mm)	49±9	48±7	49±13	0.92
LV EDV (ml)	108±40	92±39	141±18	0.04
LVEF (%)	56±18	59±18	50±20	0.42
COP, l/min	4±1	4±0	4±1	0.04
Cardiac index, l/min/m^2	2±0	2±0	2±0	0.63
LA length in 4CH view, mm	62±7	63±9	60±0	0.53
LA width in 4CH view, mm	46±10	49±10	41±6	0.15
LV mass without papillary m., g	176±25	166±5	197±37	0.03
LV mass with papillary m., g	539±477	691±527	234±35	0.12

Values are mean ± SD. Echo= echocardiography; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; th. = thickness; LV ESD = left ventricular internal dimension in systole; LV EDD = left ventricular internal dimension in diastole; IVS=inter-ventricular septum; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVEDV = left ventricular end diastolic volume; COP= cardiac output; LA =left atrium; m. = muscle.

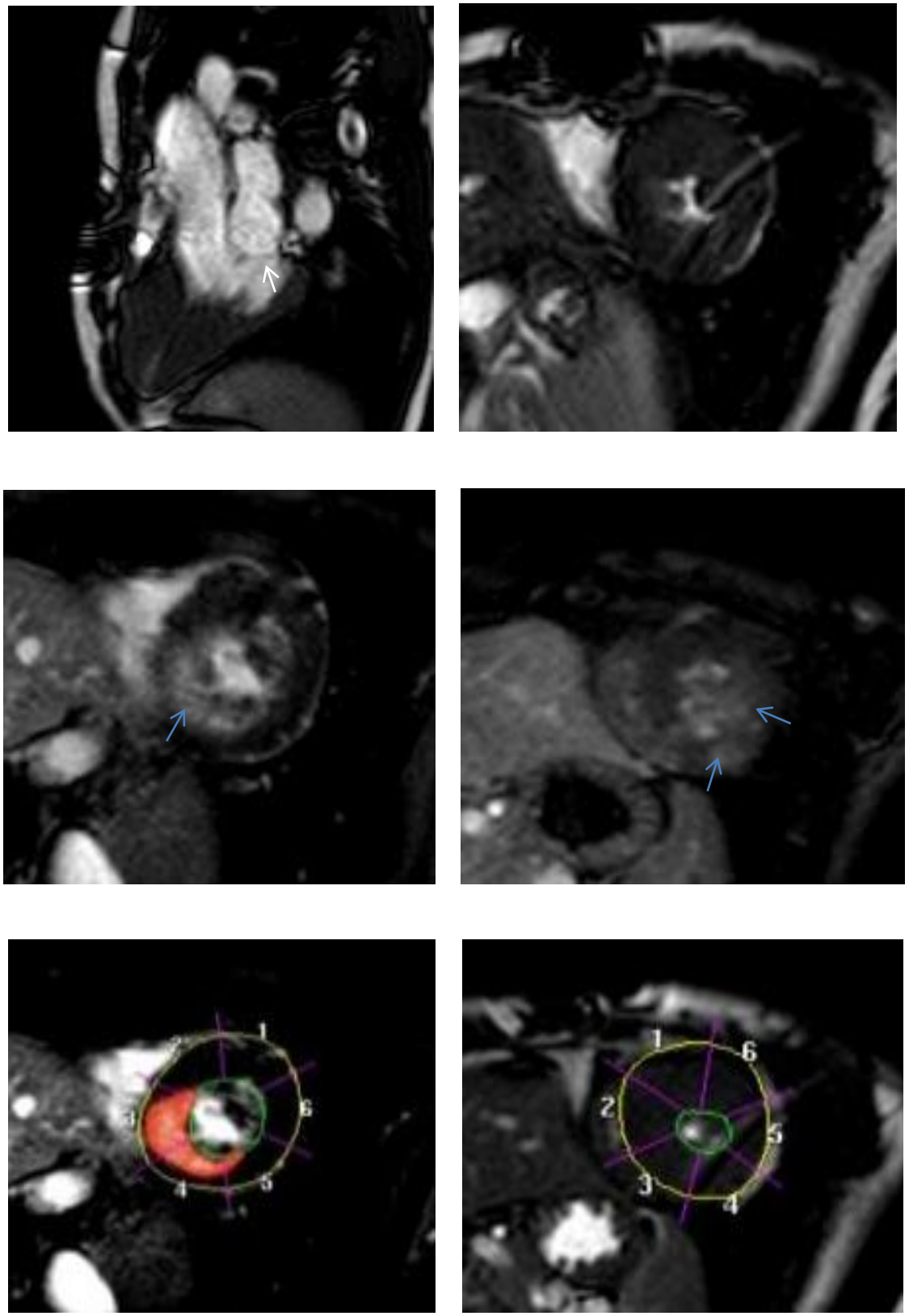

Fig. (3): CMR of HCM (septal type); Row: A: 4CH SSFP MR images showed hypertrophied LV, with thickened mitral leaflets and moderate MR signal void jet (arrow) into dilated LA in systole at left, and thickened ventricular wall with maximum thickening of IVS in diastole at right. B: At left, 3CH SSFP MR image showed a signal-void jet flow into the LVOT during systole (blue arrow) indicating AS with early grade of SAM and partial LVOT obstruction (yellow arrow). At right, short-axis IR GES image showed patchy sub-endocardial and mid-wall LGE/Fibrosis at anterior and lateral walls of LV midventricular level (›50%)(Wight arrows). C: CMR post processing images showed 2CH SA view with epi- and endocardial delineation at left, and colored diagram for relative LV wall thickness at right.

The Cox regression analysis revealed that the presence of LGE (p = 0.01) and its extent for each 1% absolute increase in LGE volume (p = 0.01), demonstrated the strongest unadjusted association with MACE as seen in (table 5).

Table (5): Univariate analysis for association with MACE in group 2 (HCM)

	HR	59% CI	LR Chi-Square	P value
Sex	5.08	0.00-39.93	8.39	0.00
HTN	1.02	0.05-2.59	0.99	0.32
DM	-	-		-
Family history of NICM or SCD	0.61	0.32-10.38	0.49	0.48
NYHA	1.02	0.05-2.59	0.99	0.32
Age	0.03	0.94-1.12	0.31	0.58
BMI	0.02	0.65-1.04	3.41	0.06
HR	0.27	0.92-1.88	10.10	0.00
CMR				
LV wall systolic th.	0.54	1.02-2.88	7.51	0.01
LV wall diastolic th.	0.16	0.93-1.48	1.93	0.16
IVS systolic th.	0.35	0.86-1.09	0.32	0.57
IVS diastolic th.	0.50	0.92-2.97	4.94	0.03
ESD	0.01	0.91-1.06	0.16	0.69
ESV	0.01	0.97-1.02	0.13	0.56
EDD	0.02	0.94-1.11	0.33	0.56
EDV	0.03	0.93-1.01	4.08	o.o4
EF	0.00	0.95-1.05	0.01	0.90
COP	2.06	0.01-0.13	4.95	0.03
Cardiac index	0.34	0.07-6.88	0.09	0.77
LA length	0.00	0.88-1.15	0.01	0.94
Myocardial mass	0.05	0.98-1.02	5.04	0.02
LGE presence	4.07	0.06-58841.81	6.50	0.01
LGE % (extent)	0.67	0.97-3.98	7.73	0.01

Analysis of ROC curves revealed a percentage of LGE by volume of > 5.5% could be used as a cutoff value (area under the curve: 0.71; sensitivity: 67%; specificity: 67%) for increased risk of MACE (Fig 4).

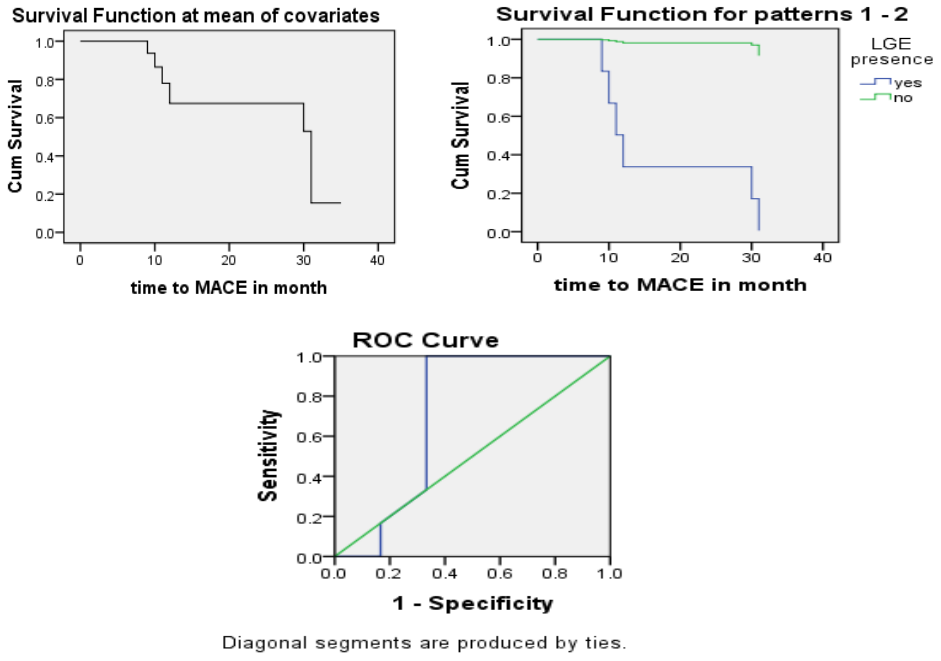

Fig. (4): The 1st row: Event-Free Survival using Kaplan-Meier curves displaying event-free survival in cohorts according to: (A) for survival function at mean of covariates (B) the dichotomous presence or absence of LGE. The 2nd row shows ROC curves for LGE extent for the association of the Composite Outcome Discharge. Analysis revealed that the percentage of LGE by volume of > 5.5% (area under the curve: 0.71; sensitivity: 67%; specificity: 67%) for prediction of events.

Group 3 (miscellaneous patients): This group included 8 patients, 4 females with PPCM, 2 males with amyloidosis and 2 females with connective tissue related cardiomyopathy with SLE. The mean age was 38 ± 15. 75% of patients

were NYHA functional class II. From table (6), patients with fibrosis (positive LGE) had statistically significant more LV septal thickening and higher LVEF mean, compared to those without fibrosis. Also, they had statistically significant more LA dilatation indicating more restrictive pattern.

Table (6): Clinical and MRI Imaging characteristics of group 3 (miscellaneous group) and their analysis according to the presence or absence of LGE.

	All patients (n=8)	**LGE Positive (n=4)**	**LGE Negative (n=4)**	**p value**
Age (years)	38±15	47±15	29±6	0.10
Male	2(25)	2(100)	0	0.06
BMI (kg/m^2)	25±6	29±5	22±5	0.12
HR (beat/min)	83±14	82±20	85±9	0.82
HTN	2(25)	2(100)	0	0.10
DM	0	0	0	-
Family history of NICM	0	0	0	-
NYHA II	6(75)	2(33)	4(67)	0.10
CMR				
LV lat. Wall systolic th. (mm)	11±4	12±6	10±1	0.42
LV lat. Wall diastolic th. (mm)	9±4	11±6	8±2	0.29
IVS systolic th. (mm)	13±5	16±6	9±0	0.05
IVS diastolic th. (mm)	12±6	16±6	8±1	0.05
LV ESD (mm)	51±19	42±8	60±23	0.19
LV ESV (ml)	117±58	69±25	166±99	0.11
LV EDD (mm)	59±17	51±13	97±19	0.22
LV EDV (ml)	172±93	128±48	217±112	0.19
LVEF (%)	36±12	46±1	27±8	0.00
COP (l/min)	4±1	5±1	4±2	0.96
Cardiac index (l/min/m^2)	2±0	2±0	3±0	0.39
LA length in 4CH view (mm)	60±9	67±3	52±7	0.01
LA width in 4CH view (mm)	50±9	52±0	49±13	0.62
LV mass without papillary m. (g)	153±56	172±65	135±46	0.38
LV mass with papillary m. (g)	211±66	218±42	203± 90	0.76

LGE was present in 50% of patients, but no one of the PPCM patients had LGE. The mean LGE percentage in positive LGE patients was 13.5% of myocardium. The LGE patterns were diffuse subendocardial progressed to transmural in 50% (Restrictive amyloid) and inferoseptal midwall in 50% (Restrictive SLE) of LGE positive patients.

MACE occurred in 25% of the patients during a mean of 12 months of follow-up. All patients with MACE were among those with LGE. Those patients who developed heart failure. Using LGE presence as a predictor for MACE in this group had a sensitivity of 100%, specificity of 67%, PPV of 50% and NPV of 100%. But, this result in this group was statistically in-significant (p value = 0.1). In total, results of MACE of the 3 groups included in our study were compared in table (7).

Table (7): Compared results of MACE between the 3 groups included in our study

MACE	**Group 1 DCM**	**Group 2 HCM**	**Group 3 Miscellaneous**
Percentage of MACE among group patients	31%	50%	25%
The main type of MACE	Ventricular arrhythmia and heart failure.	Cardiovascular related mortality	Heart failure
Cutoff value of LGE% as a predictor for MACE using ROC curves analysis	>4.5%	>5.5%	Not applicable due to different types

DISCUSSION

In our study we investigated the role of CMR imaging criteria including myocardial fibrosis assessment in the evaluation of NICM and how all these factors affect the patient outcome with highly significant risk stratification and prognostic value.

For the first group (DCM type) in our study, 26 DCM patients were tested for the relation between the conventional MRI cardiac measures and the presence of LGE/fibrosis, which showed a significantly higher LV volumes and lower LVEF in those patients with fibrosis, than those without. In addition, we detected that the presence (in 62% of patients) and extent of LGE (mean of 5.25 in positive patients) provided the strongest independent association with the endpoint of major adverse cardiac events (31% of patients) followed up for a mean of 12 months, including equal results of ventricular arrhythmias and heart failure in this group. These findings are complementary to those evaluated the prognostic value of LGE, including a similar population of 162 DCM patients, for a mean of 29 months of follow up. In that study, LGE was identified in 50% of patients, with a mean LVEF of 26% vs. 30% in LGE positive vs. LGE negative, respectively. Annual MACE rates were substantially higher in patients with LGE (24%) than in those without LGE (2%) [(11)].

In our study, analysis using ROC curves revealed a percentage of LGE by volume of > 4.5% could be used as a cutoff for the prediction of MACE. However, previous study detected that LGE of > 6.1% using the 2-SD method had an overall event rate of 50%/year [(11)]. Another study followed up a similar population of 65 patients with NIDC referred for ICD implantation for a median of 1.4 years. In that study, LGE was identified in 42% of patients with a mean LVEF of 24%, and was associated with an 8-fold higher risk for a composite of MACE, heart failure hospitalizations accounted for the majority of outcomes [(12)]. Also, a previous study performed CMR imaging in 61 patients with DCM, and followed them up for a median of 1.6 years. Scar by CMR was identified in 51% and was associated with ICD therapy, a composite of death, the need for ICD therapy or the need for heart transplantation. In that study, no patient without LGE had an adverse cardiac event [(13)].

In our study, the LGE pattern was mid-myocardial in 87% and epicardial in 13% of positive patients. The main LGE myocardial location was septal/insertional points in 38%. Compared to another DCM study, they detected a linear mid-myocardial pattern of LGE particularly in the septum, in the basal and mid-ventricular regions, which was seen in 28% of DCM patients. However, no specific enhancement was seen in 59% of these patients and a subendocardial pattern was seen in 13% of these patients. They mentioned that it may be due to an unusual nonischemic pattern of fibrosis or a silent ischemic insult caused by coronary embolus or ruptured plaques with subsequent recanalization [(14)].

For the second group (**HCM type**) in our study, 12 HCM patients were tested for the relation between the conventional MRI cardiac measures and the presence of LGE/fibrosis. There were a significantly more LV wall and IVS hypertrophy and non-significantly higher LVEF in those patients with fibrosis than those without. Matching with previous study on HCM patients [(15)], patients with fibrosis had more severe hypertrophy exhibiting significantly higher maximum LV wall thickness and indexed LV mass, compared to those without fibrosis. But not matching with our results, they detected that LV-EF was significantly lower in those with fibrosis than those without. The difference in EF results between those with fibrosis and those without might be due to the fact that EF is not only affected with fibrosis, but also affected by multiple factors such as degree of diastolic dysfunction, left ventricular outflow tract (LVOT) obstruction, degree of myocardial hypertrophy and associated mitral valve regurgitation [(16)].

Also in our study, we detected that the presence (in 67% of patients) and extent of LGE (mean of 6.75% in positive patients) provided the strongest independent association with the endpoint of MACE, which occurred in 50% of patients followed up for a mean of 12 months. The ventricular arrhythmias accounted for the majority of MACE outcomes in this group. These results are comparable to **Chun *et al.*** [(15)] study where two-thirds of their HCM patients exhibited LGE (66.2%) with a median amount of 5.9% of LV mass. The total outcome in their study divided between primary and secondary MACE outcomes along their follow-up was 10.8%. This was much lower than our MACE events as they included only SCD (sudden cardiac death), aborted SCD or cardiovascular mortality and may be also due to our patients' comorbidities. But not matching to their study on univariate analysis where they detected that amount of fibrosis was a significant predictor of outcome. However, on multivariable analysis, only LV-EF emerged as an independent predictor. Increasing amounts of fibrosis were associated with increased risk but this relationship did not hold after adjusting for LV-EF. Similar to our study, a prospective LGE-CMR study using cardiovascular mortality as an end point, was able to demonstrate that fibrosis was a statistically significant univariable predictor of outcome, but with only a total of 16 events. However, it was not sufficiently powered to demonstrate the independent prognostic significance of fibrosis with respect to SCD or cardiovascular mortality over and above potential confounders [(17)]. In particular, as in our study, fibrosis was highly associated with significant hypertrophy and indexed LV mass.

A prospective LGE-CMR study for 202 patients with HCM, evaluated the clinical significance of fibrosis using a composite primary end point of cardiovascular death or progressive heart failure, defined as a change in NYHA class. Despite the use of this broad end point, only 11 adverse cardiovascular events occurred over a mean follow-up of 1.9 years [(18)]. Their event rate was therefore insufficient to identify either the presence or the amount of fibrosis as even a univariable predictor of outcome. However, in our study using the same broad endpoint

events, statistically significant results regarding the extent of LGE (mean of 6.75% in positive patients) provided the strongest independent association with the endpoint of MACE, which occurred in 50% of patients. The same as regards the results of a latter study, their retrospective cohort study also detected the presence of fibrosis as a significant univariable predictor of SCD or appropriate ICD discharge. Only eight events occurred among their 424 patients after a mean of 3.6 years follow-up, which also was underpowered to adjust for statistically significant differences in outcome between those with and without fibrosis [(19)].

For the third group (**miscellaneous type**) in our study, 8 patients of NICM, 4 females with PPCM, 2 with amyloidosis and 2 of connective tissue related cardiomyopathy with SLE. More septal thickening, higher LVEF and more LA dilatation were significantly detected in those patients with fibrosis than those without. LGE presence was detected in 50% of patients with a mean extent of 13.5% of myocardium in positive patients. In this group, using LGE presence as a predictor for MACE had a statistically insignificant results. The heart failure accounted for the majority of MACE outcomes in this group.

For PPCM patients, our patients underwent CMR examination during postpartum period, aiming to avoid Gadolinium-related hazards in pregnancy as mentioned in multiple previous publications [(3, 20)]**.** In our patients, we detected biventricular affection with impaired EF but with no detectable LGE. These results are matching with previously mentioned in another study who mentioned that LGE has been reported in 0% to 40% of PPCM [(5)]**.**

For collagen related cardiomyopathy patients, our results for SLE patients, regarding impaired EF and mid-wall LGE of inter-ventricular septum, are matching with **Moosa and Ntusi** [(21)], who described LV dysfunction without evidence of inflammation or fibrosis as a typical pattern for SLE patients. That study mentioned that LGE is typically small and most often found in the interventricular septum.

For amyloidosis patients, our results are matching with previously published in 2016 regarding impaired LV function, more homogeneous LV wall thickening, RV involvement, biatrial enlargement and pericardial and pleural effusions with widespread subendocardial LGE distribution of amyloid sparing the midwall of the septum are also obtained [(21)]. Technically, we found difficulty to null the myocardial signal due to rapid washout from the blood pool and high myocardial uptake in the affected areas with amyloid deposition. To visualize myocardial and blood pool kinetics we used inversion time scout at 5 min after contrast administration as recommended in the previous study [(22)].

CONCLUSION

Our study concluded that, although echocardiography is the simplest more available, relatively cheap imaging technique used for diagnosis of cardiomyopathies, cardiac MR with its new additional sequences has now established itself as a crucial imaging technique for the evaluation of NICM.

It is not only providing comprehensive structural information, accurate function quantification and tissue characterization but also it evaluates fibrosis by LGE sequence. These data help in establishing the etiology of cardiomyopathy, providing guidance for endomyocardial biopsy, prognostic determination and monitoring response to therapy.

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