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Clinical Characteristics, Cardiac Magnetic Resonance Features, and Outcomes of Patients with Dilated Cardiomyopathy – An Experience from a South Asian Country

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ABSTRACT

Objectives: The objectives of the study were to evaluate the clinical presentation, cardiac magnetic resonance (CMR) features, and outcomes of patients with dilated cardiomyopathy (DCM).

Material and Methods: A retrospective study was conducted at a tertiary care center of Pakistan. All patients who underwent CMR for further evaluation of DCM during the period of 2011–2019 and in whom CMR confirmed the diagnosis of DCM, were included in the study. Patients were followed up in the year 2020 for all-cause mortality and cardiovascular hospitalizations.

Results: A total of 75 patients were included in the study. The mean age was 38.7 ± 13 with the majority (n = 57, 76%) being male. Dyspnea was the most common presenting symptom (n = 68, 90.7%). The mean left ventricle ejection fraction (LVEF) by CMR was 29.3 ± 12 and mean left ventricle stroke volume (LVSV) was 66.5 ± 31. Late gadolinium enhanced (LGE) was present in 28 (37.3%) patients. Follow-up was available in 61 patients with the mean follow-up duration of 39.7 ± 27 months. Most patients (40, 65.6%) experienced all-cause major adverse cardiovascular events (MACE) during the follow-up and mortality was observed in 10 (16.4%) patients. LVSV by CMR (P = 0.03), LVEF by CMR (P = 0.02), and presence of pericardial effusion (PE) (P = 0.01) were significantly associated with all-cause MACE. On multiregression analysis, SV by CMR was associated with all cause MACE (P = 0.048). The presence of LGE was associated with higher mortality (P = 0.03).

Conclusion: LVSV, LVEF by CMR, and PE were significantly associated with all-cause MACE. LGE was associated with higher mortality. Our cohort had a relatively younger age of presentation and diagnosis, and a greater mortality on follow-up, when compared with other regions of the world.

Keywords: Dilated cardiomyopathy, Non-ischemic cardiomyopathy, South-Asia, Cardiac magnetic resonance imaging, Late gadolinium enhancement

INTRODUCTION

Dilated cardiomyopathy (DCM) is a type of non-ischemic cardiomyopathy. It entails structurally and functionally abnormal myocardium leading to ventricular dilatation and depressed myocardial performance in the absence of abnormal loading conditions such as hypertension or valve disease.[1] The true incidence and prevalence of DCM is not known and is variable

depending on geographical location and true exclusion of common comorbid conditions such as hypertension or valvular heart disease (VHD).

DCM carries an estimated prevalence of 1:250/500 in adults[2] and has an incidence of 3.9%/100,000 person-years.[1] DCM can be genetic or non-genetic.

Cardiac magnetic resonance (CMR) has evolved as a strong tool to define etiology in DCM and carries a prognostic value.[3] It accurately measures volumes, functions, and strains. Contrast enhancement gives additional information about the myocardial tissue quality and extent of fibrosis. In DCM, CMR typically shows an intramural layer of septal fibrosis.[4]

CMR features of DCM and correlation with cardiovascular outcomes generally remain unknown for the Asian population. This brought us to the need of evaluating CMR characteristics and prognostic features at our center.

MATERIAL AND METHODS

This was a retrospective study conducted at the Aga Khan University Hospital, Pakistan. The study was done after getting approval from the ethical committee of the hospital (ERC number: 2020-5594-14863). CMR data were retrieved from the electronic medical record system of the hospital. All the patients who underwent CMR for further workup of DCM, from 2011 to 2019, were reviewed and only patients with the final diagnosis of DCM were included in the study. Patients with ischemic cardiomyopathy, amyloidosis, sarcoidosis. and arrhythmogenic right ventricular cardiomyopathy were excluded from the study. Clinical and CMR data were collected on a pre-defined data entry form, after reviewing the medical records and telephonic communication when required.

DCM on CMR was defined as left ventricle (LV) dilatation, poor systolic wall thickening, and/or reduced inward endocardial systolic motion on cine images in the absence of ischemic or VHD, with an ejection fraction (EF) <45%.[5]

Major adverse cardiovascular events (MACEs) were defined as a total of mortality, heart failure (HF) hospitalization, and arrhythmia hospitalization.

CMR data acquisition and analysis

CMR was performed using 1.5 Tesla Siemens Avanto Scanner. Each patient underwent breath-hold steady-state free-precision sequence for the assessment of ventricular function. A set of two long axis views (vertical and horizontal) and a set of serial short-axis views were acquired from the mitral plane to the apex using following parameters: A slice thickness 7 mm, a distance factor 25%, a field of view 34 cm, a matrix of 192 × 192, a flip angle 80, a TR/TE of 58.74/1.12, and a bandwidth of 930 Hz/px.

Late gadolinium-enhanced (LGE) images were taken after 8–10 min of gadolinium injection. Images were reacquired in the same sequences after the contrast injection. All CMRs were analyzed on a third-party software – Medis QMass. Analysis was done by a single reader who was qualified for and experienced in CMR interpretation. The end-diastolic volume (EDV) and end-systolic volume (ESV) were obtained by manual demarcation of endocardial and epicardial borders on the short-axis cine slices. The left ventricle ejection fraction (LVEF) was calculated (in percentages) from the EDV and ESV. The right ventricle (RV) EF was estimated visually, that is, on eyeballing.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences version 23.0.0 (IBM Corp. Released 2018). Results were presented as mean ± standard deviation for continuous variables such as age and as number (percentages) for categorical variables. Number and percentage of outcome variables (MACE) in DCM were calculated and stratified by various CMR and clinical variables. Qualitative data were compared using the two 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. A two-sided $P < 0.05$ was considered statistically significant for all tests.

RESULTS

A total of 75 patients with the final diagnosis of DCM were included in the study. Table 1 shows the baseline characteristics. The mean age was 38.7 ± 13 with the majority (n = 57, 76%) being male. Dyspnea was the most common presenting symptom (n = 68, 90.7%) followed by palpitation (n = 29, 38.7%).

The mean EF by echocardiogram was 26.4% ± 15. The mean left ventricular end-diastolic diameter (LVEDD) was 52.89 ± 8 mm and the mean left ventricular end-systolic diameter (LVESD) was 42.8 ± 10 mm.

CMR features of the patients are shown in Table 2. The mean LVEF by CMR was 29.3% ± 12 and the mean LV stroke volume (SV) was 66.5 ± 31 ml. Majority (n = 64, 85.3%) of the patients showed generalized global hypokinesia and no regional wall motion abnormalities. LGE was present in 28 (37.3%) patients. The RV systolic function was reduced in 16 (21.3%) patients.

Follow-up was available in 61 patients [Table 3] with the mean follow-up duration of 39.7 ± 27 months. Over the course of follow-up, all-cause MACE was observed in 40 (65.6%) patients whereas mortality was observed in 10 (16.4%) patients, 44.4% of patients had at least one HF hospitalization and 36% had at least one arrhythmia hospitalization.

Table 1: Baseline characteristics of patients with dilated cardiomyopathy.

Baseline characteristics	Number (total. *n*=75)	Percentage
Mean age (in years)	38.7±13	
Females	18	24
Males	57	76
DM	15	20
Dyslipidemia	11	14.7
Hypertension	14	18.7
Stroke	2	2.7
Family history of SCD	8	10.3
Family history of DCM	10	12.8
Symptoms		
Dyspnea	68	90.7
Palpitations	29	38.7
Syncope	10	13.3
Pre-syncope	3	4

DM: Diabetes mellitus, SCD: Sudden cardiac death, DCM: Dilated cardiomyopathy

Table 2: CMR features of patients with dilated cardiomyopathy.

CMR characteristics	Mean	n (%)
LVEDV	244.6±99	75
LVESV	178±87	75
LV SV	66.5±31	75
EF	29.3±12	75
Global hypokinesia		64 (85.3)
LV mass	149±52	71
RV size		62
Normal		54 (72)
Enlarged		8 (10.7)
RV function		62
Normal		46 (61.3)
Mildly reduced		4 (5.3)
Moderately reduced		6 (8)
Severely reduced		6 (8)
Pericardium		75 (100)
Normal		64 (85.3)
Pericardial effusion		11 (14.7)
LGE		28 (37.3)
No LGE		47 (62.6)
Thrombus		5 (6.7)

CMR: Cardiac magnetic resonance, LVEDV: Left ventricle end-diastolic volume, LVESV: Left ventricle end-systolic volume, LV: Left ventricle, SV: Stroke volume, EF: Ejection fraction, RV: Right ventricle, LGE: Late gadolinium enhancement

Patients were divided into two groups based on the presence or absence of MACE on follow-up. Table 4 shows the difference of clinical and CMR features among two groups. On analysis, LVEF and SV by CMR were significantly associated with MACE (P = 0.02 and 0.03, respectively). Age, gender, and presence of thrombus did not predict outcomes in DCM patients in this study. On multiregression analysis, SV by CMR was significantly associated with all-cause MACE (P = 0.048). The presence of LGE was associated with higher all-cause mortality (P = 0.03). The RV dysfunction of any degree was not associated with all-cause MACE (P = 0.13).

Table 3: Outcomes on follow-up.

Outcomes	*n* (%)
All-cause mortality	10 (16.4)
Number of HF hospitalization	
0	34 (55.7)
1	14 (23)
2	6 (9.8)
3	5 (8.2)
4	2 (3.3)
Number of arrhythmia hospitalization	
0	39 (63.9)
1	9 (14.8)
2	3 (4.9)
3	8 (13.1)
4	1 (1.6)
7	1 (1.6)
MACE	40 (65.6)
Lost to follow-up	14 (18.6)
Time from diagnosis to outcome (months)	32±17
CIED implantation on follow-up	10 (16.4)
Clinically documented arrhythmia	
Atrial fibrillation	4 (5.3)
Atrial flutter	3 (4)
Ventricular tachycardia/fibrillation	7 (9.3)
PVCs	1 (1.3)
Complete heart block	1 (1.3)
Invasive coronary angiogram	15 (20%)

HF: Heart failure, MACE: Major adverse cardiovascular event, CIED: Cardiac implantable electronic device, PVC: Premature ventricular contraction

The most common pattern of LGE encountered was mid-myocardial which was present in 12 patients (42.8% of 28 LGE + patients). Septal involvement was found in 9 patients (32.1%) [Figures 1-5]. The RV LGE was present in 4 patients (14.2%).

Table 5 highlights the difference in baseline characteristics and outcomes of patients with and without LGE.

DISCUSSION

There is a scarcity of CMR data in DCM in South-Asian population and very few studies have highlighted CMR characteristics of DCM in this part of the world.[6-9]

CMR has become the gold standard for the assessment of the right and left heart volumes and has been proven to have good reproducibility in the assessment of volumes and EFs.

Table 4: Differences in clinical and cardiac magnetic resonance features in patients with or without MACE on follow-up.

Characteristic	MACE (*n*=40)	No MACE (*n*=21)	*P* value
Age (years)	36.7±14.7	40.9±13.4	0.28
Gender			
Male	29 (72.5)	16 (76.2)	0.75
Female	11 (27.5)	5 (23.8)	
Symptoms			
Dyspnea	3 (90)	19 (90.5)	0.99
Palpitation	18 (45)	7 (33.3)	0.37
Syncope	7 (17.5)	2 (9.5)	0.47
Presyncope	2 (5.0)	1 (4.8)	0.99
LVEF by echo; *n*=33			
<30	19 (82.6)	4 (40)	0.04
30–35	1 (4.3)	1 (10)	
>35	3 (13)	5 (50)	
LVEDV by CMR			
≤170	8 (20)	7 (33.3)	0.25
>170	32 (80)	14 (66.7)	
LVESV by CMR			
≤120	8 (20)	8 (38.1)	0.12
>120	32 (80)	13 (61.9)	
LV stroke volume by CMR			
≤50	16 (40)	3 (14.3)	0.03
>50	24 (60)	18 (85.7)	
LVEF by CMR			
<30	29 (72.5)	9 (42.9)	0.02
30–35	5 (12.5)	2 (9.5)	
>35	6 (15)	10 (47.6)	
LV mass by CMR; *n*=57			
≤110	8 (21.6)	5 (25)	0.75
>110	29 (78.4)	15 (75)	
RV size CMR; *n*=50			
Normal	29 (80.6)	14 (100)	0.16
Enlarged	7 (19.4)	0	
RVF CMR; *n*=50			
Normal	23 (63.9)	13 (92.9)	0.13
Mildly reduced	2 (5.6)	1 (7.1)	
Moderately reduced	6 (16.7)	0	
Severely reduced	5 (13.9)	0	
SWMA	4 (10)	1 (4.8)	0.65
Global hypokinesia	34 (85)	17 (81)	0.72
LGE			
Hyperenhancement	21 (52.5)	7 (33.3)	0.18
Normal	19 (47.5)	14 (66.7)	
Thrombus	2 (5.0)	2 (9.5)	0.60
Pericardium			
Normal	30 (75)	21 (100)	0.01
Effusion	10 (25)	0	
Regional or global edema	4 (10)	0	0.28
Family history of			
DCM	9 (22.5)	1 (4.8)	0.14
SCD	5 (12.5)	2 (9.5)	0.99

MACE: Major adverse cardiovascular event, LVEDV: Left ventricle end-diastolic volume, LVESV: Left ventricle end-systolic volume, LV: Left ventricle, EF: Ejection fraction, RV: Right ventricle, LGE: Late gadolinium *enhancement*, DCM: Dilated cardiomyopathy, SCD: Sudden cardiac death, SWMA: Segmental wall motion abnormalities, CMR: Cardiac magnetic resonance

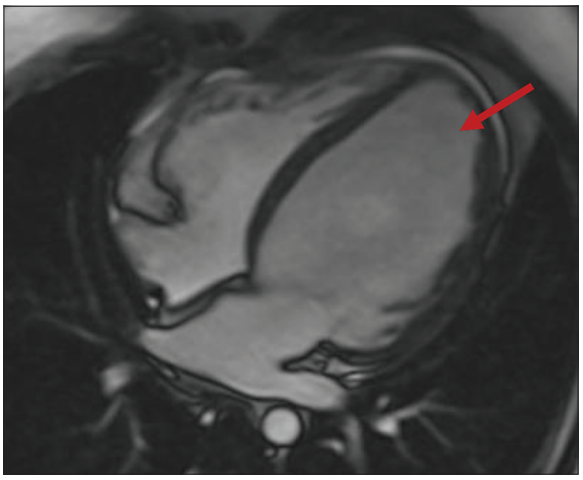

Figure 1: A 27-year-old female presented with shortness of breath and severe left ventricular systolic dysfunction on echocardiogram. Cardiac magnetic resonance steady-state free-precession still frame, 4-chamber view showing dilated left ventricle (arrow).

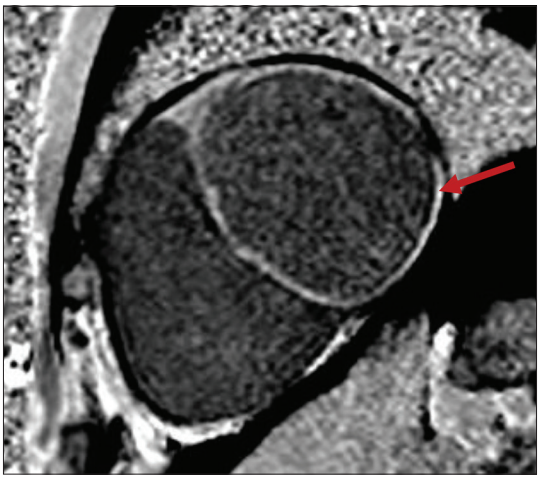

Figure 2: A 40-year-old male with 1 year history of shortness of breath and severe left ventricular systolic dysfunction on echocardiogram. Cardiac magnetic resonance late gadolinium image, short-axis view showing a rim of mid-myocardial hyperenhancement (arrow).

The three-dimensional dataset omits the error that comes by the two-dimensional assumption about the geometrical shape of heart.[3] CMR is shown to have superior reproducibility coefficient in assessment of EF ($P < 0.001$), ventricular mass ($P < 0.001$), ESV ($P < 0.001$), and EDV ($P = 0.17$).[10] Our study revealed a fair agreement between mean EF calculation by echocardiogram and CMR (26.4 ± 15 vs. 29.3 ± 12). This is consistent with the previous studies.[11,12]

Table 6 compares the baseline characteristics of our study subjects with those of Behera *et al.*,[9] Grothues *et al.*,[10] Assomull *et al.*,[13] Ibrahim *et al.*,[11] and Puntmann *et al.*[14]

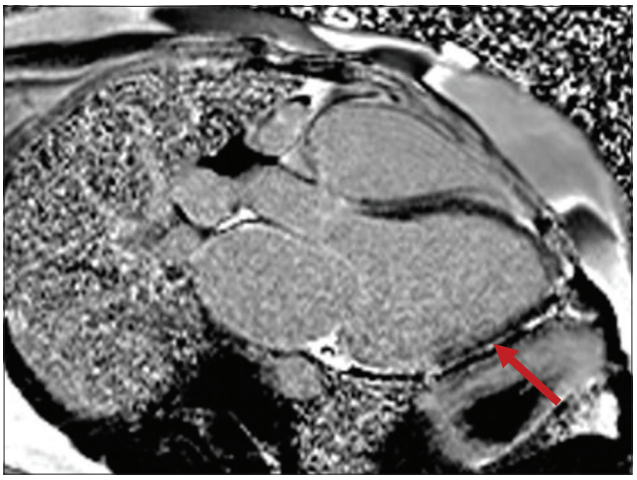

Figure 3: A 42-year-old lady with atrial fibrillation and heart failure. Cardiac magnetic resonance late gadolinium image, 3-chamber view showing mid-myocardial hyperenhancement which is subendocardial in basal inferolateral segment (arrow).

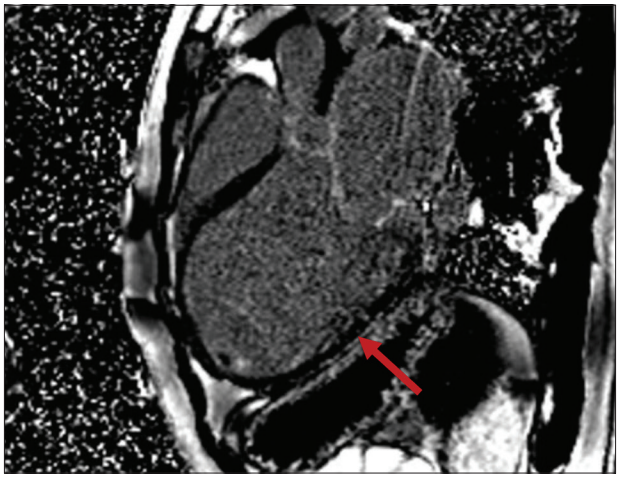

Figure 4: A 31-year-old male with signs and symptoms of heart failure and severe left ventricular systolic dysfunction on echocardiogram. Cardiac magnetic resonance late gadolinium image, 3-chamber view showing subepicardial hyperenhancement in the inferolateral wall (arrow).

We found that our patients had relatively younger age of diagnosis when compared with the other studies. Male predominance was common among all five studies. On comparison, our patients had relatively lesser SV and EF, a higher LV mass but comparable LVEDV and LVESV. Overall, we had a relatively greater all-cause mortality on follow-up. Our comparison suggests that the presence of LGE in DCM has a variable occurrence across different studies. Possible causes for greater mortality include pitfalls pertinent to a low-to-middle-income country such as lack of wide availability of HF clinics, lack of serial follow-up with primary cardiologist, lower education status and awareness about the disease, and inability to receive HF medicines and cardiac implantable electronic devices (CIEDs) implantation where indicated, all being largely driven by economic constraints.

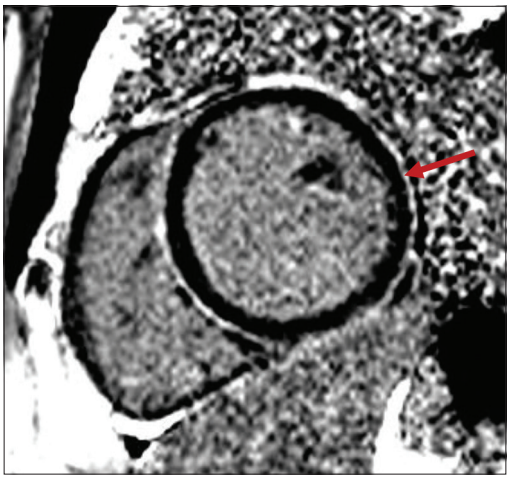

Figure 5: A 28-year-old male with a history of recurrent wide complex tachycardia, left ventricular systolic dysfunction, and normal coronary arteries. Cardiac magnetic resonance late gadolinium image, short-axis view showing a rim of subepicardial hyperenhancement (arrow).

Table 5: Comparison of baseline characteristics and outcomes of patients with and without late gadolinium *enhancement* on CMR.

Characteristics	No LGE; *n*=33	LGE+; *n*=28	*P* value
Age, years	38.8±14.8	37.3±14.0	0.69
Gender			
Male	23 (69.7)	22 (78.6)	0.43
Female	10 (30.3)	6 (21.4)	
Comorbidity			
DM	10 (30.3)	5 (17.9)	0.26
Dyslipidemia	6 (18.2)	4 (14.3)	0.74
Hypertension	8 (24.2)	3 (10.7)	0.17
IHD	1 (3.0)	2 (7.1)	0.58
Stroke	0	1 (3.6)	0.45
Family history of			
SCD	4 (12.1)	3 (10.7)	0.99
DCM	3 (9.1)	7 (25)	0.16
Symptoms			
Dyspnea	30 (90.9)	25 (89.3)	0.99
Palpitation	9 (27.3)	16 (57.1)	0.01
Syncope	4 (12.1)	5 (17.9)	0.72
Pre-syncope	2 (6.1)	1 (3.6)	0.99
Outcomes			
MACE	19 (57.6)	21 (75)	0.18
CIED	5 (15.2)	5 (17.9)	0.99
Mortality	2 (6.1)	8 (28.6)	0.03

CMR: Cardiac magnetic resonance, DM: Diabetes mellitus, IHD: Ischemic heart disease, SCD: Sudden cardiac death, DCM: Dilated cardiomyopathy, MACE: Major adverse cardiovascular event, CIED: Cardiac implantable electronic device

Table 6: Comparison of our study with five other studies in the literature across different regions of the world.

Characteristics	Our study (*n*=75)	Behara *et al.* (*n*=112)	Assomul *et al.* (*n*=101)	Grotheus *et al.* (*n*=20)	Ibrahim et al. (*n*=35)	Puntmann *et al.* (*n*=637)
Country or region of study	Karachi, Pakistan	India	Southeast England	London, England	Egypt	England, Germany (multicentered)
Mean age	38.7±13	42.7	50.5	61±12 (33–78)	46.9+9 years	50 (37–76)
Males	76%	64.2%	69%	90%	60%	62%
DM	20	25.8	4.9%	Not given	14.3%	24%
Hypertension	18.7	Not given	13.8%	Not given	31.4%	48%
Family history	12.8	3.57	Not given	17%	22.9%	9%
Mean EF by CMR	29.3±12	21.0 (13.2–34.2)	Not given	33±11 (10–58)	30%	47 (29–50)
Stroke volume	66.5±31	26.5 (21.2–50.7) (indexed)	Not given	75±15 (35–102)	Not given	Not given
LVEDV	244.6±99	137 (87.5–225) (indexed)	259.5	128±29 (84–179) (indexed)	Not given	109 (89–132) (indexed)
LVESV	178±87	102 (62.7–183.7) (indexed)	174.5	88±30 (36–152) (indexed)	Not given	48 (31–58) (indexed)
LV mass	105±17 (78–138)	Not given	73.5	201±36 (127–256) (indexed)	Not given	88 (62–98) (indexed)
LGE present	37.3%	39.2%	65.3%	Not given	77.1%	27%
Mortality on follow-up	16.4%	5.35%	9.9%	Not given	Not given	4.3%

DM: Diabetes mellitus, LVEDV: Left ventricle end-diastolic volume, LVESV: Left ventricle end-systolic volume, LV: Left ventricle, EF: Ejection fraction, LGE: Late gadolinium enhancement, CMR: Cardiac magnetic resonance

Of note, the study from our neighboring country India also exhibited a trend of younger age and lower EF than the other studies. This points toward some sociocultural, genetic, and geographical determinants given the commonality between the two countries.

The extent of fibrosis and degree of late contrast enhancement carries prognostic implications in terms of long-term all-cause mortality, future hospitalizations, and risk of arrhythmias. We found that patients with LGE had higher all-cause mortality ($P = 0.03$). Our study highlighted a trend toward increased chances of LGE in patients with MACE, however, this did not reach level of statistical significance. Overall, there was no significant difference between basic demographic characteristics and symptoms except for LGE + patients presenting more often with palpitations ($P = 0.01$).

Assomull *et al.* looked at CMR features of DCM patients in a cohort of 101 DCM patients and found that mid-wall fibrosis was present in 30% of patients and when present, it was associated with higher rates of all-cause mortality, cardiovascular hospitalizations, sudden cardiac death, and ventricular tachycardia.[13] Similarly, CMR evidence of diffuse myocardial diseases on T1 mapping predicted all-cause mortality and HF events.[15] This leads to the importance of CMR in not just defining etiology but also in risk stratification of DCM patients. Unfortunately, we did not perform T1 mapping in our patients due to the non-availability of software. More than one-third of our patients (37.3%) had LGE and mid-myocardial LGE was the most common pattern. Septal involvement was found in 32% of those with LGE. The results are consistent with those described by Halliday *et al.* whereby the mid-wall LGE was the most common pattern encountered (61.6%, 185 out of 300 LGE + patients); septal involvement was present in 86% (258 out of 300 LGE + patients) and was associated with significant increase in risk of death and SCD events, the risk being greatest when septal involvement was concomitantly present with free-wall LGE.[15] In the Indian cohort mentioned above, LGE was associated with all-cause MACE but did not predict all-cause mortality. Mid-myocardial LGE was the most common pattern and septal involvement had highest associated risk of adverse outcomes (HR 3.046, 95% CI: 1.726–5.376, $P = 0.001$).

To be labeled as familial DCM, it requires two family members with DCM or a familial history of sudden cardiac death at age <35 years. History of familial diseases warrants genetic testing, screening and serial follow-up with physical examination, serial electrocardiograms, and echocardiograms.[4] Our study population had lesser

prevalence of family history of DCM when compared to the other two studies. This could possibly be because of variation in surveillance or screening of family members across different countries and centers.

Our study reported a greater association of the presence of pericardial effusion (PE) and all-cause MACE. About 25% of patients with MACE had PE on CMR in contrast to 0% without MACE and this reached level of statistical significance (P = 0.01). It is not uncommon to have mild-moderate PE in advanced HF states.[16] The presence of hemodynamically insignificant PE in HF patients has been associated with larger LVESD (P = 0.01), lower EF (P = 0.04), a higher heart rate (P <0.0001), lower use of beta-blockers, an overall reduced survival (P = 0.02), and greater probability of dying from cardiac cause (P = 0.01); a greater number of non-ischemic CMP was present in group with PE than in control (78% vs. 61%).[17]

Limitations

It was a single-centered study with a small population size. We were limited by the lack of availability of T1 mapping software.

CONCLUSION

Our cohort had a relatively younger age of presentation and diagnosis, a lower EF and had a greater mortality on follow-up when compared with other regions of the world. LV SV, LVEF by CMR, and presence of PE were significantly associated with all-cause MACE. LGE was present in more than one-third of patients and mid-wall involvement was the most common pattern encountered. The patient with LGE had higher mortality than those without LGE. There was a trend toward increased chances of LGE in patients with MACE when compared to patients without MACE, but this did not reach level of statistical significance. The greater mortality in DCM patients of this region can be attributable to the economic constraints, lack of widely available HF clinics, and inability to receive CIED implantation where indicated.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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