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

Pirbhat Shams¹, Fateh Ali Tipoo Sultan¹

¹Department of Medicine (Cardiology), Aga Khan University Hospital, Karachi, Sindh, Pakistan.

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[1] 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.[2] 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%.[3]

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) | 75 |
| 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

### Table 3: Outcomes on follow-up.

| Outcomes                        | n (%)    |
|---------------------------------|----------|
| All-cause mortality             | 10 (16.4)|
| Number of HF hospitalization    | 34 (55.7)|
| 0                               | 14 (23)  |
| 1                               | 6 (9.8)  |
| 2                               | 5 (8.2)  |
| 3                               | 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)  |
| Lost to follow-up               | 14 (18.6)|
| Time from diagnosis to outcome (months) | 32±17     |
| 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

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).

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. 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.
The three-dimensional dataset omits the error that comes by the two-dimensional assumption about the geometrical shape of heart. 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 ($P = 0.17$). Our study revealed a fair agreement between mean EF calculation by echocardiogram and CMR ($26.4 \pm 15$ vs. $29.3 \pm 12$). This is consistent with the previous studies.

Table 6 compares the baseline characteristics of our study subjects with those of Behera et al., Grothues et al., Assomull et al., Ibrahim et al., and Puntmann et al.
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.

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.
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.13 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.13 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

### 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       |
| 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)      | Not given              | 75±15 (35–102)         | Not given            | Not given              |
| LVEDV (indexed)                     | 244.6±99         | 137 (87.5–225)        | 259.5                  | 128±29 (84–179)        | Not given            | 109 (89–132)           |
| LVESV (indexed)                     | 178±87           | 102 (62.7–183.7)      | 174.5                  | 88±30 (36–152)         | Not given            | 48 (31–58)             |
| LV mass (indexed)                   | 105±17 (78–138)  | Not given             | 73.5                   | 201±36 (127–256)       | Not given            | 88 (62–98)             |
| 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.
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.\(^\text{16}\) The presence of hemodynamically insignificant PE in HF patients has been associated with larger LVEDD ($P = 0.01$), 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%).\(^\text{17}\)

**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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**Conflicts of interest**

There are no conflicts of interest.

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