Cardiovascular Topics

Yield of family screening in dilated cardiomyopathy within low-income setting: Tanzanian experience

LS Fundikira, J Julius, P Chillo, H Mayala, E Kifai, LW van Laake, A Kamuhabwa, G Kwesigabo, FW Asselbergs

Abstract

Background: Dilated cardiomyopathy (DCM) is often familial and screening of relatives is recommended. However, studies on the yield of screening are scarce in developing countries.
Aim: The aim of the study was to identify and characterise first-degree relatives of patients with DCM in Tanzania.
Methods: We recruited first-degree relatives of 57 DCM patients. DCM in the relatives was diagnosed using the 2016 revised definition by the European Society of Cardiology working group on myocardial and pericardial diseases.
Results: We screened 120 first-degree relatives. All were asymptomatic (100%) with a median age of 39.0 years (29.5–49.0), slightly over a half (53.3%) were females and 17 (14.1%) were found to have previously unknown DCM. The mean (± SD) indexed left ventricular end-diastolic volume was significantly higher in relatives with DCM (71 ± 11.5 ml) compared to relatives without DCM (50 ± 11.5) ($p = 0.001$).
Conclusion: First-degree relatives of patients with DCM are at risk of developing asymptomatic DCM at a young age.

Keywords: dilated cardiomyopathy, first-degree relatives, screening

Submitted 26/1/23, accepted 3/7/23
Cardiovasc J Afr 2023; online publication www.cvja.co.za

DOI: 10.5830/CVJA-2023-037

Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
LS Fundikira, MD, fundikira_lulu@hotmail.com
J Julius, MD
P Chillo, MD, PhD
A Kamuhabwa, BPharm, PhD
G Kwesigabo, MD, PhD

Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht (UMCU), Utrecht, The Netherlands
LW van Laake, MD, PhD

Jakaya Kikwete Cardiac Institute, Dar es Salaam, Tanzania
H Mayala, MD, PhD
E Kifai, MD

Department of Cardiology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; and Health Data Research UK and Institute of Health Informatics, University College London, London, United Kingdom
FW Asselbergs, MD, PhD

Dilated cardiomyopathy (DCM) is a disease of the myocardium characterised by left or biventricular dilatation and systolic dysfunction in the absence of coronary artery disease, hypertension, valvular disease or congenital heart disease.[1] DCM is a major cause of heart failure worldwide, and it is the second most common cause of heart failure in sub-Saharan Africa (SSA).[2] In Tanzania, DCM is the most common type among the cardiomyopathies and the second most common cause of heart failure.[3]

DCM can be classified as either familial or non-familial.[4] Familial DCM occurs when at least two closely related relatives have been diagnosed with the disease or when one family member meets the diagnostic criteria for DCM and has a first-degree relative with autopsy-proven DCM, or sudden death below 50 years of age.[5] Non-familial DCM can be acquired (secondary to a specific cause, for example infections, autoimmunity, toxins and others) or it can be idiopathic. It has been observed that between 20 and 35% of DCM patients have the familial form of the disease.[6]

Clinically, DCM may present as an overt disease with symptoms and signs of heart failure, such as shortness of breath, lower limb swelling, abdominal distension, or it can present as chest pain, arrhythmias or cardiogenic shock.[7] However, by definition, DCM may be manifested only as reduced left ventricular (LV) systolic function without heart failure symptoms. In fact, overt DCM is believed to be the end result of a long-standing, latent, subclinical DCM.[8]

First-degree relatives of patients with DCM have shown an increased probability of developing it, therefore clinical and genetic screening of first-degree relatives of patients with DCM is indicated, according to guidelines.[9,10] Clinical screening entails history taking, transthoracic echocardiography and electrocardiogram (ECG). The aim of the screening is to identify the disease or its incomplete preclinical expression among asymptomatic relatives of a patient with DCM.[5,9,10]

Previous studies have found the prevalence of DCM among first-degree relatives to range from 5–11%.[11-15] It has been a consensus that familial DCM will be found in at least 20–35% of DCM patients following clinical screening of their first-degree family members using clinical features, ECG and echocardiography.[14,16] Consequently, screening of first-degree relatives of patients with DCM is now a clinical routine in most developed countries.[5,17]

Experience from SSA shows that, among patients with DCM, up to 26.6% have familial DCM.[18] However, most of the previous studies from SSA have been done in South Africa and screening of first-degree relatives of patients with DCM has never been

studied in Tanzania, and it is not yet a clinical routine. This study therefore aimed to use clinical, electrocardiographic and echocardiographic means to screen first-degree relatives of patients with DCM in order to characterise familial DCM in our local setting.

Methods

This was a descriptive, hospital-based, cross-sectional study at the echocardiography laboratory at Jakaya Kikwete Cardiac Institute (JKCI) from September 2021 to February 2022. JKCI is a national tertiary-level hospital that receives patients referred from regional and zonal referral hospitals in Tanzania. First-degree relatives (aged 18 years and above) of 57 patients diagnosed with DCM without a known cause, attending at JKCI who were either newly or previously diagnosed, were involved. The index patients were available from a list of an on-going DCM study cohort that enrolled patients aged 18 years and above with a clinical diagnosis of heart failure and sonographic diagnosis of DCM with ejection fraction ≤ 45% without known cause.[5]

Ethical clearance was obtained from the MUHAS Ethical Review Board, and permission to conduct the study was obtained from JKCI management. A signed, informed consent was obtained from all study participants before enrolment.

Clinical findings and results were communicated as early as possible to the respective participants. Participants found to have DCM were referred to attend the clinic at JKCI if they lived in Dar es Salaam or to their respective regional referral hospitals if they lived upcountry. Participants who were not found to have DCM were advised to repeat screening every three to five years and refrain from excessive alcohol drinking. They also received health education to decrease overall risk for lifestyle-related illnesses.

DCM among relatives is defined when an asymptomatic relative has at least one major criterion, or two minor criteria, as detailed in the position statement of the European Society of Cardiology working group on myocardial and pericardial diseases.[5] The major criteria listed are: unexplained decrease of left ventricular ejection fraction (LVEF), of values between 46 and 49%, or unexplained LV dilatation (LV size more than two standard deviations from normal values, according to gender) as measured by either LV internal diameter in diastole or LV end-diastolic volume. Minor criteria in this definition include changes in the ECG, magnetic resonance imaging (MRI) and findings of endomyocardial biopsy.[5]

First-degree relatives were defined as parents, children or siblings of the index patient. The sampling frame included all first-degree relatives who were related to DCM patients. All available relatives related to a particular index patient were asked for informed consent to participate in the study.

A clinical research form collected demographic characteristics, including age, gender, occupation as well as area of residence. It also recorded cardiovascular risk factors, including history of hypertension, diabetes mellitus, cigarette smoking and alcohol consumption.

In every participant, a thorough history and physical examination was done. Blood pressure was taken using an automated digital sphygmomanometer with the patient in a seated position. The average of two readings, taken at least five minutes apart, was recorded as the patient's blood pressure. Patient's body weight (in kg) was taken using a well-calibrated weighing scale, with the patient wearing no shoes or heavy clothing. Height (in cm) was taken using a stadiometer and recorded to the nearest centimetre. Height and weight were used to calculate body mass index (BMI) using the formula: height (kg)/weight (m^2). Overweight and obesity were defined as BMI ≥ 25 kg/m^2 and ≥ 30 kg/m^2, respectively.

A 12-lead resting ECG was obtained from all participants on a GEMAC2000 machine. Reading and interpretation of the ECG was done manually by the investigator and proofread by a cardiologist. The following parameters were recorded: rate, rhythm, axis, atrial enlargement, ventricular enlargement, bundle branch blocks, ST-segment changes, T-wave changes, QTc interval, PR interval and premature ventricular complex (PVC).

The echocardiogram was performed using the American Society of Echocardiography guidelines.[19] A Siemens Acuson machine was used. Images from two-dimensional (2D), M-mode and Doppler (colour and tissue) recordings were taken. All measurements were done during the echocardiographic examination and data were retrieved from computer-generated values inbuilt in the echocardiogram machine. The obtained data were then transferred to pre-coded recording papers for each participant. Images were also stored in the echocardiogram machine hard disc for later re-reading. All echocardiographic examinations were verified by experienced cardiologists.

LVEF was determined using Simpson's biplane method and was taken as a measure of LV systolic function. LV end-diastolic volumes were measured using Simpson's biplane methods and were indexed to body surface area of the participant to obtain indexed LV end-diastolic volume (LVEDV-I). Some minor criteria were not used due to limited availability and/or high cost: cardiac MRI, endomyocardial biopsy as well as serum organ-specific and disease-specific anti-heart antibody. Visual assessment of LV function was also applied to observe regional myocardial function.[20]

Echocardiographic variables of LVEF and LVEDV-I, as well as ECG findings of complete left bundle branch block, atrioventricular (AV) block and ventricular arrhythmias were used to define DCM among first-degree relatives. Independent variables included socio-demographics such as age, gender, level of education, occupation and residence. Dependent variables included DCM, arrhythmia and ECG and echocardiographic findings.

Statistical analysis

Data were analysed using the R statistical package and presented as median with interquartile range for continuous variables and percentages for categorical variables, as appropriate. Comparison between groups was done using Fisher's exact test for parametric variables and the Wilcoxon rank sum test for non-parametric variables. A p-value < 0.05 was considered statistically significant.

Results

A total of 216 first-degree relatives from 57 DCM index cases were invited for screening between September 2021 and February 2022. Among those, only 120 (56%) participants came for screening. Ninety-six participants did not come for several

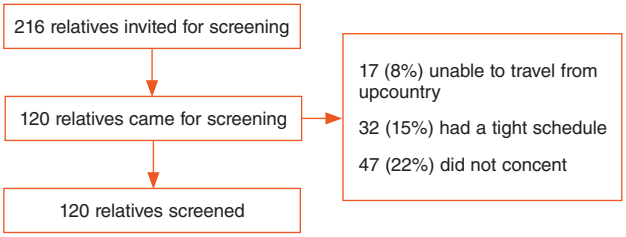

Fig. 1. Flowchart showing screening of relatives

reasons, as shown in Fig. 1.

The median (IQR) age of index patients and relatives were 53.0 (39.5–61.00) and 39.0 years (29–49), respectively ($p < 0.001$). There were more males than females in the index patient group compared to relatives, at 33 (57.9%) and 56 (46.7%), respectively ($p = 0.013$). The majority of relatives lived in Dar es Salaam (84.2%) and 48.3% were related to the index case as his or her child. Six participants (5%) were active smokers, 26 (21.6%) used alcohol, 14 (11.6%) were hypertensive and five (4.2%) were diabetic. Of the invited family members, more men refrained from participating (71; 73.9%) due to various reasons as described in Fig. 1. Other findings are as shown in Table 1.

Seventeen relatives were diagnosed with DCM. No relatives diagnosed with DCM had any symptoms during screening (17; 100%). Only two relatives (1.7%) of the study population presented with dyspnoea and had a history of hypertension. No other symptoms were found. In some patients without DCM, we recorded subtle changes in electrocardiography, which included left atrial enlargement (13; 11.1%) and incomplete right bundle branch block (6; 5%), as seen in Table 2. Relatives with and without DCM did not differ in terms of age, gender, blood pressure levels and other characteristics, as shown in Tables 1 and 2.

Relatives with DCM had significantly higher LV diastolic diameter, at 49.5 mm (46.9–51.9) ($p < 0.001$). The mean indexed LVEDVI-I was significantly higher in relatives with DCM (71 ± 11.5 ml) compared to relatives without DCM (50 ± 11.5 ml) ($p = 0.001$). The median (IQR) EF was significantly lower in relatives with DCM (62%; 61–65) compared to relatives without DCM (65%; 61–65) ($p = 0.021$). Moreover, relatives with DCM had significantly higher median (IQR) left atrial diameters (36.9 mm; 36.3–38.8) compared to relatives without DCM (35.2 mm; 32.4–27.5) ($p = 0.024$) (Table 3).

Table 1. Baseline characteristics of the study participants of family screening in DCM within a low-income setting

Characteristics	*Family (n = 120)* n *(%)/median (IQR)*	*Proband (n = 57)* n *(%)/median (IQR)*	p-*value*
Median age (years)	39.00 (29.25–49.00)	53.00 (39.50–61.00)	< 0.001
Gender, *n* (%)			
Male	56 (46.7)	33 (57.9)	0.013
Female	64 (53.3)	24 (42.1)	
Residence, *n* (%)			
Dar es salaam	101 (84.2)	43 (75.4)	0.026
Upcountry	19 (15.8)	14 (24.6)	
Relationship to index case, *n* (%)			
Parent	11 (9.2)	-	
Sibling	51 (42.5)	-	
Child	58 (48.3)	-	
Cigarette smoking, *n* (%)	6 (5.0)	3 (5.3)	1.000
Alcohol use, *n* (%)	26 (21.7)	7 (12.3)	0.103
Excessive alcohol use, *n* (%)	3 (2.5)	0 (0.0)	0.552
Known hypertensive, *n* (%)	3 (2.5)	0 (0.0)	0.552
Known diabetes mellitus, *n* (%)	14 (11.7)	0 (0.0)	0.005
Known dyslipidaemia, *n* (%)	1 (0.8)	5 (8.8)	0.014
Median body mass index, (kg/m^2)	27.95 (24.9–31.6)	26.18 (22.33–30.12)	0.032
Obesity status, *n* (%)			
Normal	32 (26.7)	26 (45.6)	< 0.001
Overweight	46 (38.3)	17 (29.8)	
Obese	42 (35.0)	14 (24.6)	

IQR, interquartile range.

Table 2. Clinical and electrocardiographic findings in first-degree relatives of patients with DCM

Variables	*All relatives (n = 120)*	*Relatives without DCM (n = 103)*	*Relatives with DCM (n = 17)*
Age (years), median (IQR)	39.0 (29.8–49.0)	40.0 (30.0–48.5)	37.0 (26.0–50.0)
Age < 45 years, *n* (%)	40 (33)	34 (33)	6 (35)
Females, *n* (%)	64 (53)	52 (50)	12 (71)
Signs and symptoms, *n* (%)			
Asymptomatic	118 (98)	101 (98)	17 (100)
Dyspnoea	2 (1.7)	2 (1.9)	0 (0)
SBP (mmHg), median (IQR)	142 (129–52)	141 (129–155)	146 (129–150)
DBP (mmHg), median (IQR)	85 (77, 93)	86 (79, 94)	81 (69, 87)
ECG findings, *n* (%)			
Prolonged QTc interval	7 (5.8)	6 (5.8)	1 (5.9)
Incomplete LBBB	1 (0.8)	0 (0)	1 (5.9)
Incomplete RBBB	6 (5.0)	6 (5.8)	0 (0)
PVCs	2 (1.6)	1 (0.9)	1 (5.9)
Left-axis deviation	2 (1.6)	2 (1.9)	0 (0)
Right-axis deviation	0 (0)	0 (0)	0 (0)

SBP, systolic blood pressure; DBP, diastolic blood pressure; ECG, electrocardiogram; LBBB, left bundle branch block; RBBB, right bundle branch block; PVCs, premature ventricular contractions.

Table 3. Echocardiographic findings in first-degree relatives of patients with DCM (*n* = 120)

Variables	*Relatives without DCM (n = 103) median (IQR)/mean (SD)*	*Relatives with DCM (n = 17) median (IQR)/mean (SD)*	p-*value*
LVIDd (mm)	43.4 (41.0–47.5)	49.2 (46.9–51.6)	< 0.001
LVEDV-I (ml/m^2)	50.7 (11.5)	71.5 (11.5)	0.000
LVPWd (mm)	10.5 (9.5–12.5)	9.2 (8.8–10.6)	0.005
IVSd (mm)	11.4 (10.0–12.3)	10.6 (9.4–11.9)	0.3
IVSs (mm)	15.8 (14.1–17.5)	14.6 (12.5–16.9)	0.2
LAs diameter (mm)	35.2 (32.4–37.5)	36.9 (36.3–38.8)	0.024
FS (%)	36.0 (32.9–40.3)	35.3 (31.9–40.1)	0.8
LAs/AOd ratio	1.26 (1.15–1.32)	1.43 (1.25–1.48)	0.014
LVEF by Simpson (%)	65 (62–70)	62 (61–65)	0.021
LVEDV by Simpson (ml)	102 (82–115)	102 (87–129)	0.5
LVMI (g/m^2)	94 (81–116)	109 (92–128)	0.2
Diastology, *n* (%)			0.094
Normal	86 (83)	12 (71)	
Grade I dysfunction	13 (13)	2 (12)	
Grade II dysfunction	3 (2.9)	3 (18)	
Grade III dysfunction	1 (1.0)	0 (0)	

LVIDd, left ventricular internal diameter in diastole; LVEDV-I, indexed left ventricular end-diastolic volume; LVPWd, left ventricular posterior wall thickness in diastole; LVEDV, left ventricular end-diastolic volume; IVSs, interventricular septum thickness in systole; LVMI, left ventricular mass index; FS, fractional shortening; LVEF, left ventricular ejection fraction: Las, left atrial size; AOd, aorta in diastole.

Table 4. Demographic and clinical details of first-degree relatives found to have DCM

Case no	Age (years)	Gender	Symptoms	ECG	Echo	
					EF (%)	LVEDV-I (ml/m²)
1	55	M	None	LBBB	45	63
2	37	F	None	Normal	62	67
3	57	F	None	PVC	64	81
4[ε]	21	F	None	Normal	72	63
5[ε]	20	F	None	Normal	69	62
6	38	F	None	Normal	66	70
7*	22	F	None	Normal	48	62
8*	26	M	None	Normal	62	93
9	39	F	None	Normal	72	68
10	27	M	None	Normal	46	99
11	56	F	None	Normal	61	68
12	46	F	None	Normal	62	64
13	52	M	None	Normal	68	75
14	23	M	None	Normal	62	87
15	26	F	None	Normal	62	64
16	50	F	None	Normal	60	67
17	32	F	None	Left atrial enlargement; left ventricular enlargement	55	63

*,[ε]Came from the same family. EF, ejection fraction; LVEDV-I, indexed left ventricular end-diastolic volume; LBBB, left bundle branch block; PVC, premature ventricular contractions.

Table 4 shows defining characteristics of relatives with DCM. There were two sets of relatives with DCM that belonged to the same index DCM case; cases 4 and 5 were related to a 26-year-old female and both were siblings, while cases 7 and 8 were related to a 63-year-old male and both were his children.

Discussion

This is the first study done in Tanzania on relatives of patients with DCM. By means of history, physical examination, electrocardiography and echocardiography, we screened 120 first-degree relatives from 57 patients with DCM attending the only specialised tertiary cardiac hospital in the country.

In our study, 17 relatives achieved the criteria for DCM, giving a proportion of 14.1% among the screened relatives. Our findings are slightly higher compared to other studies in which the prevalence of DCM among first-degree relatives of patients with DCM has been found to range between five and 11%.[11-13,21] This could be influenced by a variable proportion of participation, bearing in mind the number of family members eligible and invited for screening was 216, and the minimum proportion of affected relatives in our series was 7.8%. This calls for another study to review the challenges of screening relatives in cardiomyopathies including DCM, to fully understand the low participation rate.

Our findings suggest that familial DCM tends to occur at a young age and it is in keeping with a genetic aetiology of the disease. The difference in age between index patients and relatives could be explained by a long, subclinical, asymptomatic course of the disease.[22] A study done in Italy in which first-degree relatives of DCM patients were consecutively enrolled to be screened for familial DCM found that the mean age of onset of familial DCM was 32 years.[23] Young age, as opposed to any other clinical feature has been shown to be predictive of familial DCM.[24]

Although it is widely recognised that male gender is an important risk factor for developing systolic heart failure, studies that examine the role of gender on DCM specifically are scant.[25,26] Similar to this finding in our study, others have also found more females than males in familial DCM in screening. A study done at the Mayo Clinic in Rochester, USA, found the number of females affected by familial DCM to be 75% of all affected relatives.[12] Another familial DCM screening study from Italy showed more females among those found to be affected by DCM during screening, at 85.7%.[27] However, we cannot rule out the possibility that in our series, males could have been severely affected and died young or were very sick and refused to participate.

All affected relatives were asymptomatic during screening. This finding is similar to an Irish study that consecutively screened 200 first-degree relatives from 56 families and found that 100% of the relatives in whom DCM was diagnosed were asymptomatic.[11] Our findings are also similar to an American study that found 80% of relatives diagnosed during screening were asymptomatic.[12] Our findings reiterate the need for ongoing periodic cardiac screening of asymptomatic relatives to allow for early detection of pre-clinical disease.[28]

ECG abnormalities seen in our study are in keeping with studies done elsewhere. An Italian familial DCM screening study observed the following ECG findings among those found to be affected by DCM: chamber enlargement, low-amplitude QRS complexes, right-axis deviation, premature ventricular contractions and hemi-block.[27] In another study, the ECG findings obtained during screening of relatives of patients with DCM included atrial fibrillation, PVC, hemi-blocks, AV blocks and chamber enlargement.[21] The presence of subtle electrocardiographic and echocardiographic changes in asymptomatic first-degree relatives, as seen in our study, could be indicative of pre-clinical disease.[16]

Non-response of some of the invited family members could have created a selection bias and therefore the number may not reflect the true magnitude of familial disease. There is also a possibility that the majority of relatives who declined to participate was already affected and had ill health. Conversely, those who came were likely to be diseased and therefore came forward to get screened.

High non-response rates in familial DCM screening studies have been observed by others as well. A familial DCM screening study by McKenna *et al*. found the non-response rate among contacted first-degree relatives to be 26%. Additionally, 25% of DCM patients did not wish their first-degree relatives to be contacted.[11] In that study, the reasons for not attending for screening included residing abroad, subjects did not reply to the invitation or were still to be contacted to attend screening. In another study, the non-response rate was found to be 30% and the reasons for not participating in screening in this particular study included living too far from the medical centre, being disinterested, too high a cost of travel, and others did not give a reason.[12]

As with other screening studies, familial DCM screening studies face an inherent challenge of non-response.[12-14,21] This study sets a baseline for further studies with a larger sample size and the possibility of establishing a family screening programme in patients diagnosed with DCM.

Although it was not the focus of this study, we observed notable

incidences of cardiovascular risk factors, such as obesity, alcohol consumption and elevated blood pressure during screening. This is in agreement with previous community screening done in Dar es Salaam involving 6 691 participants in which over two-thirds of participants were alcohol consumers, 6.9% had a positive smoking history, 4.7% had a history of diabetes mellitus and 18.1% had elevated blood pressure. Overweight and obesity were observed in 34.8 and 32.4% of participants, respectively.[29] This finding alerts us to a changing society and calls for collaborative and concrete measures to control these risk factors for cardiovascular diseases.

Study limitations

This study may have over- or underestimated the true prevalence of DCM among first-degree relatives of patients with DCM because of the significant number of first-degree relatives who did not turn up for screening. Only a prospective study screening all available first-degree relatives on a regular basis would determine the exact prevalence of DCM among first-degree relatives of patients with DCM. Nevertheless, while the actual prevalence is most likely to be close to our findings, we demonstrated that the minimum prevalence of DCM at the time of screening was 7.8% of 216 relatives, including the ones who did not participate. Another limitation is the lack of access to other diagnostic modalities that have been described in criteria for family disease, such as cardiac MRI, endomyocardial biopsy as well as antibody studies. However, this was essentially a real-world study and reflects the local situation in many developing countries.

Conclusion

First-degree relatives of patients with DCM are at risk of developing asymptomatic disease at a young age. The identification of newly affected individuals with DCM may benefit from early management, even if they are asymptomatic. Also, the affected individuals need close monitoring for any complications. There is a need to create community awareness to encourage more relatives of DCM patients to be screened, as well as education of health professionals. The findings obtained from this study should raise awareness among clinicians and family member of patients with DCM beyond economically developed country settings.

We acknowledge JKCI in Tanzania for allowing us to conduct the clinical part of this research. We thank the Utrecht Global Health Program of UMCU at Utrecht in the Netherlands and the Centre of Excellence for Cardiovascular Sciences under MUHAS in Tanzania for the sponsorship. Folkert Asselbergs is supported by UCL Hospitals NIHR Biomedical Research Centre.

References

1. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. *Circ Res* 2017; **121**(7): 722–730.
2. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, *et al*. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries: results of the sub-Saharan Africa survey of heart failure. *Arch Int Med* 2012; **172**(18): 1386–1394.
3. Makubi A, Hage C, Lwakatare J, Kisenge P, Makani J, Rydén L, *et al.* Contemporary aetiology, clinical characteristics and prognosis of adults with heart failure observed in a tertiary hospital in Tanzania: the prospective Tanzania Heart Failure (TaHeF) study. *Heart* 2014; **100**(16): 1235–1241.
4. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, *et al*. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008; **29**(2): 270–276.
5. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, *et al.* Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J* 2016; **37**(23): 1850–1858.
6. Burkett EL, Hershberger RE. Clinical and genetic issues in familial dilated cardiomyopathy. *J Am Coll Cardiol* 2005; **45**(7): 969–981.
7. Heinz-Peter S, DeLisa F, LP CA, Felicitas E, Hershberger RE, Lipshultz SE, *et al*. Dilated cardiomyopathy (Primer). *Nature Rev Dis Primers* 2019; **5**(1).
8. Hershberger RE, Jordan E. Dilated cardiomyopathy overview. *Genereviews®* [internet]. 2022. https://www.ncbi.nlm.nih.gov/books/
9. Charron P, Arad M, Arbustini E, Basso C, Bilinska Z, Elliott P, *et al.* Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2010; **31**(22): 2715–2726.
10. Rapezzi C, Arbustini E, Caforio AL, Charron P, Gimeno-Blanes J, Heliö T, *et al.* Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013; **34**(19): 1448–1458.
11. McKenna C, Codd M, McCann H, Sugrue D. Idiopathic dilated cardiomyopathy: familial prevalence and HLA distrition. *Heart* 1997; **77**(6): 549–552.
12. Michels VV, Moll PP, Miller FA, Tajik AJ, Chu JS, Driscoll DJ, *et al*. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. *N Engl J Med* 1992; **326**(2): 77–82.
13. Goerss J, Michels V, Burnett J, Driscoll D, Miller F, Rodeheffer R, *et al*. Frequency of familial dilated cardiomyopathy. *Eur Heart J* 1995; **16**(suppl_O): 2–4.
14. Grünig E, Tasman JA, Kücherer H, Franz W, Kübler W, Katus HA. Frequency and phenotypes of familial dilated cardiomyopathy. *J Am Coll Cardiol* 1998; **31**(1): 186–194.
15. Baig MK, Goldman JH, Caforio AL, Coonar AS, Keeling PJ, McKenna WJ. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. *J Am Coll Cardiol* 1998; **31**(1): 195–201.
16. Mahon NG, Murphy RT, MacRae CA, Caforio AL, Elliott PM, McKenna WJ. Echocardiographic evaluation in asymptomatic relatives of patients with dilated cardiomyopathy reveals preclinical disease. *Ann Int Med* 2005; **143**(2): 108–115.
17. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, *et al*. Genetic evaluation of cardiomyopathy – a Heart Failure Society of America practice guideline. *J Cardiac Fail* 2018; **24**(5): 281–302.
18. Ntusi NB, Wonkam A, Shaboodien G, Badri M, Mayosi BM. Frequency and clinical genetics of familial dilated cardiomyopathy in Cape Town: Implications for the evaluation of patients with unexplained cardiomyopathy. *S Afr Med J* 2011; **101**(6): 394–398.
19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande

L, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**(3): 233–271.

20. Shahgaldi K, Gudmundsson P, Manouras A, Brodin L-Å, Winter R. Visually estimated ejection fraction by two dimensional and triplane echocardiography is closely correlated with quantitative ejection fraction by real-time three dimensional echocardiography. *Cardiovasc Ultrasound* 2009; **7**(1): 1–7.
21. Keeling P, Gang Y, Smith G, Seo H, Bent S, Murday V, *et al.* Familial dilated cardiomyopathy in the United Kingdom. *Heart* 1995; **73**(5): 417–421.
22. Moretti M, Merlo M, Barbati G, Di Lenarda A, Brun F, Pinamonti B, *et al*. Prognostic impact of familial screening in dilated cardiomyopathy. *Eur J Heart Fail* 2010; **12**(9): 922–927.
23. Zachara E, Caforio A, Carboni GP, Pellegrini A, Pompili A, Del Porto G, *et al*. Familial aggregation of idiopathic dilated cardiomyopathy: clinical features and pedigree analysis in 14 families. *Heart* 1993; **69**(2): 129–135.
24. Mestroni L, Rocco C, Gregori D, Sinagra G, Di Lenarda A, Miocic S, *et al*. Familial dilated cardiomyopathy: evidence for genetic and phenotypic heterogeneity. *J Am Coll Cardiol* 1999; **34**(1): 181–190.
25. Jain A, Norton N, Bruno KA, Cooper Jr LT, Atwal PS, Fairweather D. Sex differences, genetic and environmental influences on dilated cardiomyopathy. *J Clin Med* 2021; **10**(11): 2289.
26. Fairweather D, Cooper Jr LT, Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy. *Curr Prob Cardiol* 2013; **38**(1): 7–46.
27. De Paepe A, Kluyskens Y, Van Durme J, Naudts K, Claeys R, De Wagter X. Familial idiopathic dilated cardiomyopathy (IDC). *Acta Cardiol* 1991; **46**(5): 577–582.
28. Fatkin D, Johnson R, McGaughran J, Weintraub RG, Atherton JJ. Position statement on the diagnosis and management of familial dilated cardiomyopathy. *Heart Lung Cir* 2017; **26**(11): 1127–1132.
29. Pallangyo P, Mkojera ZS, Hemed NR, Swai HJ, Misidai N, Mgopa L, *et al.* Obesity epidemic in urban Tanzania: a public health calamity in an already overwhelmed and fragmented health system. *BMC Endocrine Disord* 2020; **20**(1): 1–9.