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ORIGINAL ARTICLE

Dilated cardiomyopathy in a national paediatric population

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Abstract

Dilated cardiomyopathy is the most common form of childhood cardiomyopathy and is known to result in significant morbidity and mortality. This study aims to review the aetiology and associated outcomes of DCM. The median age at diagnosis was 6 months (0–42 months); $n = 23$ (43.3%) were idiopathic; $n = 11$ (20.9%) secondary to a viral infection; $n = 12$ (22.6%) genetic disorders and $n = 7$ (13.2%) as a result of vitamin D deficiency. There was a significant correlation between aetiology and mortality, $r = 0.85$, with a lower survival rate in idiopathic and genetic cohorts. Males were significantly less likely to survive to 1 year of age, $p = 0.035$. The age at diagnosis did not alter survival to 1 year and the predicted survival beyond 1 year was 84.3% (95% CI, 71.3 to 94.5%). Severely impaired left ventricular fractional shortening at presentation (< 15%) was an independent predictor of death, $p = 0.002$, (95% CI, 11.2 to 14.2%).

Conclusion: Paediatric DCM is a heterogeneous disease resulting in significant morbidity. The aetiology alters the age of presentation. Identification of a specific cause is a useful for risk stratification and prognostication. The first year after diagnosis is a critical time period reflected by the significant morbidity and mortality.

What is Known:
- *Paediatric dilated cardiomyopathy (DCM) is the commonest of the childhood cardiomyopathies, with significant associated morbidity and mortality.*
- *DCM is most commonly idiopathic.*

What is New:
- *Identifying the aetiology of DCM in the paediatric population aids risk stratification and prognostication.*
- *The first year after diagnosis of DCM is associated with significant mortality.*

Keywords Dilated cardiomyopathy · Myocarditis · Vitamin D deficiency

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Abbreviations

ECLS	Extra-corporeal life support
DCM	Dilated cardiomyopathy
FS	Fractional shortening
MPS	Mucopolysaccharidosis
PCR	Polymerase chain reaction
SCD	Sudden cardiac death
SIMD	Scottish Index of Multiple Deprivation

Introduction

Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy in children [1]; defined by the World Health Organization as a disorder 'characterized by dilation and impaired contraction of the left ventricle or both ventricles' in the presence of normal wall thickness [2, 3]. The onset of the

disease may be subtle and insidious, or alternatively acute and life-threatening. At initial presentation, DCM may be mistakenly diagnosed as an isolated respiratory tract infection or viral illness, and not initially considered a differential diagnosis unless cardiomegaly is detected on a chest x-ray; failure to respond to conventional supportive management or profound cardiovascular collapse. Despite advances in the diagnosis and medical management of paediatric DCM, the morbidity, mortality and impact on hospital admissions remain significant [4]. The aim of our study was to review the aetiology of dilated cardiomyopathy and the associated outcomes in a national paediatric population.

Methods

A retrospective data review of 53 consecutive cases of DCM, aged < 18 years, diagnosed in a national paediatric cardiology centre from September 1, 2000, to September 1, 2018. The departmental database Heartsuite (Heartsuite, Systeria, Glasgow, UK) was used to identify patients and provide initial patient data. In addition, electronic and paper case notes were reviewed to identify the age at presentation; aetiology; need for intensive care support; mechanical ventilation; inotropic support; extra-corporeal life support (ECLS); cardiac transplantation and the associated long-term mortality. In order to determine potential links between deprivation and the incidence of DCM, the Scottish Index of Multiple Deprivation (SIMD) was utilized. SIMD is a tool employed by the Scottish government to identify areas of multiple deprivation in Scotland. The index scores Scottish regions from one to five, where five indicates the lowest level of deprivation.

Patients with structural heart disease, cardiomyopathy secondary to sustained arrhythmias or coronary artery disease were excluded from the study. Diagnosis was based upon clinical features of heart failure and echocardiographic evidence of global systolic dysfunction; left ventricular diastolic dimensional Z score of more than two standard deviations above normal, and a fractional shortening (FS), by m-mode, less than 25%. Global speckle strain imaging is currently used in our centre to assess left ventricular systolic function; however, this modality was not utilized routinely in the early cohort. Transthoracic echocardiography was used as a diagnostic tool and to monitor disease progression. Measurements of left ventricular cavity and wall-thickness at end diastole, end systole, as well as estimation of fractional shortening and ejection fraction were documented in all cases. Resolution of DCM was defined in the absence of clinical features of heart failure; normal fractional shortening and normal left ventricular dimensions reported by transthoracic echocardiography. All patients presenting with DCM in our institution undergo an extensive panel of investigation including gene panels, metabolic investigation and viral studies by PCR. Myocardial biopsy is not routinely undertaken.

Statistical analyses were performed to determine factors associated with survival to 1 year. Associations between categorical variables and survival were investigated using chi-squared, or chi-squared tests for trend. Numerical variables were tested using *t* tests or the Mann-Whitney tests as appropriate for the distribution of the data. All analyses were done using Minitab (version 17).

Results

Fifty-three consecutive patients were diagnosed with DCM during the study period; the demographics are illustrated in Table 1.

The median age at diagnosis was 6 months (range 0–42 months) with 38 (71%) patients diagnosed within the first year of life and 52 (98%) cases diagnosed before the child's second birthday (Fig. 1). DCM was more common among girls, 31 (58.5%) cases compared with 22 (41.5%) in the male population. Male to female ratio is 1:1.4. Survival to 1 year

Table 1 Patient demographics

Patients	*n* = 53
• Female	*n* = 31 (58.5%)
• Male	*n* = 22 (41.5%)
Ethnicity	
• Caucasian	*n* = 40 (75.4%)
• Black	*n* = 10 (18.9%)
• Asian	*n* = 3 (5.7%)
Aetiology	
• Idiopathic	*n* = 23 (43.3%)
• Viral	*n* = 11 (20.9%)
• Genetic	*n* = 12 (22.6%)
• Vitamin D deficiency	*n* = 7 (13.2%)
Median age at diagnosis (range)	6 months (0–42)
• Genetic	4 months (0–14)
• Vitamin D deficiency	7 months (0–9)
• Viral	14 months (0–23)
• Idiopathic	6 months (0–42)
Echocardiographic features (range)	
• Fractional shortening (median)	12.1% (2–25%)
• Ejection fraction, M-mode (median)	32% (8–59%)
• LVDED (median)	37.5 mm (14–56)
Outcomes	
• Transplant assessment	*n* = 23 (43%)
• Heart transplantation	*n* = 4 (7.5%)
• Overall mortality	*n* = 11 (20.7%)
• Survival at 1 year	*n* = 43 (84.3%)

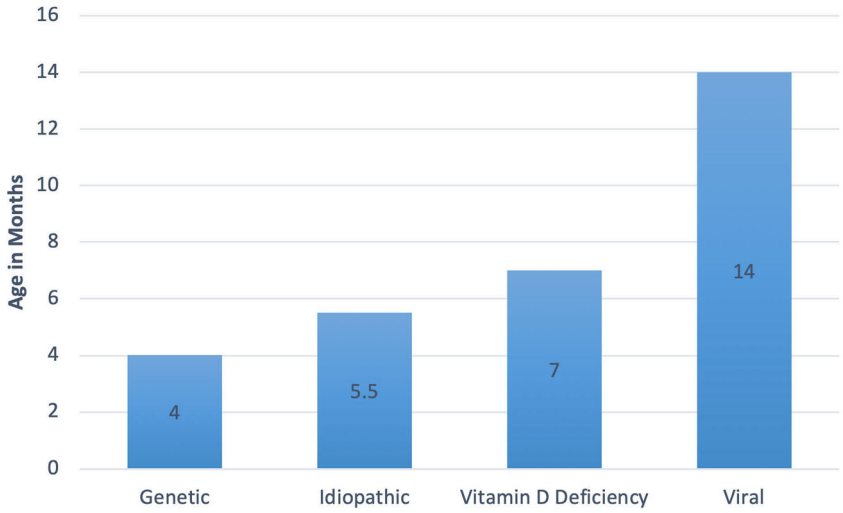

Fig. 1 Median age at presentation

after the initial diagnosis was significantly lower in the male population ($p = 0.035$), only three females did not survive. In our study population, 82% of children were Caucasian; 18.9% Black and 5.7% of Asian ethnicity. The median SIMD score was three and further analysis did not demonstrate a significant association between the incidence, mortality and the SIMD score.

Presenting features

The presenting clinical features varied in severity; 62% ($n = 33$) had overt signs of heart failure—six patients presenting with heart failure had severe cardiovascular compromise requiring resuscitation and immediate paediatric intensive care admission; 15% ($n = 8$) had isolated respiratory symptoms at presentation; 11% ($n = 6$) presented with failure to thrive and feeding difficulties. Other presenting signs or symptoms included supraventricular tachycardia 2% ($n = 1$), heart murmur 2% ($n = 1$), hydrops fetalis 2% ($n = 1$), cardiomegaly on antenatal scan 2% ($n = 1$), seizures 2% ($n = 1$) and congenital nephrotic syndrome 2% ($n = 1$).

Aetiology

$N = 23$ (43.3%) of the study population were classified as idiopathic; no cause was identified despite extensive investigations. Even when presenting with signs and symptoms of a viral illness, and despite extensive virology work up, no viruses were isolated by PCR. Endomyocardial biopsy was not routinely undertaken in our patients. When viruses were identified, this was the commonest identifiable cause of DCM, evident in 20.9% of cases, $n = 11$; 69% were secondary to Parvovirus B19; and 31% due to enteroviruses (Fig. 2). There was evidence of seasonal variation, with a peak incidence of DCM in the autumn months; $n = 18$, 34% (Figs. 3 and 4).

$N = 12$ (22.6%) of DCM had an associated, identifiable metabolic, or genetic abnormality: MYH7 mutation ($n = 4$); Barth's syndrome ($n = 1$); combination of Barth's syndrome and MYH7 mutation ($n = 1$); long-chain CoA dehydrogenase deficiency ($n = 1$), I-cell disease ($n = 1$); TCAP gene mutation ($n = 1$); Pierson syndrome ($n = 1$); MYPBC3 mutation ($n = 1$); and TNNT2 mutation ($n = 1$). Within the genetic cohort, the male to female ratio was higher 1.8:1 in comparison to the total population. Due to the small sample size the chi-squared test was not significant.

Severe vitamin D deficiency DCM was reported in 13% ($n = 7$), four children were of Asian or Black descent and three were Caucasian. Six patients with severe vitamin D deficiency underwent a full and rapid recovery after receiving oral supplementation, including one child requiring ECLS as a bridge to recovery. One family did not comply with vitamin supplementation; dietary manipulation, and clinical monitoring, the

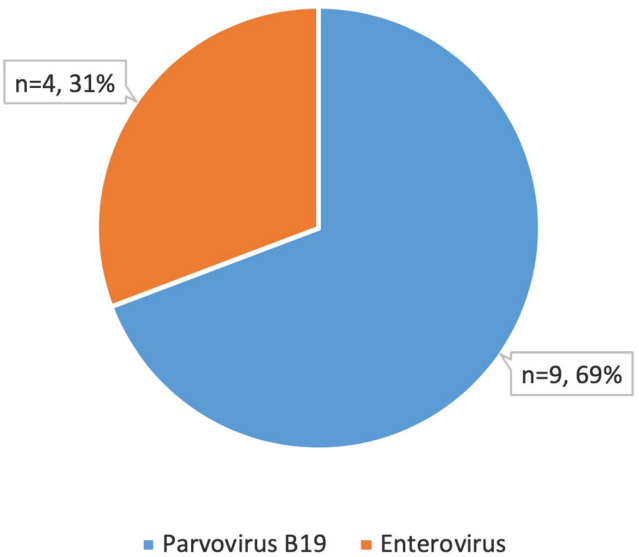

Fig. 2 Viral aetiology

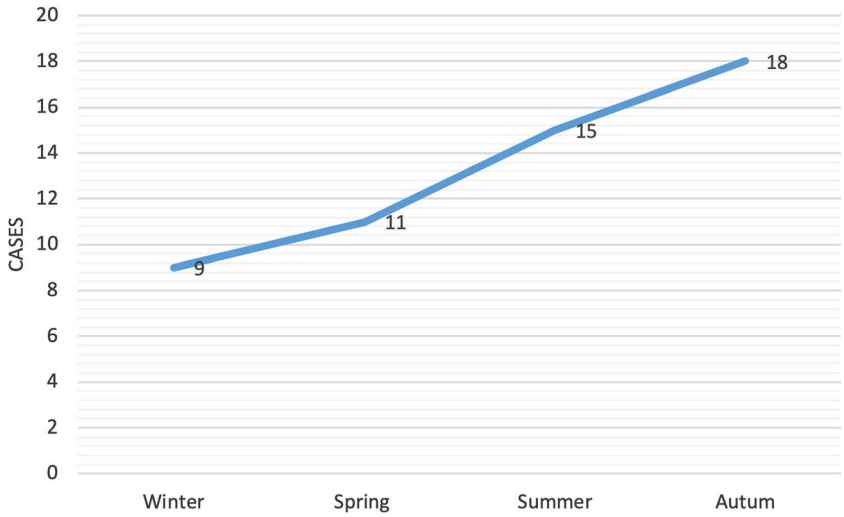

Fig. 3 Overall Seasonal variation

patient sadly decompensated and represented in end-stage heart failure. There was a significant correlation between aetiology and mortality, $r = 0.85$, with a lower survival rate in idiopathic and genetic cohorts (Fig. 5).

$N = 33$ (62%) of the DCM population required inotropic support, $n = 28$ (52%) required mechanical ventilation and $n = 8$ (15%) required ECLS as a bridge to recovery or cardiac transplant, of which five patients survived and made a full clinical and echocardiographic recovery. Transplantation is routinely discussed with families in the presence of escalating intensive care support and cardiovascular instability. In our population, 23 families (43%) consented to transplant referral (Fig. 6). Of the patients discussed, $n = 7$ were placed on the non-urgent transplant list, and all were subsequently removed from the list after resolution of the DCM. In contrast, a total of 16 were accepted onto the urgent transplant list: $n = 4$ restored normal cardiac function and were subsequently removed from the list; $n = 4$ are still alive but awaiting transplantation; $n = 4$ died awaiting transplant; and $n = 4$ were successfully transplanted and are alive to date.

Mortality

The survival from initial diagnosis to 1 year post diagnosis was 84.3%; the median age at diagnosis did not alter survival to 1 year (Fig. 7). Observationally, more deaths occurred in the winter months; however, the sample size was too small for formal statistical analysis. Males were more likely to have DCM secondary to a genetic or metabolic disorder (p value = 0.020) and were statistically less likely to survive to 1 year from diagnosis (p value = 0.035). Seven (13%) males died within the first year of diagnosis: one MYH7 gene positive, one long-chain fatty oxidation disorder, one of viral aetiology, and four idiopathic DCM. In contrast, only three (5.6%) females died within the first year of diagnosis: one secondary to idiopathic DCM, one of vitamin D deficiency and one with

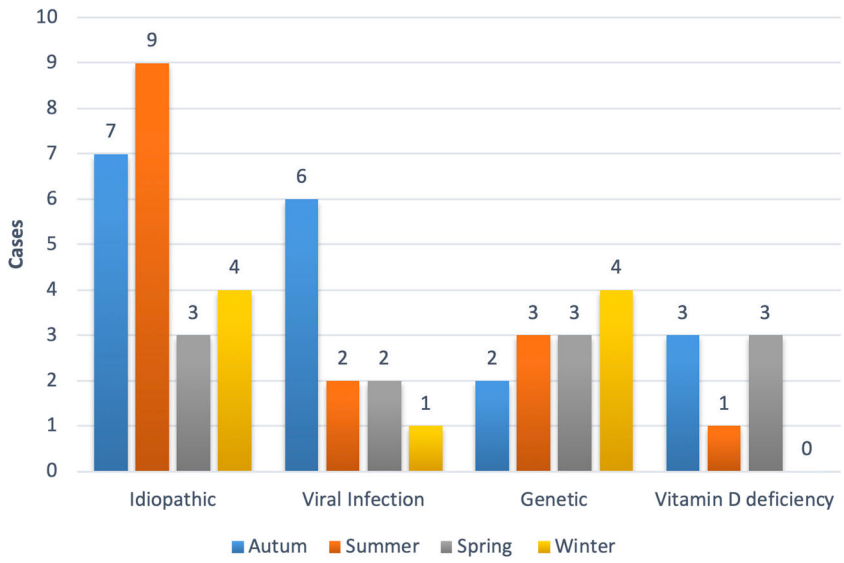

Fig. 4 Seasonal variation in aetiology

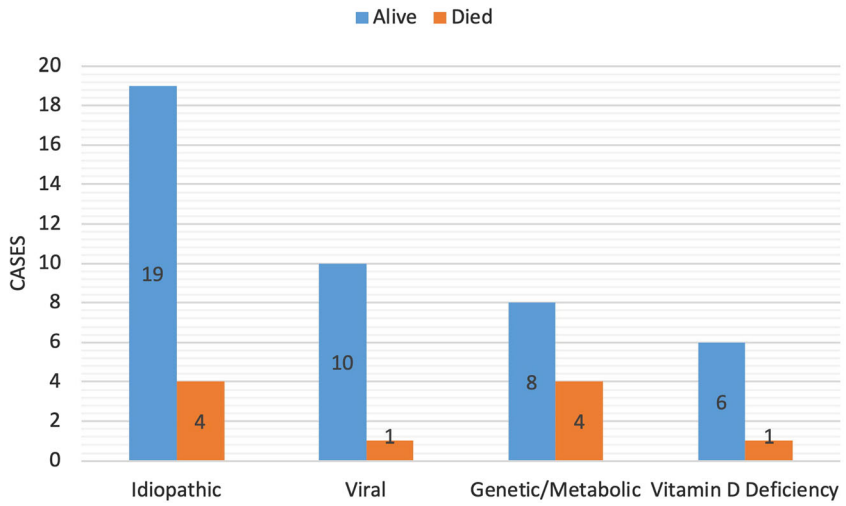

Fig. 5 Aetiology and mortality

Pierson syndrome. Children requiring ECLS were less likely to survive, but this did not reach statistical significance at the 95% CI level (p value = 0.106) which could be due to the smaller sample size.

Discussion

Dilated cardiomyopathy is a heterogeneous disease with reported prevalence in the paediatric population ranging from 1 in 140,000 to 170,000 [5]. Milder cases of dilatation may be detected during familial screening for DCM, as in our cohort; however, the majority of children presenting in the first 2 years of life are symptomatic at presentation. In the future, wider use of genetic testing may identify asymptomatic carriers of DCM in the paediatric population. Recent advances have been made in the understanding of the genetic aetiology of DCM. Hershberger et al. identified more than 30 genes of various ontologies which may contribute to 40–50% of genetic DCM [6, 7].

Despite advances, a significant proportion of paediatric DCM cases remain classified as idiopathic, in some studies as many as 66% of the reported cases [8]. Our study confirms that a significant proportion of paediatric DCM is idiopathic

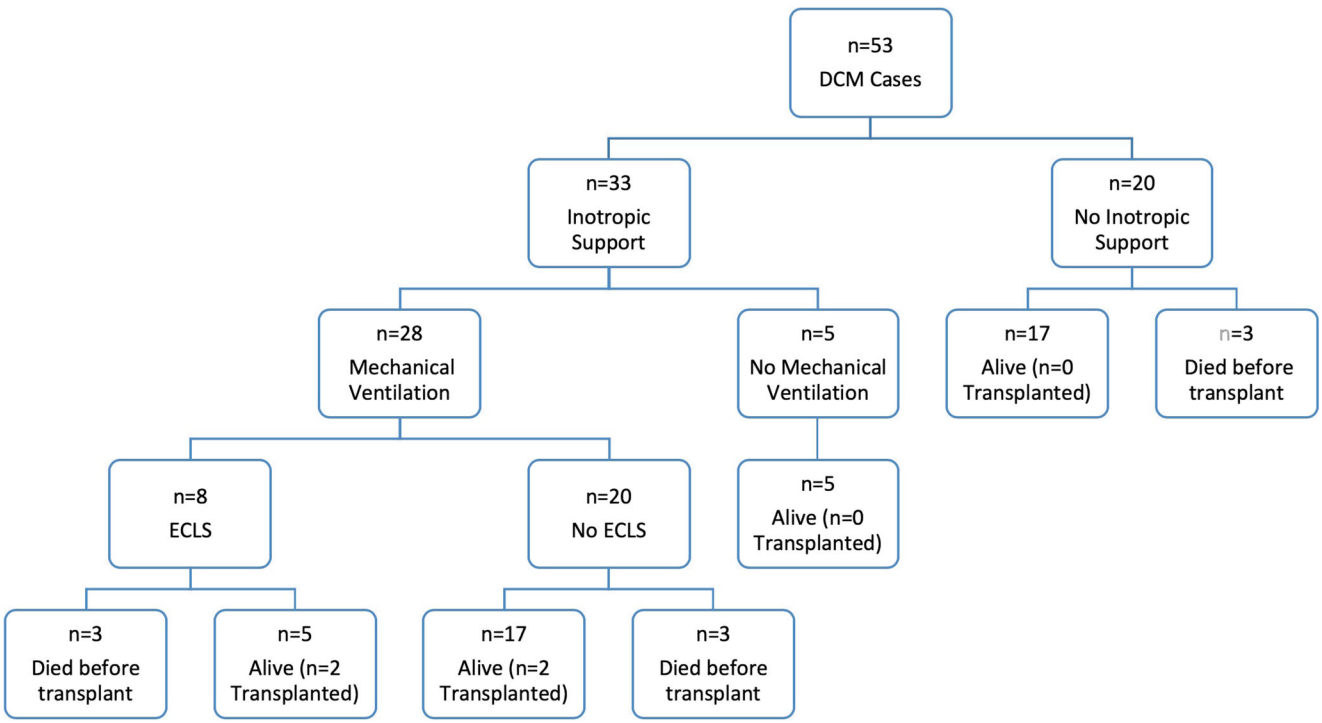

Fig. 6 Outcome after DCM diagnosis

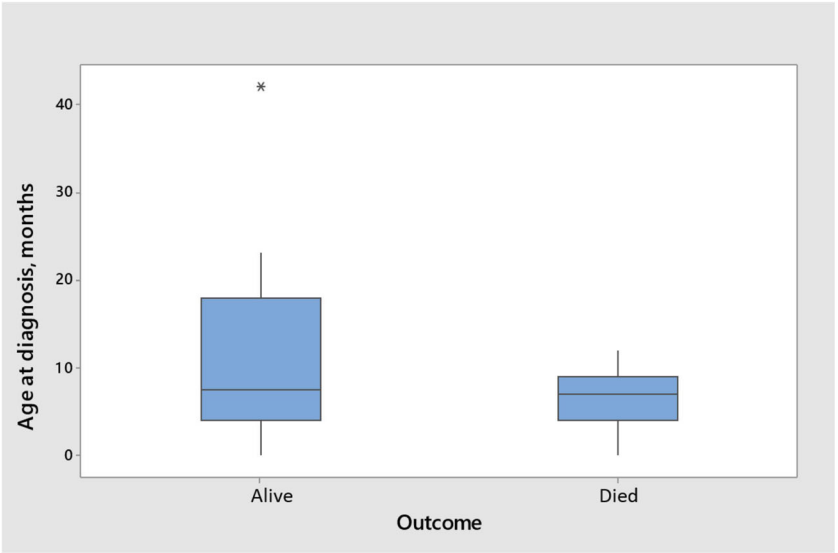

Fig. 7 Outcome related to survival

despite comprehensive metabolic, genetic investigations, and viral PCR. An endomyocardial biopsy is not a first-line investigation for DCM within our cardiac centre, thus in some cases a viral aetiology may not have been identified. Identifying an aetiology, where possible, is a useful tool for clinicians to provide risk stratification and prognostication for families. This is particularly true in the rarer cause of dilated cardiomyopathy, secondary to vitamin D deficiency. Vitamin D is a steroid hormone which binds nuclear receptors in the heart altering gene transcription [9]. Exposure of ultraviolet radiation on the skin is a crucial source of vitamin D and ethnic groups with darker skin in the UK are at greater risk, particularly between October and the beginning of April [10]. A retrospective review by Maiya et al. identified 16 paediatric patients with DCM secondary to vitamin D deficiency over a 6-year period in the South East of England [11]. All patients were of non-Caucasian ethnicity. Our study confirms that vitamin D deficiency cardiomyopathy is reversible with prompt identification and supplementation; in addition, the ECLS can successfully be used as a bridge to recovery in this cohort [12]. The role of vitamin D and cardiac function is an area of increasing study, demonstrated by the VINDICATE (vitamin D treating patients with chronic heart failure) trial in the adult population with chronic heart failure. Witte et al. demonstrated that administering a high dose of vitamin D in addition to optimal medical heart failure therapy increased left ventricular ejection fraction by 8% [13].

In spite of optimal medical management, our study confirms the first year of life is a critical period for outcome and other studies concur that a significant proportion of children will be re-hospitalized and/or require cardiac transplantation within 1 year of presentation [14, 15]. Puggia et al. demonstrated an 82% survival at 1 year; 71% and 68% survival at 6 and 9 years respectively. Their data also suggested that idiopathic DCM in the paediatric population has a poorer prognosis than the adult DCM population, even when the baseline left ventricular function was higher [5]. An Australian study by Daubenay et al. reported freedom from death or transplantation at 1 and 5 years respectively, 72% and 63%. Risk factors for a poorer outcome included familial dilated cardiomyopathy; age > 5 years at diagnosis and a lower fractional shortening at presentation [16]. This study found that fractional shortening at diagnosis less than 15% was an independent predictor of death.

An earlier study from our institution examining the outcome of DCM in the paediatric population of Scotland between 1980 and 1997 also reported all deaths occurring within the first year of life. Survival at 1 year and 9 years was 69% [17]. Our recent study demonstrates that mortality in this cohort remains significant, but has improved in the modern era, 2000–2018, with survival to 1 year 84.3%, and no cardiac deaths after 1 year in the current follow-up. This may reflect continual improvements in the medical management of heart failure, advances in intensive care support and the provision of ECLS.

Bharucha et al. reported the risk of sudden cardiac death (SCD) in the DCM population at 5% (95% CI, 2% to 11%) after 15 years of follow-up and increased risk if familial DCM, older age at diagnosis and lower fractional shortening at diagnosis [18]. This study found no evidence of SCD once the left ventricular function had normalized. In addition, Dimas et al. demonstrated a 1% risk of SCD in the paediatric idiopathic DCM population, in contrast to the adult DCM population ranging from 20 to 75% [19]. In the paediatric population with severe DCM, cardiac transplantation is the final recourse in the management of terminal heart failure [14]. with DCM continuing to be the most common indication for heart transplantation in children over the age of five [2].

Limitations

This cohort included all cases of dilated cardiomyopathy referred to a national centre; however, the study was retrospective and due to the nature of the condition the sample size was small, therefore some data did not reach statistical significance.

Conclusion

Paediatric dilated cardiomyopathy is a heterogeneous disease, with unidentified aetiology in around 43% of cases. In the paediatric population, the aetiology alters the age at presentation and is a useful tool to provide risk stratification and prognostication. Severely impaired left ventricular fractional shortening at presentation is an independent predictor of death. The first year after a diagnosis of DCM is a critical time reflected in significant morbidity and mortality.

Authors' Contributions Dr. Jammal Addin conceptualized and designed the study, drafted the manuscript, interpreted the data and completed all subsequent revisions until submission; Dr. Young carried out the statistical analysis and critically reviewed the manuscript; Dr. McCarrison assisted with drafting the manuscript, the design and conduct of the study; Dr. Hunter conceptualized and designed the study, advised in presentation of analysis results, and revised the drafts critically for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, Lurie PR, McCoy KL, McDonald MA, Messere JE, Colan SD (2003) The Incidence of Pediatric Cardiomyopathy in Two Regions of the United States. N Engl J Med 348(17):1647-1655.https://doi.org/10.1056/NEJMoa021715
2. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, Olsen E, Thiene G, Goodwin J, Gyarfas I, Martin I, Nordet P (1996) Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation 93(5):841–842
3. Kirk R, Naftel D, Hoffman TM, Almond C, Boyle G, Caldwell RL, Kirklin JK, White K, Dipchand AI, Pediatric Heart Transplant Study Investigators (2009) Outcome of pediatric patients with dilated cardiomyopathy listed for transplant: a multi-institutional study. J Heart Lung Transplant 28(12):1322–1328
4. Association AH (2015) Dilated cardiomyopathy. Dilated cardiomyopathy in children. AHA. http://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable/ucm_312224.pdf
5. Puggia I, Merlo M, Barbati G, Rowland TJ, Stolfo D, Gigli M, Ramani F, di Lenarda A, Mestroni L, Sinagra G (2016) Natural history of dilated cardiomyopathy in children. J Am Heart Assoc 5(7).
6. Hershberger RE, Hedges DJ, Morales A (2013) Dilated cardiomyopathy: the complexity of a diverse genetic architecture. Nat Rev Cardiol 10(9):531–547
7. Mestroni L, Brun F, Spezzacatene A, Sinagra G, Taylor MR (2014) Genetic causes of dilated cardiomyopathy. Prog Pediatr Cardiol 37(1–2):13–18
8. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, Messere J, Cox GF, Lurie PR, Hsu D, Canter C, Wilkinson JD, Lipshultz SE (2006) Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA 296(15):1867–1876
9. Gupta DK, Wang TJ (2016) Looking for a brighter future in heart failure: a role for vitamin D supplementation? J Am Coll Cardiol 67(22):2604–2606
10. Yilmaz O, Olgun H, Ciftel M, Kilic O, Kartal I, Iskenderoglu NY, Laloglu F, Ceviz N (2015) Dilated cardiomyopathy secondary to rickets-related hypocalcaemia: eight case reports and a review of the literature. Cardiol Young 25(2):261–266
11. Maiya S, Sullivan I, Allgrove J, Yates R, Malone M, Brain C, Archer N, Mok Q, Daubeney P, Tulloh R, Burch M (2008) Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. Heart 94(5):581–584
12. Brown J, Nunez S, Russell M, Spurney C (2009) Hypocalcemic rickets and dilated cardiomyopathy: case reports and review of literature. Pediatr Cardiol 30(6):818–823
13. Witte KK, Byrom R, Gierula J, Paton MF, Jamil HA, Lowry JE, Gillott RG, Barnes SA, Chumun H, Kearney LC, Greenwood JP, Plein S, Law GR, Pavitt S, Barth JH, Cubbon RM, Kearney MT (2016) Effects of vitamin D on cardiac function in patients with chronic HF: the VINDICATE study. J Am Coll Cardiol 67(22):2593–2603
14. Hollander SA, Bernstein D, Yeh J, Dao D, Sun HY, Rosenthal D (2012) Outcomes of children following a first hospitalization for dilated cardiomyopathy. Circ Heart Fail 5(4):437–443
15. Alexander PM, Daubeney PE, Nugent AW et al (2013) Long-term outcomes of dilated cardiomyopathy diagnosed during childhood: results from a national population-based study of childhood cardiomyopathy. Circulation 128(18):2039–2046
16. Daubeney PE, Nugent AW, Chondros P et al (2006) Clinical features and outcomes of childhood dilated cardiomyopathy: results from a national population-based study. Circulation 114(24):2671–2678
17. Venugopalan P, Houston AB, Agarwal AK (2001) The outcome of idiopathic dilated cardiomyopathy and myocarditis in children from the west of Scotland. Int J Cardiol 78(2):135–141
18. Bharucha T, Lee KJ, Daubeney PE, Nugent AW, Turner C, Sholler GF, Robertson T, Justo R, Ramsay J, Carlin JB, Colan SD, King I, Weintraub RG, Davis AM, NACCS (National Australian Childhood Cardiomyopathy Study) Investigators (2015) Sudden death in childhood cardiomyopathy: results from a long-term national population-based study. J Am Coll Cardiol 65(21):2302–2310
19. Dimas VV, Denfield SW, Friedman RA, Cannon BC, Kim JJ, Smith EO'B, Clunie SK, Price JF, Towbin JA, Dreyer WJ, Kertesz NJ (2009) Frequency of cardiac death in children with idiopathic dilated cardiomyopathy. Am J Cardiol 104(11):1574–1577