Cardiomyopathy as cause of death in Duchenne muscular dystrophy: a longitudinal observational study

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Cardiac death is the most common cause of death in adult patients with Duchenne muscular dystrophy on home mechanical ventilation, and low left ventricular ejection fraction in Duchenne cardiomyopathy is strongly associated with reduced survival https://bit.ly/43md86m

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Abstract

Background Cardiomyopathy has become an important life-limiting factor since survival in Duchenne muscular dystrophy (DMD) has greatly increased with long-term ventilation and cough assistance. The aim of this study was to investigate the association between impaired left ventricular ejection fraction (LVEF) and survival.

Methods In a >20-year observational study in patients with DMD (age ⩾16 years) with at least three echocardiograms, the association between LVEF and survival and time to cardiac or non-cardiac death was investigated using Kaplan–Meier survival analysis and Cox regression (for LVEF).

Results In 67 DMD patients (430 echocardiograms), the decrease in LVEF over a mean±SD follow-up period of 9.1±5.1 years was −10.0±13.9% absolute, but LVEF progression varied widely. 84% were receiving an angiotensin-converting enzyme inhibitor and 54% a β-blocker at last follow-up with an LVEF of 37.5±12.4% at that time-point. Median (interquartile range) survival was 33 (25–40) years. 28 out of 67 (42%) of the cohort had died and LVEF was a significant negative predictor of survival (hazard ratio 0.95 (95% CI 0.91–0.99); p<0.007). Those who died of cardiac death (53% of known causes of death) had significantly lower LVEF at the time of death (LVEF −11.0% (95% CI −21.1– −0.9%); p=0.035) compared with non-cardiac death and tended to die at a younger age.

Conclusions Cardiomyopathy with systolic heart failure is the leading cause of death and lower LVEF is an independent predictor of mortality at younger ages in patients with DMD. Patients with DMD appear to be undertreated with respect to heart failure drug therapy.

Introduction

Duchenne muscular dystrophy (DMD) is the most common form of hereditary muscular dystrophy and affects about 1:3500 males [1]. DMD results from a mutation in the Xp21 gene, which codes for dystrophin, a sarcolemmal protein in skeletal and cardiac muscle cells [2]. It is usually diagnosed in early childhood and follows a more or less predictable course with progressive skeletal muscle weakness and loss of ambulation at ∼12 years of age and the need for ventilatory support due to ventilatory failure secondary to respiratory muscle weakness at ∼18–20 years of age [3–6]. Not only skeletal muscle but also cardiac muscle is affected and cardiomyopathy with development of heart failure with reduced ejection fraction usually occurs before adulthood. After the introduction of long-term home mechanical ventilation (HMV) [7], either as noninvasive or invasive home ventilation, respiratory physiotherapy including cough assistance and interdisciplinary care, the median survival has been prolonged from <20 years to >30 years or even >35 years in some countries [7–12]. Quality of life in HMV is remarkably good and stable despite progressive physical disability and ventilator dependence [13, 14]. Death often occurs in mid-adulthood due to respiratory failure, cardiac failure or gastrointestinal complications [13, 15, 16]. The main

life-limiting factor in DMD has been respiratory failure, but progressive cardiomyopathy has become an important determinant of survival when patients are treated with HMV properly. The role of heart failure therapy on survival is less clear. It is important to remember that much of the research on DMD tends to focus on the paediatric group and there are fewer clinical studies in the adult DMD population. The natural history of cardiomyopathy and possible influencing factors have not been extensively studied in this patient group. It would be logical that the specific changes in complex dystrophin gene function play a key role (complete or almost complete loss of dystrophin and a concomitant decrease in all dystrophin-associated glycoproteins in muscle). However, identical dystrophin genotypes can have very different cardiorespiratory phenotypes [5].

Cardiomyopathy presents as dilated cardiomyopathy with diffuse hypokinesia. Histologically, DMD muscle changes are characterised by myonecrosis, reactive myofibrosis, fatty substitution and chronic inflammation [17, 18]. Early evaluation and regular follow-up by a cardiologist should be standard treatment for DMD. Physicians should be aware that the typical signs and symptoms of heart failure may not be present in DMD due to previous loss of ambulation and physical inactivity. DMD cardiomyopathy, because of its manifestation as part of a systemic disease, is often treated less aggressively and not according to general heart failure guidelines. Reasons for this may include the progressive underlying disease associated with respiratory failure, the lack of typical heart failure symptoms in patients who are wheelchair dependent and ventilated, the potentially higher complication rate with device implantation (*e.g.* defibrillator or pacemaker), and most importantly, the small evidence base for heart failure management in this rare condition. Data on cardiac outcomes are sparse and evidence on drug therapy is not always consistent. Nevertheless, guidelines recommend that echocardiography is performed regularly and heart failure treatment initiated and adjusted periodically as the disease progresses [4]. Regular Holter ECG monitoring should also be performed to look for relevant arrhythmias. Cardiac arrhythmias are also common, but malignant ventricular arrhythmias appear to be less frequent in DMD cardiomyopathy compared with other types of cardiomyopathies with severely reduced ejection fraction, especially less frequent than in ischaemic cardiopathy. DMD patients have not been included in clinical trials of heart failure therapy, and treatment recommendations are based on evidence from other populations with heart failure and expert consensus. The literature on the effect of angiotensin-converting enzyme inhibitors (ACE-Is) or β-blockers in Duchenne patients is sparse [19–21]. Little is known about the factors that might influence the course of cardiomyopathy, which is only in part genetically determined.

In this vulnerable population with a rare, inherited disease, conducting randomised controlled intervention trials is challenging, and despite the risk of various sources of bias, cohort studies are needed to understand the effect of interventions and to generate hypotheses that can be tested in controlled trials.

The aim of this study was to analyse the role of left ventricular ejection fraction (LVEF) as a severity marker of cardiomyopathy on survival and to identify predictors of cardiomyopathy progression. The hypothesis of earlier death with more severely impaired LVEF was investigated in a longitudinal analysis in a retrospective cohort study of patients with DMD treated at the University Hospital Zurich.

Methods

Patient population

Patients with DMD (age ⩾16 years) treated and followed up in the Department of Pulmonology at the University Hospital Zurich (Zurich, Switzerland) were eligible to participate. To participate in the study, echocardiographies in stable condition (*e.g.* not from an intensive care unit or from an emergency situation) had to be available in at least three different age groups (by year) per patient. These patients were followed up regularly as part of a standardised interdisciplinary care programme for DMD patients, including pulmonary function tests, arterial blood gas analysis, sleep study including transcutaneous capnometry and echocardiography.

Study design and measures

For this retrospective longitudinal study, coded personal health records of DMD patients treated in the Department of Pulmonology between 1996 and 2022 were used. This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the Zurich Cantonal Ethics Committee (BASEC 2022–02316). Demographic data, heart failure medications, echocardiography, resting ECG, respiratory function tests, arterial blood gas analyses, sleep studies (transcutaneous capnometry and pulse oximetry or respiratory polygraphy and transcutaneous capnometry), ventilator statistics and body mass index at regular follow-up (usually every 6–12 months) during treatment at our adult centre were collected.

Outcomes

The main outcomes were the time course of LVEF in relation to age and the association of LVEF with survival. An additional outcome was the association of predefined potential predictive factors with LVEF decline in cardiomyopathy in DMD (heart failure medications, respiratory failure classified by arterial partial pressure of carbon dioxide (P_{aCO_2}), bicarbonate concentration (HCO_3^-) and nocturnal transcutaneous partial pressure of carbon dioxide (P_{tcCO_2})), forced vital capacity (FVC), HMV, age at onset of HMV and type of dystrophin mutation. Another outcome of interest was the percentage of deaths due to cardiac causes.

Statistical analysis

Continuous data were expressed as mean with standard deviation or median (interquartile range (IQR)) and dichotomous data as number (%). For continuous variables, normality of distribution was tested using the Shapiro–Wilk test. Independent t-tests and tests of proportions were used for comparisons between groups for cardiac and non-cardiac death, respectively. For LVEF, Kaplan–Meier survival analysis with Cox regression was performed. Log-rank tests were used to compare equality of time to event. Linear regression models were used to determine the association between the independent variables and the change in LVEF (dependent variable). Multivariable regression analysis was performed to examine which factors (prespecified factors) were associated with the change in LVEF. Stata version 15.1 (StataCorp, College Station, TX, USA) and Prism (GraphPad, Boston, MA, USA) were used for statistical analysis and visualisation.

Results

Patient cohort

Of 90 patients with DMD treated at our adult centre between 1996 and 2022, 67 had at least three echocardiograms at different ages and in stable condition so that they could be included in the study. In total, 430 echocardiograms from 67 patients were available for analysis. Characteristics at the first visit (transition to adult care) and at the last visit are shown in table 1.

At the time of transition to adult care at a mean±SD age of 19±3.9 years, half of the cohort was on nocturnal HMV and patients had cardiomyopathy with a LVEF of 47.1±10.2%, but only 50% of the patients were treated with an ACE-I (or sartan) and 15% with a β-blocker.

TABLE 1 Patient (n=67) characteristics at first and last visit

	At first visit (transition)	At last visit
Age (years)		
Mean±SD	19.1±3.9	27.8±6.6
Median (IQR)		26 (23–32)
LVEF (%)	47.1±10.2	37.5±12.4
ACE-I	33 (49.3)	56 (83.6)
β-blocker	10 (14.9)	36 (53.7)
Aldosterone antagonist	2 (2.9)	13 (19.7)
HMV	34 (50.7)	59 (88.1)
Invasive HMV	2 (2.9)	17 (25.4)
BMI ($kg \cdot m^{-2}$)	21.8±7.2	22.9±6.9
FVC		
% pred	42.4±23.4	18.4±13.0
L	1.6±0.8	0.8±0.6
HCO_3^- ($mmol \cdot L^{-1}$)	26.1±2.7	25.4±2.4
Daytime P_{aCO_2} (kPa)	5.5±0.9	5.1±1.0
Age at start of ventilation (years)	20.0±4.8	
Percutaneous endoscopic gastrostomy	32 (47.8)	
Follow-up (years)	9.1±5.1	
Decline in LVEF during follow-up (%)	−10.0±13.9	

Data are reported as mean±SD or n (%), unless otherwise stated. IQR: interquartile range; LVEF: left ventricular ejection fraction; ACE-I: angiotensin-converting enzyme inhibitor; HMV: home mechanical ventilation; BMI: body mass index; FVC: forced vital capacity; HCO_3^-: bicarbonate (from arterial blood gas analysis); P_{aCO_2}: arterial partial pressure of carbon dioxide.

The follow-up period in adult care was 9.1±5.1 years and the decline in LVEF during this period was −10.0±13.9% absolute (figure 1). The course of LVEF between the age of 16 and 33 years of age is illustrated in figure 2. However, the course of LVEF over age was highly variable, as shown in figure 3, which depicts the individual course of LVEF.

Survival and cause of death analysis

28 out of 67 (42%) patients were deceased at the time the study was conducted. The cause of death was known in 17 out of the 28 decedents who died in the hospital and of these, the cause of death was reported as cardiac in nine (53%) and non-cardiac in eight (47%) (table 2).

The mean±SD age at death was 29.2±6.4 years. The median (IQR) survival in the cohort of 67 patients was 33 (25–40) years. Figure 4 shows the Kaplan–Meier survival estimate curve. LVEF was significantly associated with survival in Cox regression (hazard function for LVEF in time at risk of 1861 years; hazard ratio (HR) 0.95 (95% CI 0.91–0.99); p=0.007). Cox regression models showed no statistically significant difference in survival between patients with or without ACE-Is (HR 0.66 (95% CI 0.29–1.51); p=0.323) and patients with or without β-blockers (HR 0.74 (95% CI 0.35–1.57); p=0.439) at last visit. However, there was a significant association between age-adjusted duration of ACE-I use in years and survival (HR 0.88 (95% CI 0.81–0.95); p=0.001), but not between duration of β-blocker use and survival.

Those who died of cardiac death had significantly lower LVEF at the time of death (difference between groups in LVEF −11.0% (95% CI −21.1–−0.9%); p=0.035), but did not differ from those who died of another cause with respect to drug treatment for heart failure or ventilation. Patients with cardiac causes of death tended to die at a younger age than patients with non-cardiac causes of death, although there was no statistically significant difference between the two groups. Figure 5 shows the time to event comparing cardiac and other known causes of death. The log-rank test for equality of the time-to-event function comparing those with cardiac and other causes of death showed a trend towards a difference in time to event (p=0.071).

Predictors of change in LVEF

Between the ages of 16 and 33 years, at least 10 echocardiograms were available from different patients per age (mean 22 echocardiograms for each age); therefore, this age range was used for regression analysis to examine the association between potential predictors and change in LVEF (n=64). In linear regression, older age tended to be weakly associated with lower LVEF (p=0.065), whereas FVC (which, however, was

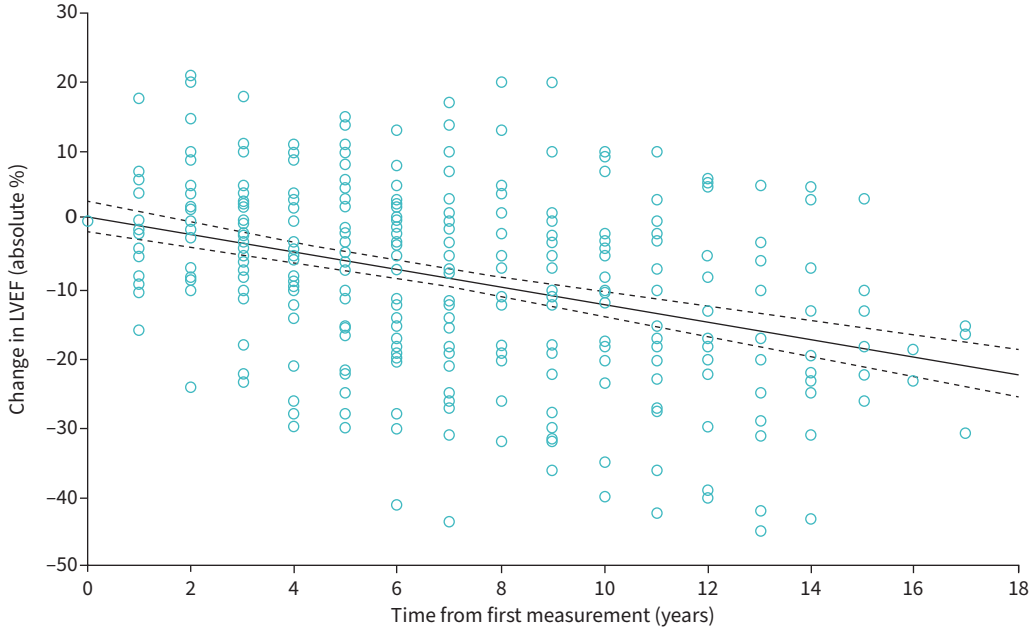

FIGURE 1 Scatter plot of difference in left ventricular ejection fraction (LVEF) over time in years from first measurement (best fitted line and 95% confidence interval).

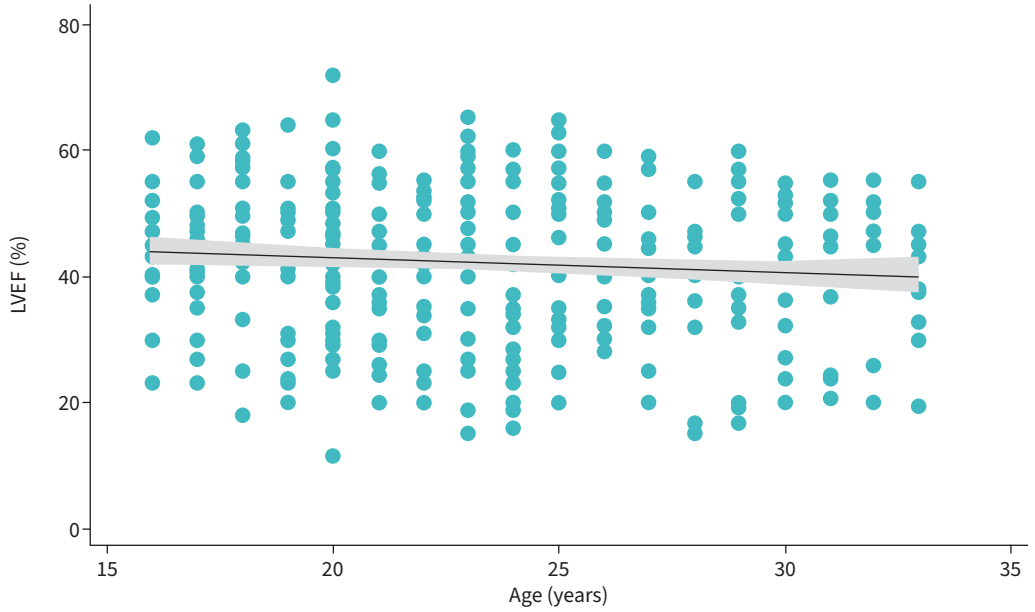

FIGURE 2 Course of left ventricular ejection fraction (LVEF) over time shown between the age of 16 and 33 years (best fitted line and 95% confidence interval).

not available in those who with 24-h ventilator dependence) and measures of respiratory failure, such as daytime arterial P_{aCO_2}, HCO_3^- and mean nocturnal P_{tcCO_2}, were not statistically significantly associated with LVEF. Use of ACE-Is, β-blockers and aldosterone antagonists was significantly associated with lower LVEF, probably reflecting more intensive heart failure treatment in advanced systolic heart failure. The steepest decline in LVEF was observed in the group taking no and three types of heart failure drugs compared with one or two drugs (figure 6). The type of dystrophin mutation (information on genetics present in all but 10 patients and exact mutation available in 50; 72% deletions of exons of the dystrophin

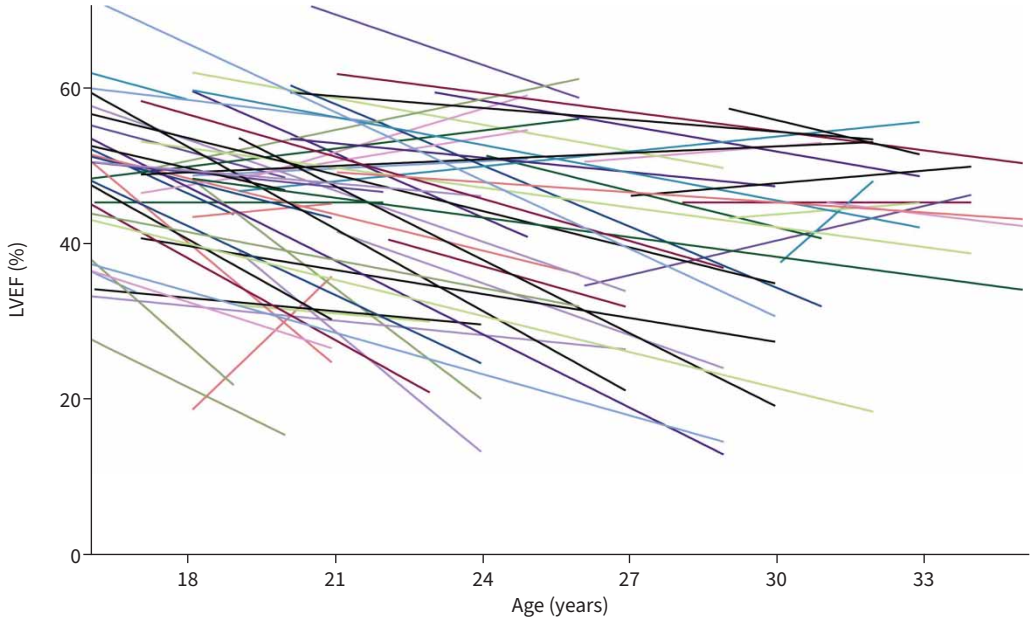

FIGURE 3 Individual course of left ventricular ejection fraction (LVEF) over time shown between the age of 16 and 35 years.

TABLE 2 Characteristics at last visit of the deceased (n=28)

Cardiac death if known cause of death	9 (52.9)
Age at death (years)	29.2±6.4
If cardiac death (n=9)	26.7±4.3
If non-cardiac death (n=8)	30.8±8.4
If cause of death unknown (n=11)	30.0±6.3
LVEF at death (%)	32.9±13.4
If cardiac death (n=9)	24.2±11.5
If non-cardiac death (n=8)	35.2±8.2
If cause of death unknown (n=11)	38.5±15.3
ACE-I	20 (71.4)
β-blocker	13 (76.4)
Aldosterone antagonist	6 (21.4)
HMV	25 (89.3)
Invasive HMV	9 (32.1)
BMI ($kg \cdot m^{-2}$)	21.1±4.9
FVC	
% pred	16.1±13.1
L	0.7±0.6
HCO_3^- ($mmol \cdot L^{-1}$)	25.4±2.4
Daytime P_{aCO_2} (kPa)	5.0±0.9

Data are reported as mean±SD or n (%). LVEF: left ventricular ejection fraction; ACE-I: angiotensin-converting enzyme inhibitor; HMV: home mechanical ventilation; BMI: body mass index; FVC: forced vital capacity; HCO_3^-: bicarbonate (from arterial blood gas analysis); P_{aCO_2}: arterial partial pressure of carbon dioxide.

gene, 7% duplications, 9% point mutations including non-sense mutations and 12% unclear) was not associated with LVEF, but 35 different mutations were described. A multivariate regression model including age, daytime P_{aCO_2}, HCO_3^-, mean nocturnal P_{tcCO_2}, FVC, mutation type, and intake of ACE-Is, β-blockers and aldosterone antagonists explained 62% of the variance in LVEF, but only intake of ACE-Is and intake of β-blockers (p=0.002 for both) were independent negative predictors of change in LVEF.

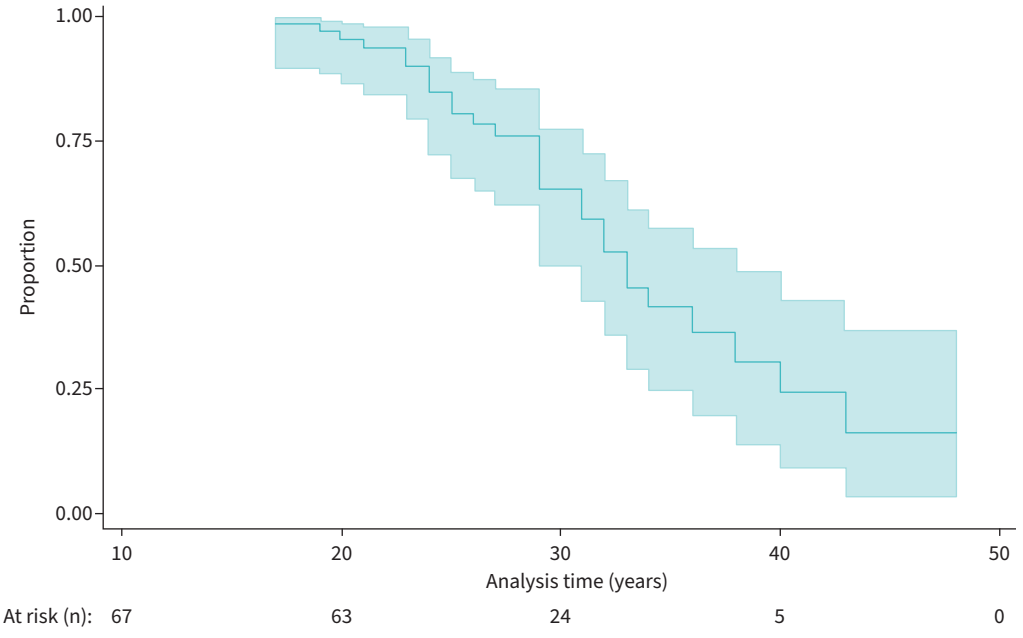

FIGURE 4 Kaplan–Meier survival estimate with 95% confidence interval of 67 patients at risk (shown from 16 to 48 years). Median (interquartile range) survival was 33 (29–40) years.

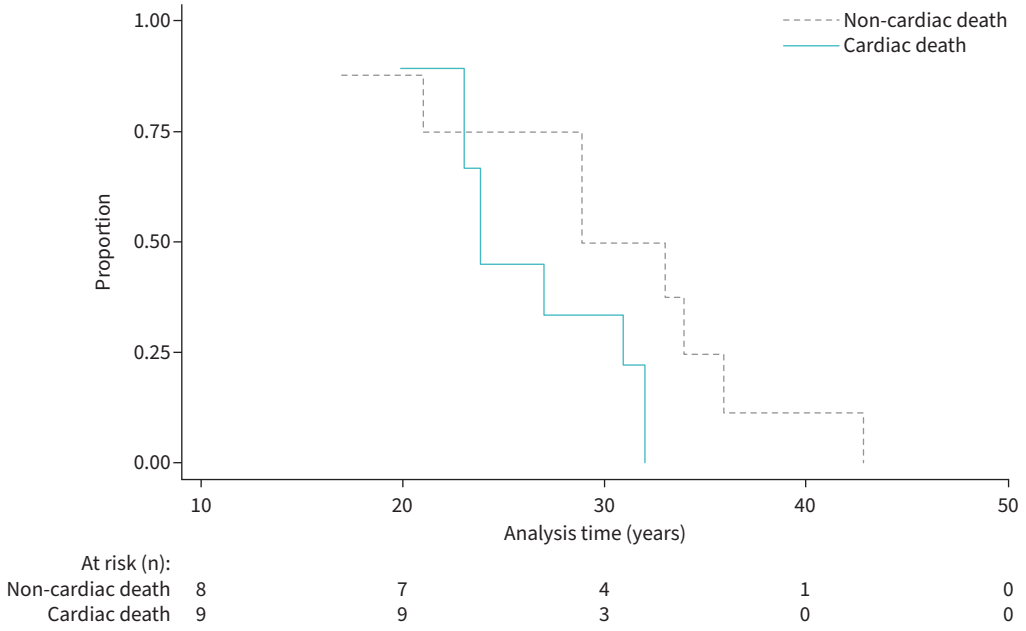

FIGURE 5 Time-to-event curves based on 17 out of 28 decedents with known cause of death, comparing those who died from a cardiac cause with those who died from a non-cardiac cause.

Discussion

In an adult DMD population treated in a tertiary HMV centre and in collaboration with a multidisciplinary care team, the cause of death was explained as cardiac in >50% in patients with known cause of death, and lower LVEF as a marker of more severe cardiomyopathy was associated with earlier death. This finding is consistent with reports from other large centres [15, 22, 23].

In individual patients in our cohort, improvement in LVEF was observed after introduction of an ACE-I or noninvasive ventilation (data not shown). LVEF decreases with age and over prolonged time (figures 1 and 2).

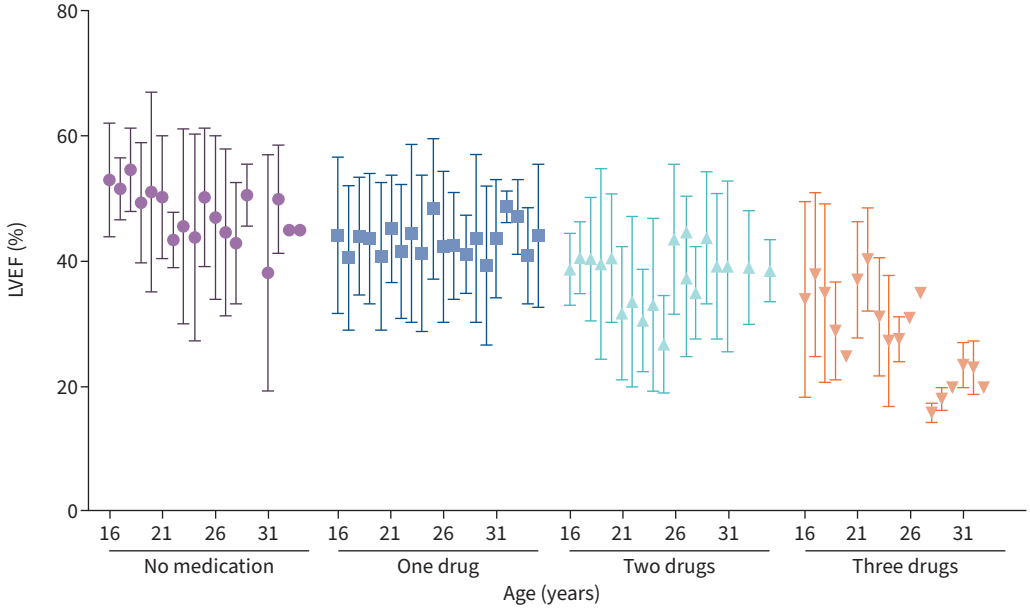

FIGURE 6 Course of left ventricular ejection fraction (LVEF) over age per number of heart failure drugs.

However, as can be seen from the spaghetti plot showing the individual progression of LVEF in figure 3, the course of LVEF over time is highly variable. Overall, the decline in LVEF was not predictable by either the mutation or measures of respiratory failure. Because there were individuals with mild cardiomyopathy only at older ages (non-cardiac phenotype), analysis of the decline in LVEF with age in the overall group (figure 2) greatly underestimates the steepness of the decline in those with a pronounced cardiac phenotype. We attempted to resolve this problem, at least in part, by plotting not only the progression of LVEF with age but also with time from the first baseline measurement in figure 1 (LVEF −10.0±13.9% over 9.1±5.1 years). The varying severity of cardiomyopathy and the existence of individual patients with only mildly impaired systolic function even in the third decade of life also explain why age was only a weak independent predictor of LVEF decline. Apart from age, only ACE-I and β-blocker use were independent predictors of LVEF. There was a strong negative association between medication use and LVEF. This is of course explained by the intensification of heart failure drug therapy at lower LVEF. However, looking at LVEF progression in separate groups without, with one, with two or with three medications (figure 6), the steepest decline is seen in the groups without medication or with three drugs (usually ACE-Is, β-blockers and aldosterone antagonists). Overall, we found that these patients tended to be undertreated compared with other patients with systolic heart failure (see percentages under medication and LVEF at transition to adult medicine and at last visit in table 1) and considering current heart failure guidelines [24]. These figures are comparable to a recently published cohort study from another tertiary centre [25]. Among the 32 out of 67 patients in our study with LVEF <35%, an ACE-I was used in 25 out of the 32 (78%) at some point during follow-up with LVEF <35%. Considering all echocardiography measurements in which LVEF <35% was documented, an ACE-I was used in 75.3% and a β-blocker in 56.7%. This indicates less use of these heart failure medications compared with other causes of heart failure with reduced ejection fraction.

Annual echocardiography from the age of 10 years is recommended in DMD and the use of ACE-Is and β-blockers as soon as abnormalities are detected [26]. However, there is little evidence to guide the management of heart failure in DMD. A randomised controlled trial in children with DMD highlighted the importance of early initiation of ACE inhibition in childhood to delay a decline in LVEF <45% [27, 28]. Several studies of different designs in children with DMD found improvement in LVEF in response to initiation of ACE inhibition [29–31]. However, the evidence on the effect of ACE-Is or β-blockers on the progression of cardiomyopathy in adults is less clear. One randomised controlled trial demonstrated beneficial effects of the aldosterone antagonist eplerenone on circumferential strain [32]. The risks and benefits of an implantable cardioverter defibrillator for primary prevention in DMD at risk of ventricular tachycardia or ventricular fibrillation have never been studied. While glucocorticoids have been shown to slow muscle strength decline and may have cardiac function benefits in the paediatric population [33, 34], the side-effects and risks of systemic glucocorticoids probably outweigh the potential benefits in non-ambulatory adult patients with DMD and systolic heart failure.

Since a cardiac cause of death is the most common cause of death in DMD patients treated in a centre that ensures long-term mechanical ventilation and mechanical insufflation/exsufflation (cough assistance) for secretion management, lower LVEF is a significant predictor of mortality, and the quality of life in these patients is generally good despite alveolar hypoventilation and up to 24-h ventilator dependency [14, 35], it would be desirable to be able to favourably influence cardiomyopathy. However, specific studies are lacking in this ventilator-dependent group with a rare cause of cardiomyopathy. As patients survive longer nowadays, comorbidities have to be increasingly considered in the follow-up of an ageing Duchenne population.

The fact that this is a retrospective observational study is certainly a limitation, but in patients with DMD (a rare disease, *i.e.* less than 1:2000), prospective and especially controlled studies are difficult to conduct to study survival or heart failure outcomes, and data come primarily from retrospective observational studies and registries. The study size of 67 patients may seem small, but we did not encounter any study that examined 430 echocardiograms during follow-up, so this is probably the largest study on LVEF follow-up. One limitation is certainly that modelling the association between ACE-I type and dose with LVEF progression is not possible with these data. However, in this cohort, the age-adjusted and absolute duration of ACE-I use were significantly associated with survival (HR 0.88 for adjusted duration of drug use). The association would have been expected more in the other direction, *i.e.* the longer the ACE-I use, the longer the survival, but perhaps the longer ACE-I use simply reflects the early onset of systolic heart failure. In another recent cohort study, longer usage of heart failure drugs during follow-up was associated with a smaller decline of LVEF during follow-up, but the authors did not study survival [25].

Overall, this study has yielded several important findings. On the one hand, the course of LVEF in DMD cardiomyopathy is variable over age and not necessarily genetically determined, lower LVEF is strongly associated with shorter survival, and cardiac death is the most common cause of death nowadays. On the other hand, DMD patients are at risk of undertreatment with respect to current heart failure management, although the most effective heart failure therapies in this patient population remain to be explored. These findings suggest that close collaboration between neuromuscular centres treating DMD patients and cardiologists is important, and international studies of heart failure therapy in DMD are needed to determine specific recommendations.

Conclusions

Cardiomyopathy with systolic heart failure is a leading cause of death and lower LVEF is an independent predictor of mortality at younger ages in patients with DMD. Increasing age in adults with DMD was only weakly associated with a decrease in LVEF. Patients with DMD may be undertreated with respect to heart failure therapy compared with other disease groups. Identification of predictors of LVEF decline and modifying factors is of interest to eventually improve survival.

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Data availability statement: The data are available from the corresponding author on request.

Conflicts of interest: The authors have no conflicts of interest to declare.

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