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Cardioprotective medication in Duchenne muscular dystrophy: a single-centre cohort study

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Background: Duchenne muscular dystrophy (DMD) is a neuromuscular disorder characterised by progressive muscle wasting impacting mobility, ventilation and cardiac function. Associated neuromuscular cardiomyopathy remains a major cause of morbidity and mortality. We investigated the effects of cardioprotective medications [angiotensin-converting enzyme inhibitors (ACE-I), beta-blockers] on clinical outcomes in DMD patients.

Methods: This was a retrospective cohort study (reference: 2021/12469) of DMD patients at a tertiary centre between 1993–2021 screening the electronic records for demographics, comorbidities, medication, disease specific features, echocardiography, hospitalisations, and ventilator use.

Results: A total of 68 patients were identified aged 27.4 (6.6) years, of which 52 were still alive. There was a difference in body mass index (BMI) between survivors and deceased patients [23.8 (5.9) *vs.* 19.9 (3.8) kg/m^2, P=0.03]. Home mechanical ventilation (HMV) was required in 90% of patients, 85% had DMD associated cardiomyopathy. About 2/3 of all hospitalisations during the observation period were secondary to cardiopulmonary causes. The left ventricular ejection fraction (LVEF) at initial presentation was 44.8% (10.6%) and declined by 3.3% [95% confidence interval (CI): 0.4% to −7.0%] over the follow up period (P=0.002). A total of 61 patients were established on ACE-I for 75.9% (35.1%), and 62 were on beta-blockers for 73.6% (33.5%) of the follow up period. There was a significant LVEF decline in those taking ACE-I for limited periods compared to those permanently on ACE-I (P=0.002); a similar effect was recorded with beta-blockers (P=0.02).

Conclusions: Long-term use of ACE-I and beta-blockers is associated with a reduced decline in LVEF in patients with DMD and may be protective of adverse cardiovascular ill health.

Keywords: Respiratory failure; non-invasive ventilation (NIV); cardiomyopathy; neuromuscular disorder

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Introduction

Duchenne muscular dystrophy (DMD) is an X-chromosome linked neuromuscular disorder affecting one in 3,600–6,000 live male births (1), resulting in progressive skeletal muscle failure with generalised effects on the muscles in the entire body, including the cardiovascular and the respiratory system.

DMD typically presents with first clinical signs before the age of five with gait disturbances and difficulty in climbing stairs, with a full loss of ambulation by the age of 13 years (2). Eventually, deterioration of the skeletal muscles involved in the respiratory and cardiac system leads to respiratory failure and, commonly, dilated cardiomyopathy (3-5). Cardiorespiratory complications are the leading cause of mortality in DMD patients (6). However, with advancing respiratory support, such as home mechanical ventilation (HMV), respiratory failure can be better controlled. This development shifts the focus towards cardiovascular causes as the life-limiting factor in DMD (7,8), and left ventricular function is an important clinical marker for the DMD associated cardiomyopathy (9).

Studies have suggested the prophylactic use of angiotensin-converting enzyme inhibitors (ACE-I) (10,11), and the 2010 DMD care considerations support the use of ACE-I or angiotensin receptor blocker (ARB) by the age of ten (12), although there is no mentioning on the effects of beta-blockers.

This cohort study sought to investigate the effect of ACE-I and beta-blockers on clinical progression of the cardiomyopathy of DMD patients during their follow up in a tertiary referral centre, with specific focus on the left ventricular function. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1528/rc).

Highlight box

Key findings

- Long-term use of ACE-inhibitors and beta-blockers is associated with a reduced decline in the LVEF in patients with DMD, and may be protective of adverse cardiovascular ill health.

What is known and what is new?

- Patients with DMD typically have life-limiting complications due to cardiorespiratory complications, including the developing feature of DMD-associated cardiomyopathy.
- It is important to notice that continuous protection of cardiomyopathic progression can be delivered by ongoing prescription of ACE-inhibitors and betablockers.

What is the implication, and what should change now?

- The long-term care of patients with complex needs due to DMD requires the coordinated guidance by a multidisciplinary team, including the respiratory physician and the cardiologist to guarantee optimal treatment and preserve cardiac function.

Methods

This was a retrospective, single-centre cohort study of patients with DMD who required HMV with follow up period. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Guy's & St Thomas' NHS Foundation Trust as service review (reference No: 2021/12469) and individual consent for this retrospective analysis was waived. The local electronic patient records (EPRs) were screened to identify patients with DMD between 1st January 1993 and 15th June 2021. Patients were selected from the Lane Fox Unit, a large tertiary referral centre for HMV, for more information on the protocol please refer to the online supplement.

In- and exclusion criteria

Patients with a diagnosis of DMD clearly stated in the records and under the Lane Fox service were selected for analysis, excluding any intermediate phenotypes. Patients of any age were included (excluding patients <18 years). Due to the nature of DMD (X-chromosome recessive), patients were male.

Outcome parameters

The primary outcome parameter was decline in the left ventricular ejection fraction (LVEF; %). Secondary outcomes parameters included morbidity, HMV, hospitalisations and mortality.

Statistical analysis

Data were initially collected in a spreadsheet on MS Excel (version 16.54, Microsoft, Seattle, WA, USA). The Kolmogorov-Smirnov test was used to tested for normality using IBM SPSS Statistics for Macintosh (version 27.0, IBM Corp., Armonk, NY, USA). Mean and standard deviation (SD) were reported for normally distributed data, while

Table 1 ABG analysis

ABG analysis	Survivors	Deceased	Combined	P value (survivors *vs*. deceased)
pH	7.41 (0.07)	7.34 (0.21)	7.39 (0.13)	0.07
pO_2 (mmHg)	10.15 (3.59)	8.91 (3.73)	9.79 (3.63)	0.31
pCO_2 (mmHg)	6.26 (1.93)	7.21 (2.95)	6.55 (2.3)	0.20
HCO_3^- (meq/L)	26.43 (4.08)	27.80 (5.47)	26.85 (4.54)	0.35
BE	1.37 (4.12)	3.82 (5.17)	2.21 (4.59)	0.12

Data are presented as mean (SD). The P value was derived from an unpaired *t*-test. ABG, arterial blood gas; pO_2, partial pressure of oxygen; pCO_2, partial pressure of carbon dioxide; HCO_3^-, bicarbonate; BE, base excess; SD, standard deviation.

Table 2 Ventilator settings

NIV settings	Survivors	Deceased	All patients	P value (survivors *vs*. deceased)
IPAP (cmH_2O)	20.0 (5.0)	21.6 (5.0)	20.4 (5.2)	0.29
EPAP (cmH_2O)	5.2 (2.0)	4.9 (2.0)	5.0 (2.0)	0.71
BUR (breaths/min)	16.3 (2.9)	16.7 (2.3)	16.4 (2.7)	0.58
Ti (ms)	1.3 (0.1)	1.3 (0.1)	1.3 (0.1)	0.4

Data are presented as mean (SD). The P value was derived from an unpaired *t*-test. NIV, non-invasive ventilation; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; BUR, back-up rate; Ti, inspiratory time; SD, standard deviation.

median and interquartile range (IQR) was stated for non-normally distributed data. Unpaired two-tailed *t*-tests were used to compare the body mass index (BMI), HMV settings, arterial blood gasses (ABGs), the LVEF (% change), and differences in LVEF change when taking ACE-I and beta-blockers between different patient groups. The group change in the observed LVEF was tested using paired *t*-tests, and LVEF decline was further described using the 95% confidence intervals (CIs). The Mann-Whitney U test was used to assess the difference in severity measures and hospitalisations between survivors and deceased patients. The level of significance was defined as P<0.05.

Results

Baseline demographics

A total of 68 patients were included in this study aged 27.4 (6.6; range, 18–46) years, 76.5% were still alive {28 [7] years}; 23.5% of the cohort had died with an average age of 26 [6] years. The BMI for the entire cohort was 22.7 (5.6) kg/m^2, while survivors had a higher BMI than deceased patients [23.8 (5.9) *vs* 19.9 (3.8) kg/m^2, P=0.03]. At the time of the initial diagnosis, patients were 11 [7] years old, and they were seen in regular follow up intervals of 6 [1] months in the HMV services; the total follow up period in the Lane Fox service was on average 133.7 (31.1) months. A DMD mutation type was identified in 54.4% patients (Table S1). A total of 69.1% patients had ABGs at the last follow up, of which 70.2% were still alive and 29.8% had died (*Table 1*). For further information on hospitalisations please refer to Appendix 1.

HMV

A total of 89.7% of the patients had been established on HMV for an average of 94 [79] months. Hypercapnic respiratory failure had been diagnosed 95 [77] months after initially being diagnosed with DMD (Table S2). There were no significant differences in the ventilator settings or devices between the survivors and the deceased patient [P= not significant (NS); *Table 2*, for devices refer to Table S3]. In patients established on HMV, overnight monitoring confirmed sufficient respiratory control with the average percutaneous arterial oxygen saturation (SpO_2) at 97.0% (2.1%), the apnoea-hypopnoea index (AHI) was 8.5 (5.8)/hour, the 4% oxygen desaturation index (ODI) was 2.2 (0.8–8.3)/hour, and the time below an SpO_2 of 90% (T<90) was 6.0% (0.0–11.0%) of the night.

Table 3 Dosage of ACE-I and beta-blockers

Medication	No. of patients at final follow up	Dosage (mg), mean (SD)
ACE-I		
Lisinopril	12	10.2 (4.5)
Ramipril	28	4.6 (3.0)
Perindopril	10	3.0 (1.1)
Captopril	1	25.0 (0.0)
Beta-blockers		
Bisoprolol	55	3.6 (2.2)
Carvedilol	6	11.1 (7.6)

ACE-I, angiotensin-converting enzyme inhibitors; SD, standard deviation.

Table 4 Co-medications

Other key medications	No. of patients	Length of time taken (months), mean [SD]
Corticosteroids	11	115 [41]
Antidiabetic medication	4	104 [69]
Mineralocorticoid receptor antagonist	3	44 [8]
Ivabradine	13	49 [25]
Candesartan	5	50 [50]
Other medications		–
Digoxin	1	
Eplerenone	2	
PPI	20	
H2 receptor blocker	7	
Antihistamines	5	
Bisphosphonates	8	
Anticoagulants	3	
Antiplatelets	2	
Osteoporosis prophylaxis	20	

PPI, protein-protein interaction; H2, histamine type 2; SD, standard deviation.

Morbidity status

All patients were non-ambulatory, and were under joint respiratory and cardiology follow up. 68.8% patients used a mechanical insufflation-exsufflation (MIE) device, 44.8% had a feeding tube [percutaneous endoscopic gastrostomy (PEG)] for an average of 75 [50] months, and 40.0% had undergone spinal surgery. The associated cardiomyopathy was developed after 102 [76] months (Table S1). The morbidity severity score was 1.4 (1.0), with 23.5% of the patients scoring zero points, 27.9% scoring one point, 29.4% with two points, and 19.1% of the patients had the highest score of three points. The mean morbidity score for alive patients was 1.3 (1.1) points, and 1.8 (0.8) points for deceased patients (P=0.11). Following comparison of the initial and the final electrocardiograms (ECGs) for each patient, there was in increase in pathological findings over time (Table S4).

Medication

A total of 89.7% of patients took ACE-I at some point in the follow up period for 96 [40] months (*Table 3*), although 25.0% patients did not remain on the medication due to side effects with hypotension, cough, renal failure, angioedema, headache, and rash. A total of 91.2% of patients were established on beta-blockers at some point in the follow up period for 87 [39] months (*Table 3*), with 10.3% coming off/never starting the medication due to wheeze/asthma, hypotension, and peripheral circulation problems; some patients had multiple reasons for not taking the above medications (more details on medication are listed in *Table 4*).

Echocardiography

Echocardiography was repeatedly recorded in intervals of 84 [48] months. The LVEF at initial presentation was 44.8% (10.6%) and at most recent follow up 41.9% (12.0%) (P=0.002), with a change of −3.3% (95% CI: 0.4% to −7.0%). The proportion of LVEF decline, comparing the final LVEF to the initial recordings, was −10.0% (95% CI: −3.5% to −16.5%). The proportionate decline in LVEF for survivors was −7.1% (95% CI: −0.3% to −13.9%) (P=0.008) and −19.8% (95% CI: −3.8% to −35.8%) (P=0.02) for deceased patients.

ACE-I and LVEF

Patients were established on ACE-I during 75.9% (35.1%), or 95.9 (39.6) months of the follow up interval. The proportionate change in LVEF for those established on ACE-I for the entire interval (100%) was −4.3% (95% CI:

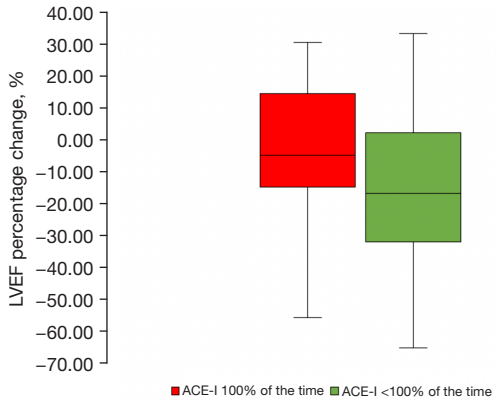

Figure 1 Box-Whisker plot comparing the LVEF (proportionate change, %) of patients who took ACE-I for the entire follow up period (red box) *vs.* those who did not (green). There was no significant change in the LVEF in the patients who were established on ACE-I for the entirety of the observation period (P=0.4). In contrast, there was a significant decline in those who were not [LVEF decline −15.7% (95% CI: −6.2% to −25.2%), P=0.002]. LVEF, left ventricular ejection fraction; ACE-I, angiotensin-converting enzyme inhibitors.

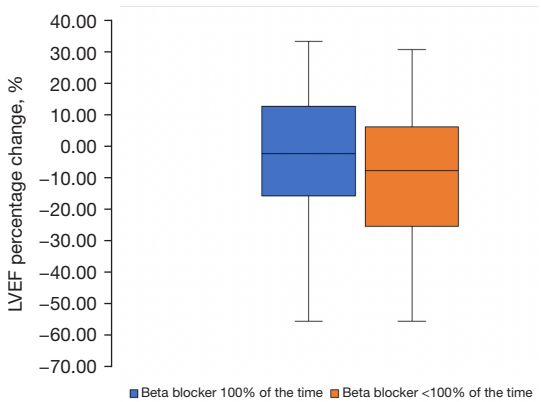

Figure 2 Box-Whisker plot comparing the LVEF (proportionate change, %) of patients who took beta-blockers for the entire follow up period (blue box) *vs.* those who did not (orange). While there was no significant decline in the LVEF for those permanently on beta-blockers (P=0.2), there was a significant decline in the patients who were not [LVEF −7.6% (95% CI: −0.9% to −14.3%), P=0.02]. LVEF, left ventricular ejection fraction.

4.2% to −12.8%) (P=0.4; n=29). In contrast, there was a significant decline in those taking ACE-I for less than the entire follow up interval (<100%) [LVEF −15.7% (95% CI: −6.2% to −25.2%), P=0.002, n=39; *Figure 1*].

Betablockers and LVEF

Patients were established on beta-blockers for 73.6% (33.5%), or 87.1 (38.8) months of the follow up interval. The proportionate LVEF change for those established on beta-blockers (n=22) for the entire period (100%) was non-significant [LVEF −5.73% (95% CI: 4.97% to −16.73%), P=0.2]. For those taking the medication for less than the entire follow up period (<100%) there was a significant decline [LVEF −7.6% (95% CI: −0.9% to −14.3%), P=0.02; *Figure 2*].

Discussion

In a cohort of DMD patients who were followed for over a decade in a tertiary referral centre patients developed hypercapnic respiratory failure and cardiomyopathy about 8 years following diagnosis of the disease, requiring joint cardiorespiratory specialist input (HMV/pacemaker). The permanent use of both ACE-I and beta-blockers over the follow up period was associated with preserved left ventricular pump function and protective of progression of the disease-specific cardiomyopathy. In this cohort study, lower body mass was associated with mortality. Morbidity and mortality did not significantly differ between survivors and those who died during the follow up. However, patients with DMD have a high carer burden due to developing comorbidities and other issues.

Clinical significance of the findings

ACE-I usage has previously been reported to prevent cardiomyopathic features in DMD patients (10,11), likely due to an inhibition of the "cardiac remodelling" properties of this drug class. Studies show that beta-blockers alongside ACE-I also have beneficial effects on survival and heart failure progression (1). Consistent with these reports, our study observed a protective inhibition of the LVEF decline when patients were established permanently on both ACE-I and beta-blockers. Following NHS advice the majority of the patients in our cohort study were established on ACE-I and beta-blockers (13). Previous studies look at the effects of maintenance doses of ACE-I and beta-blockers, in the future investigating the effects of higher doses providing tolerability could give more insight into cardiac management.

Furthermore, there were 11 patients who took corticosteroids for 115 [41] months to prevent loss of

ambulation and, more recently, corticosteroids have been reported to reduce the progression of the left ventricular dysfunction in DMD (14,15). Furthermore, it has been highlighted that Ivabradine may provide benefits for DMD patients in reducing acute adverse cardiac events (16). In our cohort, 13 patients took Ivabradine, five of whom died during the observation period; it is possible that the use of Ivabradine may be indicated in the more severe cases of DMD with progressing features of cardiomyopathy and, thus, may represent a selection bias. Five other patients were established on Candesartan as an alternative to ACE-I (17). However, these subgroups were small and the data could not be analysed in a meaningful manner to draw further firm conclusions.

There is a so-called "obesity paradox" in patients with heart failure, where cachectic patients are more likely to have a worse prognosis (18). This is also found in patients with chronic obstructive pulmonary disease (COPD) (19). In our study, there was a statistically significant difference in the BMI between survivors and deceased patients, with poorer outcomes associated with lower BMI. In the context of a cohort of patients that frequently requires nutritional support, it is important to highlight the appropriate nutritional intake and, if indicated, the involvement and early consultation of dietitian and the gastrointestinal specialist to decide future treatment (e.g., PEG insertion).

Substantial ventilator settings indicate the need to support ventilator pressures and reduce the risk of hypoventilation in DMD (20). Consistent with these descriptions, the group of deceased patients in our study required higher backup rates and higher inspiratory pressures to achieve sufficient ventilatory control. Furthermore, deceased patients were identified with respiratory acidosis and notably higher partial pressure of carbon dioxide (pCO_2) and lower partial pressure of oxygen (pO_2) levels during emergency admission, indicating life-limiting hypercapnic respiratory failure. In contrast, relatively normal blood gas samples in the cohort of survivors indicated good respiratory control during regular usage of the non-invasive ventilation (NIV), as previously described in similar cohort studies (21).

A MIE device is indicated for DMD patients with associated respiratory failure, as the respiratory muscle weakness causes hypoinflation of the lungs, leaving the patients to breathe at low lung volume as the disease progresses; this contributes to narrowing of the lower airways, increased airway resistance, hypoinflated and dystelectatic lung regions, and an ineffective cough (22). Due to the progressive muscle weakness, a third of the patients have swallowing difficulties (23), requiring feeding tubes. Spinal surgery is required in patients with scoliosis, with the aim to improve posture, function, balance, and quality of life (24). Ambulation was lost in our cohort at the age of 13 years. The morbidity scores indicated in this study reveal the serious impact of the condition on patients with DMD and highlight the need for a supportive care package to facilitate ambulation, chest clearance, diet, and have a meaningful impact on quality of life for patients who live with a lifelong condition.

Limitations of the study

Due to the relatively small sample size and the retrospective nature of this cohort study there are certain limitations to the generalisability of the data. Two different software systems were used to collect the clinical data but some information was missing, sometimes due to late referral. Incomplete records were passed on during the referral and transitioning process, making it difficult to identify onset of the conditions and rule out that cardiac function had not been assessed earlier on, or medication had been issued at an earlier stage. As a result, we cannot determine the effect of implantable cardioverter defibrillator (ICD)/cardiac resynchronisation therapy (CRT) implantation on cardiac progression. However, given the consistent findings of ACE-I and beta-blockers improving outcomes and comorbidities, such as respiratory failure and cardiomyopathies, being diagnosed the authors feel that the current dataset is a true representation of a clinical cohort sample of DMD patients in a tertiary referral centre.

Conclusions

Long-term follow up of patients with DMD is important, as they develop life-limiting comorbidity with hypercapnic respiratory failure and cardiomyopathy. The permanent use of ACE-I and beta-blockers is important to improve long-term outcomes and may be protective of the cardiac remodelling associated with the development of the disease specific cardiomyopathy. Patients with DMD should be followed up in multidisciplinary settings, involving the respiratory physician, the cardiologist, the dietitian, and gastrointestinal team, as well as a dedicated care coordinator.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Guy's & St Thomas' NHS Foundation Trust as service review (reference No: 2021/12469) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 DMD mutations present in the patients

Mutation type	Number of patients
14 base pair deletion intron 49	1
Deletion exon 18	1
Deletion exon 18–23	1
Deletion exon 30–43	1
Deletion exon 45	4
Deletion exon 45–50	1
Deletion exon 45–52	1
Deletion exon 46–47	1
Deletion exon 46–49	1
Deletion exon 46–52	1
Deletion exon 46–53	1
Deletion exon 47–48	1
Deletion exon 47–52	1
Deletion exon 47–53	1
Deletion exon 47, 48, 50	1
Deletion exon 49–50	1
Deletion exon 49–55	1
Deletion exon 52	4
Deletion exon 53	1
Deletion exon 54	1
Deletion exon 56–61 (out of frame transcript)	1
Deletion exon 8–9	1
Deletion on chromosome 50	1
Duplication exon 3–7	1
Hemizygous deletion exon 8–44	1
Nonsense mutation exon 52	1
Nonsense mutation exon 69	1
Point mutation exon 24	1
Point mutation exon 55	1
Point mutation exon 6	1
Stop mutation exon 19 (relatively less aggressive phenotype)	1
Total	37

DMD, Duchenne muscular dystrophy.

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Appendix 1

Methods

Short protocol

The patient's EPRs (iSoft V1.6, IBA Health Group Company 2004, Bruxelles, Belgium) and critical care software [CareVue 2012, IntelliSpace Critical Care and Anaesthesia (ICCA) Release F.01.00, PhilipsRespironics, Amsterdam, Netherlands] were used to collect the following parameters:

(I) Demographics, including age (years), gender (male only), BMI (kg/m^2), alive (yes/no), cause of death.

(II) Disease-specific details, including age at diagnosis (years), DMD mutation type, follow up period (months). Age at diagnosis was recorded as the earliest mentioning of the diagnosis.

(III) Comorbidities, classified into "cardiorespiratory" and "other" (including date of diagnosis and time lapse between diagnosis of DMD and comorbidity).

(IV) Medication, including ACE-I (yes/no), beta-blockers (yes/no), Glucocorticoids (yes/no), antidiabetics (yes/no), mineralocorticoid receptor antagonist (yes/no), others (listed). The start date and period of treatment (months) were noted. Patients not taking medication at the time of data collection, even if they had previously, were excluded.

(V) Hospitalisations during follow-up period between 01/1993–06/2021, either classified as hospitalisation secondary to "cardiopulmonary" causes or 'other'; any documented hospitalisation on medical records was included. Cardiopulmonary hospitalisations were further subclassified as (i) respiratory (respiratory review, pneumonia, ventilation wean, HMV initiation, ventilatory failure, elective assessment of sleep-disordered breathing, atelectasis, aspiration, tracheostomy change, intubation, bronchitis, hypoxia, hypercapnia, airway obstruction and bronchoscopy post tracheostomy change), or (ii) cardiovascular [ICD and pacemaker insertion, pulseless electrical activity (PEA) arrest, echocardiography, cardiological review].

(VI) ABG analysis, including the most recent ABG [date, pO_2 (mmHg/kPa), pCO_2 (mmHg/kPa), bicarbonate (HCO_3^-, meq/L), base excess (BE), SpO_2 (%)]. It should be noted that ABGs were not routinely undertaken, they were carried out during acute hospital admissions.

(VII) Sleep study, including the most recent (date), nocturnal pulse oximetry with 4% ODI, heart rate variability (pulse rise index >6 bpm per hour), AHI, average SpO_2 (%), T<90.

(VIII) Ventilation (if applicable), including type (invasive/non-invasive), date of initiation, time elapsed between DMD diagnosis and initiation of ventilation, inspiratory positive airway pressure (IPAP, cmH_2O), expiratory positive airway pressure (EPAP, cmH_2O), pressure support (cmH_2O), back-up rate (BUR, breaths/min), inspiratory time (Ti, s), usage (hours/day).

(IX) Indicators of morbidity, including ambulatory (yes/no), length of time non-ambulatory (years), MIE support (yes/no), feeding assistance [nasogastric tube, PEG, yes/no], length of time on feeding assistance (years), spinal surgery (yes/no). The use of an MIE with/without NIV, the need of feeding assistance, or undergoing spinal surgery was each assigned a score of "0" (not present) or "1" (present) point. The scores were then totalled with a range of 0–3 points to generate a severity score for disease impact on morbidity; more severely affected patients had a higher score.

(X) Echocardiogram (ECHO), including dates of first and most recent ECHO, initial and most recent LVEF (%), proportionate change in the LVEF over time [(first measured LVEF – last LVEF)/first LVEF × 100], left ventricular (LV) systolic and diastolic diameter (cm), right ventricular (RV) systolic and diastolic area (cm^2), RV fractional area change (%), RV systolic and diastolic pressure (mmHg), acceleration time (ms), regional wall motion abnormalities (RWMA, yes/no), and examiners comments. If a range was reported for the LVEF, the mid-range point (half-way between min and max) was quoted.

(XI) ECG, including date of initial and most recent ECG, initial and most recent comments. Reports from cardiologists were used to group abnormalities into the following pathologies: arrhythmia (tachycardia, bradycardia, general arrhythmia), bundle branch block (left, right, incomplete), T-wave flattening/inversion, dominant R-wave V1/2, pathological Q-waves (lateral, high lateral, inferior, and anterior leads), axis deviation

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(left, right, extreme), and normal.

Rules were created to identify the date of diagnosis, the length of time elapsed between diagnosis and other conditions/severity measures/ventilation, and period established on each medication.

(I) For the initial date of the DMD diagnosis:
Take the first mention of DMD OR loss of ambulation OR osteoporosis/scoliosis OR ventilation OR DMD related hospitalisations [spinal surgery, tenotomy/respiratory review/cardiac assessment/respiratory arrest/tracheostomy/lower respiratory tract infection (LRTI)] OR DMD related medication (ACE-I/clinical trial participant) OR age of diagnosis.

(II) For any condition or medication: take the start date as the date of first mention.

(III) For any condition or medication start date where only the year is recorded: take the start date as January of that year.

(IV) Data for passed patients was collected from the first records available, and any final dates used to measure the length of time were taken as the date of passing.

(V) The age of the patients (alive) was calculated for 15th June 2021.

Additional results

Hospitalisations

Each patient experienced 3 (2–5.8) hospitalisations during the follow up period. 66% of hospitalisations were secondary to cardiopulmonary causes {2 [1–3] hospitalisations/patient}, and a further hospitalisation period {1 [0–2] hospitalisation/patient} was due to other causes. The median of the total hospitalisations of survivors was 3 (1–5.8) hospitalisations, with 2 [0–3] due to cardiopulmonary and 1 [0–2] due to other causes. Deceased patients experienced 3.5 (2.3–5.8) hospitalisations, with 2 (1.3–3.8) hospitalisations as a result of cardiopulmonary causes, and 2 [1–2] for other causes. There was no significant difference in total hospitalisations between survivors and deceased patients (P=0.39).

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Table S2 Comorbidities

Condition	Number of patients
Cardiomyopathy	58
Respiratory failure	49
Chest wall deformity (scoliosis/kyphoscoliosis)	37
Type 2 diabetes mellitus	13
Sleep disordered breathing/OSA	10
Anxiety	7
Delayed puberty	5
Fracture	5
Bulbar dysfunction/poor swallow	5
ICD/CRT	4
Total	189
Total other conditions	118

OSA, obstructive sleep apnoea; ICD, implantable cardiac defibrillator; CRT, cardiac resynchronisation therapy.

Table S3 Ventilator device

Type of ventilator	Number of patients
NIPPY III+	55
A40	1
NIPPY III+ → BIPAP	1
NIPPY III+ → CPAP	1
NIPPY junior support	1
Trilogy ventilator	1
Not stated	1
Total	61

NIPPY, non-invasive positive pressure ventilation; BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

Table S4 ECG abnormalities

ECG finding	Initially presenting, n	Presenting at final follow up, n
Arrhythmia	9	10
Bundle branch block	13	13
T wave flattening/inversion	5	8
Dominant R-wave V1/2	5	22
Pathological Q-waves	29	30
Axis deviation	10	13
Total	71	96

ECG, electrocardiogram.

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