The association between cardiac involvement and long-term clinical outcomes in patients with Duchenne muscular dystrophy

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Abstract

Aims Despite advances in contemporary cardiopulmonary therapies, cardiomyopathy remains the leading cause of death in patients with Duchenne muscular dystrophy (DMD). Also, the long-term clinical outcomes of patients with DMD and cardiomyopathy is unknown. This study investigated long-term clinical outcomes and their associated factors in patients with late-stage DMD.

Methods and results A total of 116 patients with late-stage DMD (age > 15 years) were enrolled in this retrospective study. All enrolled patients were followed up at a single tertiary referral hospital. LV systolic dysfunction was dichotomously defined as reduced [left ventricular ejection fraction (LVEF) ≤ 40%] vs. preserved [>40%] based on the initial echocardiographic result. The primary endpoint was all-cause death. The secondary endpoint was a composite event defined as death or unexpected hospitalization due to cardiovascular reasons including chest pain, dyspnoea, and generalized oedema. The patients were divided into preserved (n = 84, 72.4%) and reduced LVEF groups (n = 32, 27.6%). The mean age was 20.8 ± 5.9 years, the mean disease duration, 8.8 ± 3.7 years, and the mean follow-up duration, 1708 ± 659 days. For primary endpoint, the reduced LVEF group showed a lower rate of overall survival (Reduced LVEF vs. Preserved LVEF; 81.3% vs. 98.8%, log-rank P = 0.005). In the multivariable Cox regression analysis, brain-natriuretic peptide (BNP) level (adjusted hazard ratio [HR] 1.088, 95% confidence interval [CI] 1.019–1.162, P = 0.011) and diuretic use (adjusted HR 9.279, 95%CI 1.651–52.148, P = 0.011) were significant predictors of all-cause death in patients with DMD. For the secondary endpoint, the reduced LVEF group showed a lower rate of overall survival (Reduced LVEF vs. Preserved LVEF; 81.3% vs. 98.8%, log-rank P = 0.005). In the multivariable Cox regression analysis, BNP level (adjusted HR 1.057, 95%CI 1.005–1.112, P = 0.032) and diuretic use (adjusted HR 4.189, 95% CI 1.704–10.296, P = 0.002) were significant predictors of the composite event in patients with DMD.

Conclusions Patients with DMD and reduced LVEF had worse clinical outcomes than those with preserved LVEF. BNP level and diuretic use were associated with adverse clinical outcomes in patients with late-stage DMD, irrespective of LVEF.

Keywords Duchenne muscular dystrophy; LV systolic dysfunction; Long-term clinical outcome; Brain-natriuretic peptide; Diuretics

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked disorder involving the absence of the sarcolemmal protein dystrophin. The clinical manifestations of DMD include skeletal muscle degeneration, respiratory insufficiency, and progressive cardiac dysfunction. Recent advancements in contemporary cardiopulmonary therapies—including ventilator...
support—have increased the survival of patients with DMD. However, DMD-associated cardiomyopathy remains the leading cause of death.

Cardiovascular manifestations of DMD vary and include dilated cardiomyopathy, arrhythmias, and congestive heart failure. Because cardiovascular events frequently occur during DMD progression, non-invasive imaging techniques and laboratory tests can help identify patients at risk of clinical deterioration and assess treatment response. However, early prediction of disease progression for DMD is challenging despite emphasizing the increased mortality rate of DMD patients due to cardiomyopathy. However, despite emphasizing the increased mortality rate of DMD patients due to cardiomyopathy, early prediction of disease progression for DMD is challenging due to the rarity of DMD and the difficulty of gathering data to investigate long-term effects regarding left ventricular systolic functions. In this study, we investigated the association between cardiac involvement and long-term clinical outcomes in patients with late-stage DMD.

Methods

Study population

We retrospectively analysed patients diagnosed with DMD (age > 15 years) who were treated between 2006 and 2017 at a single tertiary referral hospital. All patients were transferred to the respiratory rehabilitation centre of the tertiary institution due to respiratory failure while being treated for DMD. A total of 116 patients were enrolled in the study. We excluded patients diagnosed with Becker muscular dystrophy and those with unmeasured brain natriuretic peptide (BNP) levels or missing transthoracic echocardiography. Mutations within the dystrophin gene were identified using one or more of the following methods: polymerase chain reaction, Southern blotting, DMD gene sequencing, and/or genomic hybridisation array, depending on the technology that was available at the time of diagnosis.

Baseline characteristics, medications, BNP, and echocardiographic data were collected from the patients’ medical records. Basal initial echocardiography was performed after the patients were transferred to the tertiary hospital. According to the American Society of Echocardiography recommendations, we collected data on chamber size, interventricular septal thickness at end-diastole (IVTd), interventricular septal thickness at end-systole (IVTs), left ventricular internal diameter at end-diastole (LVEDI), left ventricular internal diameter at end-systole (LVESD), ejection fraction (EF), and fractional shortening. Doppler measurement data included mitral E, mitral A, E/A, tissue Doppler septal e', and E/e'.

Definition and clinical outcomes

LV systolic dysfunction was dichotomously defined as reduced vs. preserved (i.e. LVEF ≤40% vs. >40%) following recommendations from the American Society of Echocardiography. Based on the initial echocardiographic results after being diagnosed with DMD, the dichotomous division between two groups for ventricular dysfunction was established. The primary endpoint was all-cause death. The secondary endpoint was a composite event defined as death or unexpected hospitalization due to cardiovascular reasons including chest pain, dyspnoea, and generalized oedema.

Statistical analysis

After comparison using the $\chi^2$ or Fisher’s exact tests, categorical variables are expressed as numbers (percentages). Continuous variables were compared using Student’s t-test for parametric data and the Mann–Whitney U-test for nonparametric data and are expressed as means ± standard deviations. Cumulative incidences of clinical events are presented as Kaplan–Meier estimates after comparison using the log-rank test. Univariate Cox proportional hazards regression analyses using baseline clinical status, BNP level, and echocardiographic variables were performed to identify factors associated with clinical events. Variables with $P$-values < 0.20 in the univariate analysis were candidate in multivariate analysis, using backward elimination, multivariable Cox regression to determine the independent predictors of clinical events. All statistical analyses were performed using SPSS (version 24.0; IBM Corp., Armonk, NY, USA). All tests were two-sided, and statistical significance was set at $P < 0.05$.

Results

Baseline characteristics

The baseline clinical characteristics of patients with reduced LVEF during index admission are summarized in Table 1. Of the 116 DMD patients, 84 (72.4%) were categorized into the preserved LVEF group (LVEF >40%), and 32 (27.6%) into the reduced LVEF group (LVEF ≤40%). The entire cohort’s mean age and disease duration from the time when enrolled patients were under the care of the tertiary referral hospital were 20.8 ± 5.9 and 8.8 ± 3.7 years, respectively (total disease duration; about 18.8 years, the average age of diagnosed DMD: about 7.8 years old). One hundred patients (86.2%) were non-ambulatory phase. Among them, 59 patients are wheelchair. During the follow-up period, no patients in the ambulation phase became non-ambulatory phase. Compared with the patients in the preserved LVEF group, those
Clinical outcomes and independent predictors

The mean follow-up duration was 1708 ± 659 days. The Kaplan–Meier curves in Figure 1 illustrate the overall survival and freedom from composite events stratified by LV systolic dysfunction. The reduced LVEF group showed a lower rate of 6-year overall survival (81.3% vs. 98.8%, log-rank P = 0.005, Figure 1A) and freedom from composite events (65.6% vs. 86.9%, log-rank P = 0.005, Figure 1B) than the preserved LVEF group. A multivariable Cox regression analysis was performed to investigate the predictors that affect clinical outcomes in patients with DMD. Reduced LVEF (<=40%) was significantly associated with clinical outcomes in the univariate analysis. However, in multivariate analysis, reduced LVEF was not an independent predictor of overall survival and composite events. BNP level (adjusted HR 1.088, 95% CI 1.019–1.162, P = 0.011) and use of diuretics (adjusted HR 9.279, 95% CI 1.651–52.148, P = 0.011) were significant predictors of overall survival in patients with DMD after adjusting various confounding variables (Table 3). In addition, BNP level (adjusted HR 1.057, 95% CI 1.005–1.112, P = 0.032) and diuretic use (adjusted HR 4.189, 95% CI, 1.704–10.296; P = 0.002) were significant predictors of composite events in patients with DMD (Table 4).

Discussion

There are few studies on the long-term clinical outcomes regarding cardiac involvement in patients with DMD. In this study, 116 patients with DMD were enrolled and were divided into two groups according to LV systolic function for investigating long-term clinical outcomes in patients with DMD. As expected, patients with DMD and systolic dysfunction had higher mortality and more cardiovascular events than those without systolic dysfunction. However, in the multivariate analysis, diuretic use and BNP level rather than reduced LV systolic function were independent predictors of survival and cardiovascular events.

Table 1 Baseline characteristics of patients with reduced and preserved LVEF

|                        | Total          | Preserved LVEF (EF > 40%) | Reduced LVEF (EF ≤ 40%) | P   |
|------------------------|----------------|---------------------------|-------------------------|-----|
|                        | (N = 116)      | (N = 84)                  | (N = 32)                |     |
| Age, years             | 20.8 ± 5.9     | 20.1 ± 5.0                | 22.4 ± 7.6              | 0.133|
| Follow up duration, years | 4.7 ± 1.8     | 4.8 ± 1.7                 | 4.3 ± 2.0               | 0.144|
| Non-ambulatory phase   | (86.2%)        | (84.5%)                   | 29 (90.6%)              | 0.551|
| BMI, kg/m²             | 16.7 ± 5.1     | 16.5 ± 5.1                | 17.1 ± 5.0              | 0.599|
| Systolic BP, mmHg      | 108.0 ± 14.7   | 109.8 ± 15.7              | 103.3 ± 10.5            | 0.013|
| Diastolic BP, mmHg     | 70.6 ± 12.5    | 72.0 ± 13.5               | 66.6 ± 8.3              | 0.012|
| Pulse rate             | 91.9 ± 15.9    | 94.4 ± 16.5               | 85.5 ± 12.1             | 0.007|
| Ventilatory support    | 110 (94.8%)    | 81 (96.4%)                | 29 (90.6%)              | 0.208|
| BNP, pg/mL             | 43.8 ± 59.4    | 26.0 ± 24.5               | 90.3 ± 91.6             | <0.001|
| Use of corticosteroid  | 21 (18.1%)     | 15 (17.9%)                | 6 (18.8%)               | >0.999|

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CCB, calcium channel blocker.

Echocardiographic characteristics

The mean LV end-diastolic dimension and LVEF were 42.5 ± 7.1 mm and 49.4 ± 14.8%, respectively. Compared with the preserved LVEF group, the group with reduced LVEF had a higher incidence of chamber enlargement (43.8% vs. 8.3%, P < 0.001), increased LV end-diastolic dimension (48.9 ± 7.1 mm vs. 40.0 ± 5.3 mm, P < 0.001), increased end-systolic dimension (41.8 ± 7.9 mm vs. 28.6 ± 5.1 mm, P < 0.001), higher LA size within normal LA dimension (24.1 ± 7.1 mm vs. 19.9 ± 5.0 mm, P = 0.005), a higher incidence of reduced shortening fraction (<25%) (93.8% vs. 19.0%, P < 0.001), and decreased E wave velocity (64.38 ± 13.52 cm/s vs. 77.75 ± 15.69 cm/s, P < 0.001). There were no significant between-group differences in the E/A and E/e' ratios (Table 2).

Clinical outcomes and independent predictors

in the reduced LVEF group had lower systolic (103.3 ± 10.5 mmHg vs. 109.8 ± 15.7 mmHg, P = 0.013) and diastolic blood pressure (66.6 ± 8.3 mmHg vs. 72.0 ± 13.5 mmHg, P = 0.012), a lower pulse (85.5 ± 12.1 vs. 94.4 ± 16.5, P = 0.007), higher BNP levels (90.3 ± 91.6 pg/mL vs. 26.0 ± 24.5 pg/mL, P < 0.001), and more frequent use of angiotensin-converting enzyme inhibitors (ACEi) (59.4% vs. 20.2%, P < 0.001) and diuretics (37.5% vs. 7.1%, P < 0.001). There were no significant between-group differences in diabetes duration, age, body mass index, non-ambulatory phase rate, or corticosteroid use.
Although the life expectancy of patients with DMD is increasing as a result of advances in contemporary cardiopulmonary therapies, several studies reported a range of overall mortality of DMD patients from 5% (for 2 years) to 24% (for 15 years). As similar results with previous studies, the present study reported the occurrence of seven deaths (6%), of which six (85%) were in the reduced LVEF group (Supporting Information, Tables S1 and S2) during the follow-up period. In addition, unexpected hospitalization due to cardiovascular events was more frequent in the reduced LVEF group. Our results are comparable to those of Wang et al., who reported the worse clinical outcome of DMD patients with congestive heart failure compared with those without congestive heart failure in 57 patients with DMD. In the present study, although the reduced LVEF was an independent predictor of clinical outcome in univariate analysis, the reduced LVEF was not a significant predictor in multivariate analysis. Because the small number of the total patients was investigated, the lack of a significant correlation between the reduced LVEF and adverse clinical outcomes could be due to lack of power. Nevertheless, our results suggest that diuretic use and BNP levels are independent predictors for clinical outcomes irrespective of LVEF. The current treatment consensus of heart failure favours using diuretics for patients diagnosed with DMD and fluid retention to achieve a euvolaemic state. Although using diuretics in both paediatrics and adults showed a reduction of fluid overload and improvement of heart failure symptoms,
Table 3  Independent predictor of all-cause death in DMD patients

|                        | Univariate (HR and 95% CI) | P     | Full model (HR and 95% CI) | Final model stepwise backward elimination (HR and 95% CI) |
|------------------------|-----------------------------|-------|----------------------------|----------------------------------------------------------|
| Age                    | 0.934 (0.786–1.111)         | 0.443 | 1.048 (0.982–1.119)         | 1.062 (0.998–1.131)                                      |
| Body mass index        | 1.025 (0.888–1.185)         | 0.732 |                            |                                                           |
| Systolic blood pressure| 0.979 (0.928–1.033)         | 0.437 |                            |                                                           |
| Diastolic blood pressure| 0.991 (0.929–1.057)        | 0.783 |                            |                                                           |
| Pulse rate             | 0.979 (0.932–1.028)         | 0.391 |                            |                                                           |
| Reduced LVEF           | 17.970 (2.160–149.464)      | 0.008 | 6.327 (0.155–258.491)       |                                                           |
| Enlarged chamber size  | 8.074 (1.781–36.600)        | 0.007 | 1.186 (0.142–9.918)         |                                                           |
| Severe MR              | 8.245 (1.593–42.681)        | 0.012 | 0.748 (0.058–9.730)         |                                                           |
| BNP (per 10)           | 1.121 (1.057–1.190)         | <0.001| 1.062 (0.933–1.209)         | 1.088 (1.019–1.162)                                      |
| ACEi                   | 5.701 (1.105–29.403)        | 0.038 | 1.292 (0.184–9.082)         |                                                           |
| Beta-blocker           | 1.582 (0.306–8.186)         | 0.585 |                            |                                                           |
| Diuretics              | 13.751 (2.662–71.029)       | 0.002 | 5.015 (0.531–47.386)        | 9.279 (1.651–52.148)                                    |
| Digoxin                | 2.881 (0.346–23.979)        | 0.328 |                            |                                                           |
| Corticosteroid         | 3.411 (0.763–15.250)        | 0.108 | 1.189 (0.177–7.986)         |                                                           |
| Reduced fractional shortening | 9.198 (1.193–82.481)    | 0.034 | 0.684 (0.013–37.075)        |                                                           |
| IVTdiastole            | 1.008 (0.539–1.885)         | 0.980 |                            |                                                           |
| IVT systole            | 0.830 (0.531–1.298)         | 0.414 |                            |                                                           |
| LA diameter            | 1.173 (1.061–1.298)         | 0.002 | 1.007 (0.865–1.172)         |                                                           |

ACEi, angiotensin converting enzyme inhibitor; BNP, brain natriuretic peptide; IVTdiastole, end-diastolic interventricular septum thickness; IVTsystole, end-systolic interventricular septum thickness; LA, left atrial; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

Table 4  Independent predictor of composite event in DMD patients

|                        | Univariate (HR and 95% CI) | P     | Full model (HR and 95% CI) | Final model stepwise backward elimination (HR and 95% CI) |
|------------------------|-----------------------------|-------|----------------------------|----------------------------------------------------------|
| Age                    | 1.042 (0.983–1.106)         | 0.168 | 1.048 (0.982–1.119)         | 1.062 (0.998–1.131)                                      |
| BMI                    | 0.966 (0.887–1.053)         | 0.436 |                            |                                                           |
| SBP                    | 0.994 (0.965–1.024)         | 0.698 |                            |                                                           |
| DBP                    | 0.974 (0.937–1.012)         | 0.177 | 0.979 (0.931–1.029)         |                                                           |
| Pulse rate             | 0.993 (0.967–1.020)         | 0.628 |                            |                                                           |
| Reduced LVEF           | 3.111 (1.345–7.194)         | 0.008 | 1.183 (0.298–4.705)         |                                                           |
| Enlarged chamber size  | 2.209 (0.861–5.672)         | 0.099 | 0.475 (0.119–1.889)         |                                                           |
| Severe MR              | 3.372 (0.994–11.438)        | 0.051 | 1.474 (0.252–8.627)         |                                                           |
| BNP (per 10)           | 1.076 (1.030–1.102)         | <0.001| 1.056 (0.969–1.152)         | 1.057 (1.005–1.112)                                      |
| ACEi                   | 1.519 (0.649–3.559)         | 0.335 |                            |                                                           |
| Beta-blocker           | 2.058 (0.835–5.075)         | 0.117 | 0.903 (0.260–3.138)         |                                                           |
| Diuretics              | 4.177 (1.780–9.799)         | 0.001 | 4.195 (1.299–13.543)        | 4.189 (1.704–10.296)                                    |
| Digoxin                | 0.777 (0.104–5.778)         | 0.805 |                            |                                                           |
| Corticosteroid         | 1.410 (0.520–3.823)         | 0.948 |                            |                                                           |
| Reduced fractional shortening | 3.042 (1.273–7.270)    | 0.012 | 1.711 (0.428–6.847)         |                                                           |
| IVT diastole           | 0.941 (0.665–1.330)         | 0.729 |                            |                                                           |
| IVT systole            | 0.833 (0.649–1.071)         | 0.154 | 0.838 (0.615–1.142)         | 0.794 (0.607–1.039)                                      |
| LA diameter            | 1.058 (0.980–1.143)         | 0.147 | 0.994 (0.910–1.086)         |                                                           |

ACEi, angiotensin converting enzyme inhibitor; BNP, brain natriuretic peptide; IVTdiastole, end-diastolic interventricular septum thickness; IVTsystole, end-systolic interventricular septum thickness; LA, left atrial; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

no survival benefit has been reported. In our results, there was no difference in primary outcome in the preserved LVEF group regarding the use of diuretics. However, in the reduced LVEF group, the patient who used diuretics had higher mortality (42.6% vs. 5.0%, P = 0.029). In addition, the diuretics use is an independent predictor of other adverse clinical outcomes in the multivariable Cox regression analysis. A plausible explanation is that rapid volume depletion by diuretics in late-stage DMD patients who had small body mass index and were bedridden status may lead to reflex tachycardia, which causes an increase in oxygen consumption and aggravated HF symptoms. But, because the study was observational, the results should be considered hypothesis-generating, highlighting the need for further randomized clinical trials. In addition, it is not clear whether diuretics were used in more critical patients or the drug itself had adverse effects on patients. Nevertheless, our finding suggested that DMD patients also may be faced with the progression of heart failure and needs caution to use diuretics.

In addition, our results suggested that an elevated BNP level was an independent predictor of clinical outcomes irrespective of LVEF in the multivariable Cox regression analysis.
It has been known that BNP levels correspond to LV filling pressure and LV systolic dysfunction in patients with DMD. However, various studies showed discrepancies in the association between BNP levels and LV systolic dysfunction in patients with DMD. Recent ventilator support for patients with DMD might be one of the plausible explanations for those discrepancies. The ventilatory support may contribute to a relatively lower BNP level by unloading the left ventricle. The authors found that patients with idiopathic dilated cardiomyopathy had a higher BNP level compared with those with muscular dystrophy who used ventilatory support in a similar LV end-diastolic dimension. However, there was still lacking evidence of the association between ventilatory support and BNP level. In context, the present study suggests that a high BNP level despite maintaining ventilator support may indicate more advanced heart failure and the likelihood of adverse clinical outcomes in patients with DMD.

The present study observed that although there was no difference in using of ventilatory support rate between the two groups, the mean BNP level was significantly different regarding LVEF. In the preserved LVEF group, the mean BNP was 26.0 ± 24.5 pg/mL, consistent with the previously reported BNP level in normal males in the 20-year-old population. In the reduced LVEF group, the BNP level of the reduced LVEF group was higher than that of the preserved LVEF group (90.3 ± 91.6 vs. 26.0 ± 24.5 pg/mL, P < 0.001). Moreover, the BNP level of the patients who meet the primary endpoint was 136.0 ± 115.3 pg/mL. Although BNP levels in DMD patients are relatively lower than heart failure patients who are not DMD, an association between even moderately elevated BNP levels and mortality in patients with DMD has been reported. Also, in our results, BNP level was an independent predictor for worse clinical outcomes in multivariable Cox regression analysis. Therefore, elevated BNP levels should be importantly considered as a poor prognostic factor in DMD patients who require ventilator support.

The current guidelines recommend corticosteroids, ACEi, mineralocorticoid receptor antagonists, and beta-blockers for reducing cardiovascular events in patients with DMD. Gernot et al. reported that patients with DMD treated with corticosteroids showed significant reductions in all-cause death and cardiomyopathy compared with the no-steroid-therapy group. However, because improved clinical outcomes in DMD patients were observed in patients with preserved LVEF only, the evidence of corticosteroid treatment in DMD patients with reduced LVEF is insufficient. Moreover, the beneficial association of corticosteroid treatment in late-stage DMD patients had few evidence. Nevertheless, the lower rate use of corticosteroids in the present study is one of the limitations. Although corticosteroid acts non-selectively contributing to many associated complications which impact the quality of life, a recent position statement recommended that corticosteroid treatment is the gold standard for DMD patients. Thus, our results should be considered with caution. Meanwhile, renin-angiotensin-aldosterone system inhibitors and BB are used as first-line drugs for heart failure. Some observational studies reported the improvement of LVEF in early-stage DMD patients with heart failure medication including ACE-I or BB. However, most DMD patients had intolerance of combination treatment due to lower BP. Thus, the patient in the present study had been prescribed ACE-I/angiotensin receptor blocker over 97%, and relatively lower use of BB. In addition, unlike in the early-stage DMD patients, there are few studies that reported the effect of heart failure medication in late-stage DMD patients. In the present study, ACE-I/angiotensin receptor blocker or BB had no association with clinical outcomes in the late-stage DMD patients.

Our results should be considered with caution and within the context of some of our study’s limitations. First, this was a non-randomized, observational, single-centre study of DMD—a rare condition. However, the single-centre design affords consistency in our analysis of laboratory and echocardiographic data. In addition, patients at our tertiary care hospital received high-level standard-of-care treatment for their cardiovascular and respiratory issues. Second, the present study was conducted for late-stage DMD patients. Thus, there should be caution that it is not generalizable to the younger population. Third, although the patients with DMD were divided according to the severity of LV systolic dysfunction, as recommended by current guidelines, echocardiographic analysis alone may be inferior to cardiac magnetic resonance imaging techniques due to limitation of echo window (especially in apical view). Future research should continue to use better techniques to evaluate LV systolic function in patients with DMD. Fourth, an elevated BNP level independently predicted clinical outcomes in our study; however, post-treatment changes in BNP levels and the way these changes affect clinical outcomes are beyond the scope of this study. Finally, because the present study was conducted for long period, current heart failure therapies were not fully applied to the DMD patient. In addition, due to the fragility of late-stage DMD patients, physicians might have the decision to simply reflected conservative management. Thus, further prospective research will be required to the potential of current heart failure drugs on the reduction of adverse clinical outcomes in late-stage DMD patients.

**Conflict of interest**

None declared.
Clinical outcomes in late-stage DMD patients regarding LVEF

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of patients who died.

Table S2. Echocardiographic characteristics of patients who died.

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