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ORIGINAL ARTICLE

Pulmonary function tests for evaluating the severity of Duchenne muscular dystrophy disease

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Abstract

Aim: In Duchenne muscular dystrophy (DMD), lung disease contributes significantly to morbidity and mortality. This study aimed to assess the usefulness of various pulmonary function tests in evaluating DMD severity.

Methods: This retrospective study analysed lung function tests of patients with DMD-treated in the multidisciplinary respiratory neuromuscular clinic at Schneiders' Children Medical Center of Israel. Data were analysed according to age, ambulatory status and glucocorticoid treatment.

Results: Among 90 patients with DMD, 40/63 (63.5%) ambulatory patients and 22/27 (81.5%) nonambulatory patients successfully performed spirometry. Significant annual declines were demonstrated among nonambulatory patients, in percentile predicted forced vital capacity (3.8%) and in total lung capacity (5.5%) per year. The decline correlated with age and loss of ambulation but not with steroid treatment. Peak cough flow values were randomly distributed and did not correlate with age, ambulation or treatment. In nonambulatory patients, transcutaneous carbon dioxide measurement correlated significantly with age ($r = 0.55$, $p = 0.02$).

Conclusion: Forced vital capacity, total lung capacity and transcutaneous carbon dioxide correlated with the clinical severity of disease in children with DMD. These measures may be useful in follow-up and clinical trials. A comparable correlation was not found for peak cough flow.

KEYWORDS

Duchenne muscular dystrophy, forced vital capacity, lung function, peak cough flow, restrictive lung disease

Abbreviations: (CO_2), carbon dioxide; (DMD), Duchenne muscular dystrophy; (FVC), forced vital capacity; (MEP), maximal expiratory pressure; (MIP), maximal inspiratory pressure; (PCF), peak cough flow; (PEF), peak expiratory flow; (PFT), pulmonary function test; (TLC), total lung capacity.

Hagit Levine and Itai Goldfarb contributed equally to this study.

1 | INTRODUCTION

Duchenne muscular dystrophy (DMD), an X-linked recessive disorder, is one of the most common neuromuscular disorders of childhood. A systematic review and meta-analysis of 31 studies from around the world reported that DMD globally affected approximately 1:5000 newborn males.[1] Due to mutations in the dystrophin gene, deficiency in dystrophin protein leads to progressive skeletal muscle atrophy.[2,3] This causes continuous deterioration, weakness and loss of ambulation and motor skills. Ultimately, respiratory and cardiac failure commonly follow and typically result in death in the third decade of life.[4]

Respiratory insufficiency in DMD results from progressive respiratory muscle weakness that causes restrictive respiratory disease.[5] Respiratory morbidity is heralded by decreased lung volume, exhibited by decreased vital or total lung capacity (TLC). Thus, DMD may eventually impair the ability to inhale and exhale fully, cough effectively and ventilate properly. This may lead to the need for airway clearance assistance and mechanical ventilation in young adulthood.[5,6]

Regular assessment of static airway pressures and pulmonary function by spirometry is part of the current standard of care in DMD.[6] This monitoring typically starts late in the first decade of life. It includes annual assessments of lung volume that use forced vital capacity (FVC), together with measurements of respiratory muscle strength. The latter uses maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP).[7] The serial pulmonary function tests (PFTs) included in the monitoring enable early identification and treatment of pulmonary complications. Relations of these assessments with diaphragmatic and chest wall weakness and fibrosis have been reviewed in previous studies.[8–10]

In patients with DMD, progressively decreased cough efficacy is expected, as well as impairment of other respiratory functions. Cough ability is assessed by peak cough flow (PCF), which is one of the most utilised measurements in the clinical evaluation of DMD. Multiple studies have established PCF values in healthy adults as greater than 360–400 L/min. A PCF value greater than 270 L/min is considered normal, whereas a value below 160 L/min is classified as an ineffective cough.[11] PCF values of 160–270 L/min at a steady state are expected to drop below 160 L/min during acute pulmonary disease.[11] Treatment for improving mucous drainage and pulmonary ventilation in DMD consists of respiratory physiotherapy and the use of a cough assist device. Internationally accepted guidelines for treating DMD delineate indications to begin cough assistance. These indications are the following: FVC less than 50% predicted for age, PCF less than 270 L/min and MEP less than 60 cm water, or PCF less than 160 L/min.[12] International guidelines issued in 2018 recommended earlier initiation of cough assistance devices compared with previous guidelines.[6,12] Bach and Saporito studied 49 patients with chronic ventilator failure due to primary neuromuscular disease. They suggested that a PCF greater than 160 L/min was a discriminating threshold for decannulation failure.[13] However, the current literature contains limited data concerning the standardisation of normal and abnormal values of PCF in healthy children[14] and in children with DMD.[15]

Key Notes

- Lung function tests are used to assess disease progression in Duchenne muscular dystrophy and to direct treatment according to guidelines.
- Among children with this disease, forced vital capacity, total lung capacity and transcutaneous carbon dioxide were correlated with clinical severity and may be useful measures for follow-up and clinical trials.
- Peak cough flow values were randomly distributed and thus not useful for predicting disease severity.

Corticosteroids are the current standard of care for DMD. Corticosteroid treatment has been shown to modify the natural progression of the disease by slowing the decline of motor and pulmonary function, and extending survival.[16–18] The benefits of corticosteroids have been attributed to their anti-inflammatory effects in dystrophic muscles, thus contributing to preserved ambulation, by delaying the loss of muscle strength.[19] Overall, steroid treatment has been associated with preserved pulmonary function relative to no treatment.[20] However, prolonged glucocorticoid steroid treatment has been associated with complications such as linear growth failure, excessive weight gain and an increased risk of osteoporosis.[19] The glucocorticoids most commonly used in DMD include prednisone/prednisolone and deflazacort, an oxazoline derivative of prednisolone. Among patients who received deflazacort compared with prednisone, better pulmonary functions were demonstrated, with higher FVC predicted for age.[21] However, no significant relation was demonstrated between any corticosteroid treatment and the preservation of cough strength.[22]

This study aimed to assess the usefulness of various PFTs in evaluating DMD severity. The study also assessed correlations between PFTs and clinical status, as indicated by ambulatory status and steroid treatment, in children with DMD.

2 | PATIENTS AND METHODS

This was a cross-sectional retrospective study conducted in the multidisciplinary respiratory neuromuscular clinic at Schneider Children Medical Center of Israel. Data were collected from the medical files of children with DMD. They were all assessed at routine follow-up appointments, between 1 January 2017 and 31 December 2021. Clinical data were retrieved from electronic medical records. All the patients with a typical clinical phenotype of DMD and a confirmed genetic dystrophin mutation, who were able to perform PFTs, were included. No specific intervention was implemented. The most recent PFT performed was recorded for

analysis. Patients were classified as ambulatory if they were able to walk independently, without any assistive device or braces, for a distance of 10 m.[23]

The DMD care guidelines published in 2018 were generally followed.[12] Daily glucocorticoid therapy was recommended to patients at the discretion of the treating physician. This included either prednisone (0.75 mg/kg/day, maximum 30 mg/day) or deflazacort (0.9 mg/kg/day, maximum 36 mg/day).

Annual routine PFTs were obtained for each patient, from age 5 years, and according to the patients' ability to perform appropriate tests. Tests were carried out in a seated position, in a chair with no armrest, using the American Thoracic Society standard. Spirometry, MIP, MEP, PCF and lung volumes were assessed accordingly. We used the Polgar prediction equations for children aged up to 18 years. We used the European Community for Steel and Coal/European Respiratory Society or Knudson prediction equation references values for patients aged 18 years and above. The PFTs were normalised based on the predicted PFTs for age, as mentioned. PFTs are thus presented as percentile (%) predicted for age and not as absolute number. An exception is PCF, for which there are no standard predicted values. PCF was measured by a spirometer. Patients were instructed to inhale deeply and then cough as forcefully and quickly as possible, without assistance. The patients completed at least three qualified measurements and the highest PCF value was recorded. Only valid PFTs were included in the study.[24,25]

Transcutaneous CO_2 was measured for each patient in the morning on the day of their PFT. This measurement was found to be a prognostic parameter, also for night hypoventilation status.[26]

2.1 | Statistical analysis

Data obtained from the medical records were compared between ambulatory and nonambulatory patients, and between patients according to steroid treatment, by age on the test date.

All PFT variables were first tested for normality, using the D'Agostino-Pearson test. If normal, an unpaired parametric *t*-test was performed to assess differences between two groups. For comparisons of more than two groups, a one-way analysis of variance with the post-hoc Tukey's test was performed. For variables without normal distribution, an equivalent nonparametric Mann–Whitney *U* test was performed. For comparisons of more than two groups, a nonparametric Kruskal–Wallis analysis of variance test was performed.

Normally distributed variables included the %MIP, %MEP and the PCF. Skewed variables included the %FVC, %TLC, percent residual volume (RV), %RV/TLC and transcutaneous CO_2. Additionally, Pearson and Spearman correlation (r), and simple linear regression were used to evaluate associations with age. Due to the interaction with ambulation status, we adjusted the analysis and subdivided the population into ambulatory and nonambulatory children. Pearson correlation was performed for normally distributed variables, such as %TLC, %RV/TLC, %MIP, %MEP and PCF. Otherwise, the Spearman correlation was performed, namely for %FVC, %RV and transcutaneous CO_2.

Finally, to analyse the differences in all PFTs according to treatment, a Kruskal–Wallis test was performed with the Dunn's multiple comparisons test. This test was performed due to not normally distributed variables and the small sample size.

All the statistical analyses were performed using GraphPad Prism version 9.0 for Windows (GraphPad Software Inc). A *p*-Value ≤0.05 was considered significant.

The study was approved by the Rabin Medical Center International Review Board. The approval number was 0191-21-RMC.

3 | RESULTS

Of 90 patients with DMD, 62 (68.9%) had successfully documented PFTs and were further analysed. These 62 patients, median age of10.5 years (range 6–24), comprised 40/63 (63.5%) of the ambulatory patients and 22/27 (81.5%) of the nonambulatory patients. Of the 28 children (31.1%) who did not perform PFTs, this was due to age ≤6 years for 12 (42.8%) and to technical difficulties for 16 (57.1%). The median age of the ambulatory group was 9 years (range 6–19), and the median age of the nonambulatory group was 14 years (range 10–24). The median body mass index measure at the time of the PFT was 19 kg/m2 (range 14–28) for the ambulatory group. The comparative measure was 22 kg/m2 (range 11–32) for the nonambulatory group. The difference between the groups was not statistically significant, $p = 0.17$. The median body mass index percentiles for age were 93% and 86% for the ambulatory and nonambulatory groups, respectively.

The PFT performance rates included spirometry, lung volume, respiratory pressures and transcutaneous CO_2. For spirometry, performance rates were 62/90 (68.9%) for FVC and 45/90 (50%) for PCF. For lung volume, performance rates were 33/90 (36.7%) for TLC and 32/90 (35.6%) for RV. The performance rates for maximum respiratory powers were 31/90 (34.4%) for both MIP and MEP and 45/90 (50%) for transcutaneous CO_2.

3.1 | Analysis by ambulatory status

In children who were nonambulatory compared to those who were ambulatory, PFT values were lower for %FVC, %TLC, %MIP and %MEP ($p < 0.01$ for all), and transcutaneous CO_2 was higher ($p = 0.04$). Statistically significant differences were not found in the %RV ($p = 0.41$), %RV/TLC ($p = 0.16$) and PCF ($p = 0.80$) between the ambulatory and nonambulatory groups (Table 1).

3.2 | Analysis by age

Among nonambulatory patients, %FVC and %TLC decreased annually, by 3.8% and 5.5%, respectively, and were significantly

TABLE 1 Pulmonary function tests (PFTs) in ambulatory and nonambulatory DMD children (Mean ± SD).

PFTs	ADMD ($n = 40$)	NADMD ($n = 22$)	[a]p-Value
FVC (%)	87.2 ± 14.3 $n = 40$	61.8 ± 19.7 $n = 22$	**$p < 0.0001$**
TLC (%)	101.8 ± 10.7 $n = 21$	80.3 ± 24.6 $n = 12$	**$p < 0.01$**
RV (%)	129.9 ± 49.6 $n = 20$	126.8 ± 88.0 $n = 12$	$p = 0.41$
RV/TLC (%)	100.2 ± 23.2 $n = 17$	129.0 ± 76.1 $n = 10$	$p = 0.16$
MIP (%)	86.6 ± 26.0 $n = 19$	51.5 ± 22.8 $n = 12$	**$p < 0.001$**
MEP (%)	65.2 ± 14.5 $n = 19$	40.5 ± 14.7 $n = 12$	**$p < 0.0001$**
PCF (L/min)	208.8 ± 57.0 $n = 28$	214.1 ± 78.9 $n = 17$	$p = 0.80$
$PtcCO_2$ (mmHg)	35.2 ± 3.7 $n = 28$	39.5 ± 6.8 $n = 17$	**$p = 0.04$**

Abbreviations: ADMD, Ambulatory ambulatory DMD; DMD, Duchenne Muscular muscular Dystrophydystrophy; FVC, Forced forced Vital vital Capacitycapacity; MEP, Maximal maximal expiratory Pressure pressure– MEP; MIP, Maximal maximal Inspiratory inspiratory Pressurepressure; NADMD, Nonnon-ambulatory DMD; PCF, Peak peak Cough cough Flowflow; $PtcCO_2$, Pressure pressure of CO_2 transcutaneous.RV, Residual residual Volumevolume; TLC, Total total Lung lung Capacitycapacity.

p values written in bold if statistically significant, ≤ 0.05.

[a]between groups using the unpaired parametric t-test or nonparametric Mann–Whitney test according to the D'Agostino and Pearson omnibus normality test.

correlated with increasing age. Other PFTs, including PCF, showed no significant correlation with age ($r = 0.25$, $p = 0.33$) (Figure 1).

In the ambulatory group, %FVC showed a mild reverse correlation with age. PCF increased with increasing age ($r = 0.50$, $p < 0.01$). Other PFT parameters were not found to correlate with age (Figure 1).

Transcutaneous CO_2 significantly correlated with age in nonambulatory patients ($r = 0.55$, $p = 0.02$) but not in ambulatory patients ($r = -0.05$, $p = 0.78$).

3.3 | The effect of corticosteroids on PFTs

The majority, 53/62 (85.5%), of the patients were treated with corticosteroids: 44/53 (83%) were treated with prednisone, 7/53 (13.2%) with deflazacort and 2/53 (3.8%) with vamorolone. Medical treatments, including corticosteroids, are presented in Table 2.

After stratification by steroid treatment (Figure 2), no significant differences were found in PFTs between those treated and those not treated. This applied to both the ambulatory and nonambulatory groups ($p > 0.05$).

We further subdivided the steroid treatments into age groups, characterised by children up to and including age 9 years, aged 10–15 years and above 15 years. Still, no significant differences were found between the treated and untreated children ($p > 0.05$).

We note that PCF did not demonstrate any significant differences in the treated versus untreated children and between all the age groups ($p = 0.09$).

Among the corticosteroid regimens, deflazacort showed no difference from prednisone in any of the PFTs ($p > 0.05$). However, as

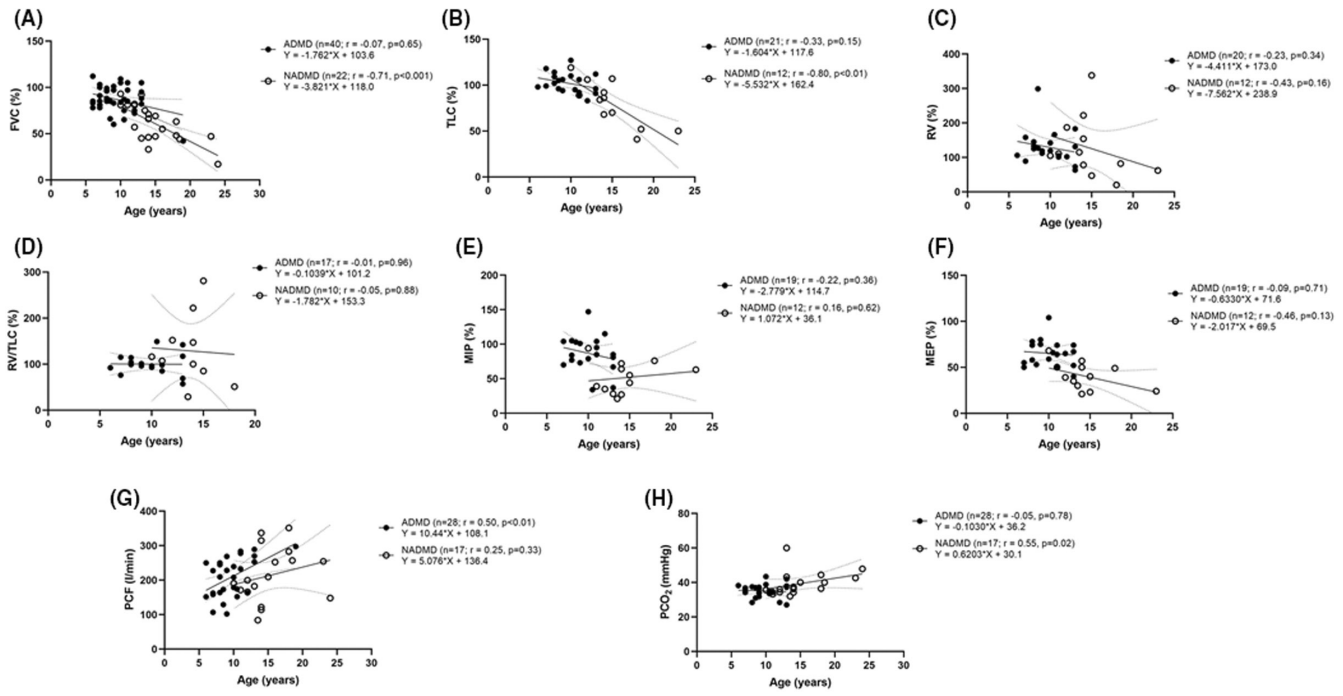

FIGURE 1 Correlation between pulmonary function tests and age in children with DMD.

only six ambulatory patients and one nonambulatory patient were treated with deflazacort, the statistical significance of this difference could not be assessed.

4 | DISCUSSION

In this study, we described the use of various PFTs in evaluating the severity of DMD. Additionally, we examined correlations of the test results with age, ambulatory status and corticosteroid treatment. We found that FVC, TLC and transcutaneous CO_2 were correlated with age and ambulation and may be valuable measurements for respiratory follow-up in children with DMD. However, PCF showed no significant relation with age or ambulatory status.

MEP was less indicative of disease severity. By contrast, MEP has demonstrated usefulness as a marker of respiratory muscle weakness and greater sensitivity than pulmonary volumes in detecting respiratory muscle weakness.[27]

The results of our cross-sectional study were consistent with those of a large longitudinal pulmonary function study. That study, the Cooperative International Neuromuscular Research Group Duchenne Natural History Study, demonstrated a correlation between FVC and the loss of upper extremity function.[17] However, in contrast to our study, they showed correlations of glucocorticosteroid with higher absolute peak expiratory flow (PEF), MIP and MEP. Notably, their measurements did not include PCF. Additionally, they did not calculate the slope of deterioration with increasing age for measurements other than FVC and PEF.

A retrospective chart review of children with various neuromuscular disorders also found that PCF was not statistically different between ambulatory and nonambulatory patients. In contrast to our findings, PCF was lower among children under age 10 years than among older children.[28] A retrospective study that comprised 41 patients reported strong linear correlations of PCF with PEF and FVC.[29] The authors suggested that these may be surrogate measures of cough effectiveness in children with neuromuscular disorders. Contrary to our research, they concluded that PCF may be used as a screening tool to identify patients at risk for pulmonary morbidity.

The current international guidelines state the importance of evaluating PCF and address the thresholds for starting cough assistance and respiratory physiotherapy.[12] These guidelines rely mostly on FVC, PCF and MEP measures, which are widely accepted in evaluating disease severity. Percentile FVC predicted for age is the most used PFT. This test is easy to perform and was found to best correlate with lung volume loss. Our study supports the high performance and good predictability of FVC for respiratory disease severity in DMD. This is due to the close correlation of this parameter with ambulation status. Percentile TLC predicted for age was also shown to be a valuable predictor of respiratory status, as it

TABLE 2 Treatments in ambulatory and nonambulatory DMD patients ($n = 62$).

	ADMD ($n = 40$)	NADMD ($n = 22$)
Corticosteroids *n* (%)	36(90%)	17(77%)
Prednisone/Danalone	28 (70%)	16 (73%)
Deflazacort	6 (15%)	1 (5%)
[a] Vamorolone	2 (5%)	0
None	4 (10%)	5 (23%)
Other treatment (*n* (%))		
Ataluren (Transelerna)	2	2
Eteplirsen (Exondys)	5	2

Abbreviations: ADMD, Ambulatory ambulatory DMD; D, Deflazacortdeflazacort; DMD, Duchenne Muscular muscular Dystrophydystrophy; NADMD, Nonnon-ambulatory DMD. Additional corticosteroids treatment; N, Nonenone; P, Prednisoneprednisone.
[a]Vamorolone—Corticosteroid under investigation.

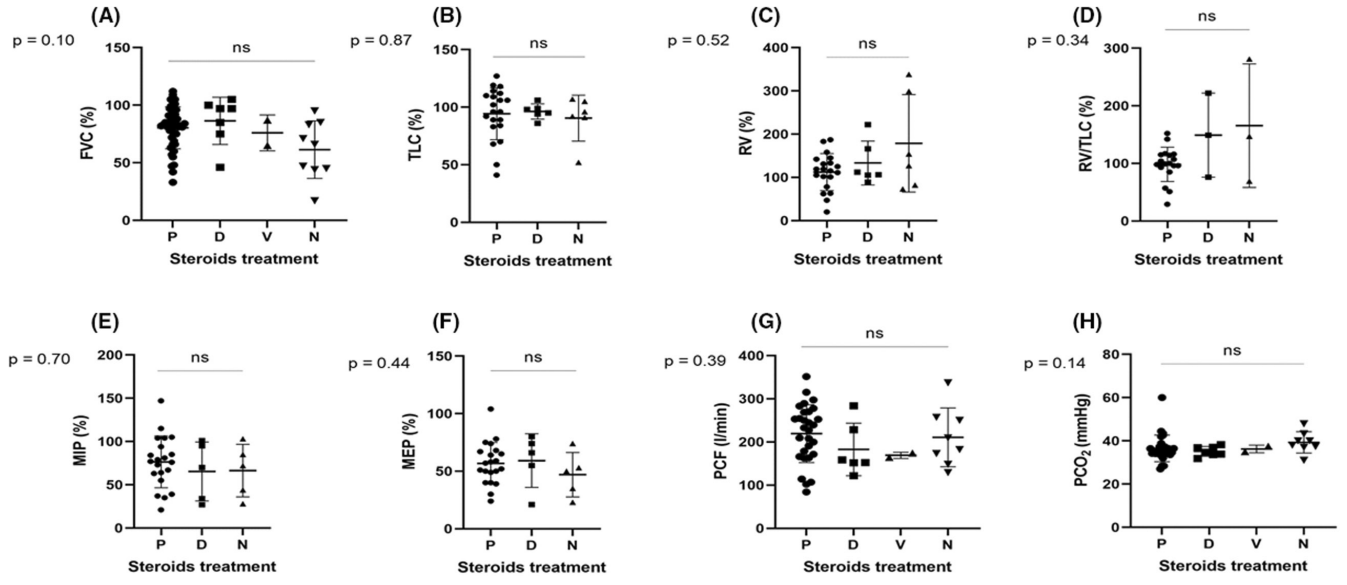

FIGURE 2 Pulmonary function tests in corticosteroids treated and untreated children with DMD.

correlated to age and ambulation. This supports the accuracy of FVC as a prognostic predictor. Nonetheless, PCF should be cautiously valued as a main measurement for directing clinical decisions in the treatment of DMD according to universal guidelines.

In the paediatric population, standard values and predicted percentiles for age are lacking.[14] Our demonstration that PCF did not correlate with other PFTs or with ambulatory abilities contributes to the current knowledge. Explanations for our findings include the lack of predictive value of PCF for age and the wide range of values for patients.[14] Reasons for the latter include differences in patient cooperation at the time of testing and technical issues. The latter arose due to the lack of accurate standardisation for performance. Further, PCF values were randomly distributed and significant differences according to clinical characteristics were not found. Clear relations to ambulatory status or steroid treatment were also not observed. Thus, PCF should not be the sole measure in determining the initiation of cough assistance for patients with DMD.

Our study was limited by its observational retrospective cross-sectional nature and by its not including repeated PFTs over time. The number of patients was relatively small, though it yielded enough power to assess differences between the groups evaluated. Despite the limitations, the observed data are concerning enough to encourage further investigation of PCF measurement in patients with DMD. The results may suggest the reconsideration of current treatment guidelines.

5 | CONCLUSION

FVC, TLC and transcutaneous CO_2 were correlated with the clinical severity of disease in children with DMD. These measures may be useful for follow-up and clinical trials. Similar correlations were not found for PCF.

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This study did not receive any specific funding.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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