Clinical Profile and Pulmonary Function of Pediatric Patients with Duchenne Muscular Dystrophy at a Tertiary Government Hospital

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ABSTRACT

Objective. Our study aimed to determine the clinical profile and pulmonary function of pediatric patients with Duchenne Muscular Dystrophy (DMD). We also characterized the stages of progression of the disease and determined their potential association with spirometry variables.

Methods. In this cross-sectional study, we used data obtained from a review of medical records of all pediatric patients (0-18 years old) with DMD seen in a multidisciplinary neuromuscular clinic of a tertiary government hospital from August 2018 until March 2020.

Results. Included were 30 patients subdivided into groups according to the stage of disease progression. Overweight (26.7%), obesity (20%), and scoliosis (26.7%) were common among non-ambulatory patients. Only one late ambulatory patient had evidence of ineffective airway clearance. Symptoms of sleep-disordered breathing, particularly snoring (66.7%) and apnea (6.7%), were common across all disease stages. All patients had normal peripheral oxygen saturation on room air. The mean peak expiratory flow rate was 215.6 (±84) L/min. The mean Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV1), and FEV1/FVC were 66.2% (±23.7), 67.7% (±23.8), and 97.5 (±3.2), respectively. Among patients with polysomnography results, the average apnea-hypopnea index (AHI) per hour was 3 (±1.6). When patients were compared according to their stage disease progression, however, no significant differences exist.

Conclusion. This is the first study on the pulmonary function of Filipino pediatric patients with DMD. Spirometry patterns characteristic of restrictive lung disease were observed. Prospective studies may help identify respiratory variables that significantly correlate with pulmonary function.

Keywords: Duchenne muscular dystrophy, children, pulmonary function, cross-sectional

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INTRODUCTION

Duchenne muscular dystrophy (DMD) is a rare neuromuscular disease inherited in an X-linked recessive pattern, affecting 7.1 per 100,000 males and 19.8 per 100,000 live male births.[1] The Philippine Pediatric Society Registry of Childhood Disease recorded 204 cases of Muscular Dystrophy (ICD 10 code: G71.0), including both Duchenne and Becker muscular dystrophies in the past 15 years, from January 2006 to June 2021.[2]

DMD is caused by mutations in the dystrophin gene, which result to absent or reduced dystrophin expression in neurons, and cardiac, smooth, and skeletal muscles.[3] The absence of functional dystrophin, a 427kDa cytoskeletal protein critical for muscle membrane stability, increases membrane permeability.[4] The subsequent muscle fiber degeneration, and damage of satellite cells, are followed predominantly by replacement with fibrosis and fat, and some muscle regeneration.[3] Progressive loss of muscle strength begins between 3 to 5 years old.[5] Affected toddlers have difficulty running, climbing stairs, rising from the floor, frequent falling, lordotic posture, waddling gait, and a positive Gower's sign.[6,7] DMD is diagnosed based on clinical features and confirmed by dystrophin gene deletion and duplication testing, genetic sequencing, immunohistochemistry, or Western blot of a muscle biopsy sample.[6]

Alteration of lung function in Duchenne muscular dystrophy is detected around eight years old.[8,9] Respiratory insufficiency because of progressive respiratory muscle weakness leads to ineffective cough, atelectasis, pneumonia, sleep-disordered breathing, nocturnal alveolar hypoventilation, and eventually, even daytime respiratory failure.[10] With the loss of ambulation between 8 to 14 years old, they typically become wheelchair-bound, develop scoliosis, and thoracic chest malformations, which further contribute to pulmonary function impairment.[5] Other factors leading to respiratory failure include malnutrition and dysphagia with aspiration.[10–12] Cardiac and respiratory failure ensue by the second decade of life, which commonly causes death.[5] With the introduction of mechanical ventilatory support, cardiac failure became the leading cause of mortality.[13]

Researches describing the clinical profile, evaluation, pulmonary function, and management practices for DMD have been published internationally, including nearby Asian countries like Japan, China, and Thailand.[14–17] Since the start of the University of the Philippines - Philippine General Hospital (UP-PGH) Multidisciplinary Neuromuscular Clinic in August 2018, more patients with DMD were brought for evaluation and management in our institution. While research on Duchenne muscular dystrophy is gradually being spearheaded locally, there are no published data on the pulmonary function of pediatric patients with DMD in the Philippines.

OBJECTIVES

The main objectives of this study were to determine the clinical profile and pulmonary function of Filipino children with DMD and identify the potential variables that affect the extent of their respiratory insufficiency.

Specifically, this paper aimed:

A. To determine the demographics, clinical manifestations, pulmonary function, anticipatory guidance, and pulmonary management of pediatric patients diagnosed with DMD based on the following variables:
    1. demographic profile:
        a. age at initial diagnosis (years)
        b. age at enrollment to the UP-PGH Multidisciplinary Neuromuscular Clinic (years)
        c. sex (male or female)
        d. manner of confirmation of diagnosis (genetic testing, genetic sequencing, muscle biopsy)
        e. family history of DMD or progressive muscular weakness
        f. stage of disease progression (Stage I-V)
    2. clinical manifestations:
        a. nutritional status (BMI Z –score)
        b. scoliosis (as documented by the note of uneven shoulders, waist or hips, or radiograph showing Cobb angle ≥10 degrees)
        c. frequency of pneumonia episodes per year, atelectasis on chest radiograph
        d. symptoms of sleep-disordered breathing (snoring, apnea, nocturnal awakening, hypersomnolence, hyperactivity)
    3. pulmonary function:
        a. oxygen saturation (SpO_2, %)
        b. peak expiratory flow rate (PEFR, L/min)
        c. spirometry [Forced Vital Cavity, FVC (% predicted), Forced expiratory volume in the first second, FEV1 (% predicted), FEV1/FVC ratio, and Peak expiratory flow rate, PEFR (L/minute)]
    4. presence of sleep-disordered breathing confirmed by polysomnography (Apnea-Hypopnea Index, per hour)
    5. cardiac evaluation by 2D echocardiography [left ventricular end-diastolic volume (%) and pulmonary artery pressure (mmHg)]
    6. respiratory support and management:
        a. manually-assisted coughing (glossopharyngeal breathing, air stacking, PPV with self-inflating bag-mask, PPV with ventilator)
        b. mechanically-assisted coughing (Mechanical insufflator-exsufflator)
        c. non-invasive Nocturnal Ventilation
        d. continuous Non-invasive Ventilation
        e. continuous Invasive Ventilation via tracheostomy
    7. other treatments given
        a. spinal surgery for scoliosis
        b. corticosteroids
        c. others
    8. anticipatory guidance
        a. frequency of clinic visits (yearly, every six months, every three months)
        b. updated vaccination (Flu vaccine within one year, Pneumococcal vaccine)
        c. nutrition and dietary counseling

B. To characterize the stage of progression of the disease (Stage I to V) and determine their potential association with the pulmonary function variables (SpO_2, PEFR, FVC, FEV1, and FEV1/FVC)

METHODS

Study Design

This is a cross-sectional study conducted at the UP-PGH. The primary investigator reviewed the medical records of pediatric patients diagnosed with DMD who were seen at the Multidisciplinary Neuromuscular Clinic from August 2018 until March 2020.

Study Population

Inclusion Criteria

The study included all patients aged 0 to less than 19 years old with genetically-confirmed DMD seen at the UP-PGH Multidisciplinary Neuromuscular Clinic from August 2018 until March 2020. The UP-PGH Multidisciplinary Neuromuscular Clinic was held initially on a quarterly basis and then every two months by 2020. However, due to the restrictions brought by the COVID-19 pandemic, the last multidisciplinary clinic was held in March 2020.

Exclusion Criteria

Patients with other neuromuscular disorders were not included in this study. Likewise, patients seen beyond the study dates indicated in this paper were not included in our review and analysis.

Data Collection

The investigators retrospectively reviewed all medical records of the pediatric patients diagnosed with DMD aged 0 to less than 19 years old seen at the UP-PGH Multidisciplinary Neuromuscular Clinic from August 2018 to March 2020. The diagnosis of DMD was based on characteristic clinical manifestations and confirmed by genetic testing. Data were gathered from a standardized medical record used in the multidisciplinary clinic for patients with DMD. The said standardized medical record was developed based on clinical guidelines in diagnosing and managing DMD.[18–20]

The primary investigator used a separate data collection form. An alphanumeric code was assigned to each patient for this study. No identifying patient data were found in the said data collection form.

The patients' demographics and clinical profile included the following: (1) age at diagnosis (years); (2) age at enrollment to the multidisciplinary clinic (years); (3) gender (male or female); (4) manner of confirmation of the diagnosis – genetic testing, genetic sequencing, or muscle biopsy; (5) family history of Duchenne muscular dystrophy or progressive muscular weakness; and (6) stage of disease progression – stage I to V.[6] There are five stages of the disease in DMD: (1) pre-symptomatic[6],(2) early ambulatory (approx. age 5–7 years), (3) late ambulatory (approx. age 8–11 years), (4) early non-ambulatory (approx. age 12–15 years), and (5) late non-ambulatory (approx. 16 years of age, or older).[21] During the pre-symptomatic stage (stage I), the patients may seem asymptomatic but can be diagnosed based on elevated creatinine kinase or a family history of the disease. The patients may show some developmental delay but have no gait disturbance. The early ambulatory stage (stage II) is characterized by a positive Gower sign, waddling gait, toe walking, but with the ability to climb the stairs. Increasing labored gait and losing the ability to climb stairs and rise from the floor are seen during the late ambulatory stage (stage III). There is a low risk for respiratory problems during the first three stages. Once they reach the early non-ambulatory stage (stage IV), they have an increased risk for respiratory impairment. At this stage, the patients might be able to self-propel for some time and maintain posture but might also start developing scoliosis. The late non-ambulatory (stage V) is characterized by increasingly limited upper limb function and postural maintenance hence with a higher risk of respiratory impairment.[6]

Clinical manifestations of DMD upon enrollment to the multidisciplinary clinic were also recorded. These included: (1) weight (kg), (2) height or arm span for non-ambulatory patients (cm), (3) nutritional status (body mass index z-score plotted on the WHO growth chart); (4) scoliosis documented by uneven shoulders, waist or hips, or Cobb angle >10 degrees on upright, posteroanterior radiograph[22]; (5) frequency of pneumonia episodes per year or atelectasis on chest radiograph; (6) symptoms of sleep-disordered breathing - snoring, apnea, nocturnal awakening, hypersomnolence, and hyperactivity based on the review of the medical records.

When available, the results of their initial pulmonary function tests – oxygen saturation (SpO_2, %), and spirometry (FVC, FEV1, FEV1/FVC, PEFR) were reviewed and recorded. The spirometry or pulmonary function tests had been performed by pediatric pulmonology fellows-in-training using the Koko Legend Portable Office Spirometry and interpreted based on the guidelines on standardization of spirometry by the American Thoracic Society/European Thoracic Society.[23] The interpretations of spirometry results had been verified by pediatric pulmonology consultants.

The results of baseline polysomnography (PSG) for patients with clinical features of sleep-disordered breathing, including obstructive sleep apnea (OSA) were also reviewed. OSA is characterized by repeated events of partial or complete upper airway obstruction during sleep, resulting in disruption of normal gas exchange and sleep patterns[24] and the gold standard test is polysomnography.[25] Although there is no universal consensus on cut off values for pediatric patients, many studies use the apnea hypopnea index (AHI) to categorize OSAS as mild (AHI 1–4.9), moderate (AHI 5–9.9), severe (AHI >10), and very severe (>30).[26]

The results of 2D echocardiography were also recorded when these were available. If performed, the results of the left ventricular ejection fraction (LVEF) and pulmonary artery pressure measured by 2D echocardiography were also noted. Normal values for LVEF in children are between 56 and 78%.[27] Pulmonary arterial hypertension (PAH) is defined as mean pulmonary artery pressure (PAP) ≥25mmHg at rest with a normal pulmonary capillary wedge pressure (≤15mmHg) and increased pulmonary vascular resistance index (≥3 Woods units x m^2).[28]

Furthermore, we reviewed the respiratory support and management received by the patients, if any. These include: (1) manually-assisted coughing; (2) mechanically-assisted coughing; (3) ventilatory support; (4) corticosteroid use (including duration); and spinal surgery (for patients with concomitant scoliosis). If any of these were given, the age at which it was initiated were also recorded.

Data on anticipatory guidance, whether implemented or not, were also reviewed and recorded. These include (1) frequency of follow-up clinic visits, (2) immunization status with Influenza and Pneumococcal vaccines, and (3) nutritional counseling. Lastly, we also documented referrals to other subspecialty services such as Otorhinolaryngology for patients with obstructive sleep apnea or Orthopedics for patients with scoliosis.

Sampling Method

Because there is a limited eligible population for this study, the investigators retrospectively reviewed the medical records of all pediatric patients diagnosed with DMD aged 0 to less than 19 years old seen at the UP-PGH Multidisciplinary Neuromuscular Clinic from August 2018 to March 2020 instead of random sampling.

Statistical Analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, mean and standard deviation for continuous variables. Relationship between pulmonary function variables (SpO_2, FVC, FEV1, FEV1/FVC, PEFR) and stage of disease progression (Stage I to V) was analyzed via Spearman's r correlation. Comparison according to age group were done using One-way ANOVA for continuous variables and Chi-square for categorical data. The level of significance was at 5%.

When available, the pulmonary function variables were presented using box plots.

Ethical Considerations

The study protocol was submitted to the University of the Philippines Manila Research Ethics Board (UPMREB) for ethics review and approval. This study was started only when ethical approval was obtained from the UPMREB (UPMREB Code 2020-464-01). In compliance with the Data Privacy Act of 2017 National Ethical Guidelines for Health-Related Research (NEGHRR), only relevant patient data required by Table 1 (Demographic Profile) were gathered. Personal details of the patient were not included. A unique alphanumeric code was assigned to each patient's medical record, and their names did not appear on any of the data collection tools.

The data gathered were protected by keeping the electronic files in an encrypted, password protected external hard drive. Only the study investigators have access to these records. After five years of study completion, all paper files will be shredded. Likewise, the hard drive containing the electronic files will be reformatted five years after the completion of this study. In cases of breach of privacy, the matter will be reported to the PGH Data Privacy Officer.

RESULTS

Demographics and Clinical Profile

Thirty-nine (39) pediatric patients were seen at the UP-PGH Neuromuscular Multidisciplinary Clinic from August 2018 to March 2020. Nine patients were excluded because of alternative working diagnoses – Spinal muscular atrophy, Limb-girdle muscular dystrophies, and Charcot-Marie-Tooth disease.

A total of 30 pediatric patients with DMD were included in the study. Most patients were at stages IV to V (n=14 for Stage IV, n=1 for Stage V), six patients at stage III, and nine at stages I to II (n=1 for Stage I, n=8 for Stage II) of disease progression. Table 1 shows that the average age at diagnosis was eight years old (±2.6), while the average age at enrollment to the multidisciplinary clinic was nine years old (±3.1).

All of the patients were male, whose diagnoses were confirmed by genetic testing. Ten percent (10%) had a family history of DMD, while 33.3% had a family history of progressive muscular weakness. The resulting p-value denotes that regardless of the stage of disease progression, they have the same demographic and clinical profile.

Clinical Manifestations

The clinical manifestations of pediatric patients with DMD are shown in Table 2. Although most of the patients had normal nutritional status based on the WHO Z –scores for BMI-for-age, 23.3% were classified as overweight (z-score >1), 13.3% as obese (z-score >2), 13.3% as thinness (z-score < -2), and 3.3% as severe thinness (z-score < -3). Most patients at stage IV to V had normal nutritional status.

Among the patients, 26.7% had scoliosis, which was more prevalent in patients in stages IV and V. However, there was no significant difference across the different stages of disease progression.

Most patients (96.7%) did not have or had one bout of pneumonia per year. Only one patient had evidence of ineffective airway clearance – pneumonia of 2 or more per year, and he was at stage V. No patient had atelectasis on chest radiograph. For symptoms of sleep-disordered breathing, 66.7% presented with snoring, while 6.7% had either apnea or

Table 1. Clinical Profile of DMD Patients in Different Stages of the Disease

	All (n=30)	Stages I-II (n=9)	Stage III (n=6)	Stages IV-V (n=15)	*p* value
Age at diagnosis (years)	8.1 ± 2.6	7.3 ± 4.1	7.8 ± 0.8	8.7 ± 1.95	0.479ns
Age at enrollment	9.0 ± 3.1	7.8 ± 4.3	8.3 ± 1.0	10.0 ± 2.5	0.192 ns
Sex					
Male	30 (100)	9 (100)	6 (100)	15 (100)	-
Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Confirmation of diagnosis					
Genetic testing	30 (100)	9 (100)	6 (100)	15 (100)	-
Genetic sequencing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Muscle Biopsy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Family history					
Duchenne muscular dystrophy	3 (10.0)	2 (22.2)	1 (16.7)	0 (0.0)	0.2055 ns
Progressive muscular weakness	10 (33.3)	4 (44.4)	1 (16.7)	5 (33.3)	
None	17 (56.7)	3 (33.3)	4 (66.7)	10 (66.7)	

**significant, ns not significant*

Table 2. Clinical Manifestations of Pediatric Patients with Duchenne Muscular Dystrophy at Enrollment to the Multidisciplinary Clinic

	All (n=30)	Stages I-II (n=9)	Stage III (n=6)	Stages IV-V (n=15)	*p* value
BMI-for-age Z-score					
>+2SD	4 (13.3)	1 (11.1)	0 (0.0)	3 (20.0)	0.7415 ns
>+1SD	7 (23.3)	2 (22.2)	1 (16.7)	4 (26.7)	
-2SD to +1SD	14 (46.7)	4 (44.4)	4 (66.7)	6 (40.0)	
<-2SD	4 (13.3)	2 (22.2)	1 (16.7)	1 (16.7)	
<-3SD	1 (3.3)	0 (0.0)	0 (0.0)	1 (6.7)	
Scoliosis					
Present	8 (26.7)	2 (22.2)	1 (16.7)	5 (33.3)	0.7565 ns
Absent	22 (73.3)	7 (77.8)	5 (83.3)	10 (66.7)	
Ineffective airway clearance					
Pneumonia 0 to 1 per year	29 (96.7)	9 (100)	6 (100)	14 (93.3)	1.0000 ns
Pneumonia 2 or more per year	1 (3.3)	0 (0.0)	0 (0.0)	1 (6.7)	
Pneumonia 3 or more since birth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Atelectasis on CXR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Sleep-disordered breathing					
Snoring	20 (66.7)	6 (66.7)	5 (83.3)	9 (60.0)	0.6982 ns
Apnea	2 (6.7)	1 (11.1)	0 (0.0)	1 (6.7)	1.0000 ns
Nocturnal awakening	2 (6.7)	1 (11.1)	0 (0.0)	1 (6.7)	1.0000 ns
Hypersomnolence	1 (3.3)	1 (11.1)	0 (0.0)	0 (0.0)	0.5000 ns
Hyperactivity	1 (3.3)	1 (11.1)	0 (0.0)	0 (0.0)	0.5000 ns

**significant, ns not significant*

nocturnal awakening. However, when compared at different stages of disease progression, no significant difference exists.

Initial Peripheral Oxygen Saturation, Pulmonary Function Test Values, Apnea Hypopnea Indices (AHI), and 2D Echocardiography parameters of Pediatric Patients with Duchenne Muscular Dystrophy

Table 3 shows the initial peripheral oxygen saturation, pulmonary function test parameters, Apnea Hypopnea Indices (AHI) based on PSG, and echocardiography parameters of pediatric patients with DMD.

All patients had normal pulse oximetry on room air, and the average Sp02 (%) was 98.5% (±1.1). The mean peak expiratory flow rate (L/min) for stages I to II, III, and IV to V were 248 ± 116.9, 185 ± 63.6, and 204.4 ± 69.7, respectively. The mean FVC (% predicted) for stages I to II, III, and IV to V were 77.4 ± 9.2, 65.2 ± 26.6, and 60.0 ± 30.0, respectively. The mean FEV1 (% predicted) for stages I to II, III, and IV to V were 79.7 ±9.6, 68.2 ± 28.8, and 60.3 ± 29.1, respectively.

Although there was apparent regression of the values for FVC and FEV1 as the stage of decrease progresses, no significant difference exists. The mean FEV1/FVC is 97.5 (±3.2).

Table 3. Initial Peripheral Oxygen Saturation, Pulmonary Function Test Values, Apnea Hypopnea Indices (AHI), and 2D Echocardiography Parameters of Pediatric Patients with Different Stages of Duchenne Muscular Dystrophy

	All		Stages I-II		Stage III		Stages IV-V		*p* value
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	
SpO_2 (%)	30	98.5 ± 1.1	9	98.8 ± 0.8	6	98.5 ± 1.5	15	98.3 ± 1.0	0.544 ns
Pulmonary Function Test									
PEFR (L/min)	16	215.6 ± 84	5	248 ± 116.9	2	185 ± 63.6	9	204.4 ± 69.7	0.590 ns
FVC (% predicted)	10	66.2 ± 23.7	3	77.4 ± 9.2	2	65.2 ± 26.6	5	60.0 ± 30.0	0.657 ns
FEV1 (%predicted)	10	67.7 ± 23.8	3	79.7 ±9.6	2	68.2 ± 28.8	5	60.3 ± 29.1	0.594 ns
FEV1 / FVC	10	97.5 ± 3.2	3	99.0 ± 1.8	2	98.1 ± 1.6	5	96.4 ± 4.1	0.575 ns
Polysomnography									
Apnea-hypopnea index (per hour)	5	3.0 ± 1.6	1	2.5 -	2	1.7 ± 0.7	2	4.6 ± 0.9	0.138 ns
2D echocardiography									
Left ventricular ejection fraction (%)	14	62.4 ± 10.9	4	61.0 ± 14.1	2	53.5 ± 6.4	8	65.4 ± 9.9	0.403 ns
Pulmonary artery pressure (mmHg)	7	19.5 ± 37.9	3	13.2 ± 34.2	1	32 -	3	21.6 ± 54.7	0.934 ns

**significant, ns not significant*

The AHI across disease stages I-II, III, IV-V were 2.5, 1.7 ± 0.7, 4.6 ± 0.9, respectively. Of the five patients with polysomnography results, four patients at stages II-IV had mild OSA, while one patient at stage IV had moderate OSA. 2D echocardiography results showed that the mean left ventricular ejection fraction (%) for stages I to II, III, and IV to V were 61.0 ± 14.1, 53.5 ± 6.4, and 65.4 ± 9.9, respectively. There were 15 patients with values for LVEF, one for each stage II, III, and IV had low LVEF while one patient at stage IV had high LVEF. The average pulmonary artery pressure for stages I to II, III, and IV to V were 13.2 ± 34.2, 32, and 21.6 ± 54.7, respectively. Four out of seven patients with PAP values showed pulmonary hypertension, one for each stage I, III, IV, and V. When the patients were compared according to their stage of disease progression, no significant difference exists.

Figure 1 further illustrates the distribution of pulmonary function tests across stages I-V of disease progression in our cohort of patients with DMD. The data are shown as box plots.

Respiratory Management and Anticipatory Guidance for Pediatric Patients with Duchenne Muscular Dystrophy

Table 4 shows the respiratory management and anticipatory guidance received by our pediatric patients with DMD.

No patient was advised manually- or mechanically-assisted coughing or were on ventilator support.

Results also show that 30% of patients had a history of receiving corticosteroids before enrollment to the neuromuscular clinic, with an average length of use of 13 months. The mean age of commencement of corticosteroids before and upon enrollment to the multidisciplinary clinic was 9 (±2.5) years. No patient underwent spinal surgery for scoliosis. Most patients (50%) visited the multidisciplinary clinic yearly, while 40% were seen quarterly. Around 53% have updated immunization for influenza within the past year, while 56.7% have received pneumococcal vaccine. All patients underwent nutrition and dietary counseling. Only 20% were referred to Otorhinolaryngology while 76.7% were referred to Orthosurgery.

DISCUSSION

We report the demographics, clinical manifestations, pulmonary function, anticipatory guidance, and pulmonary management of pediatric patients diagnosed with DMD seen at the UP-PGH Multidisciplinary Neuromuscular Clinic quarterly since August 2018 and ended in March 2020, when restrictions due to the COVID-19 pandemic began. To our knowledge, this is the first study on the pulmonary function of Filipino patients with DMD. Information gathered from our study results may help clinicians improve the existing approach to pulmonary evaluation and management with this rare condition.

Included were 30 patients subdivided into groups according to the stage of disease progression. There are five stages of disease progression in DMD: (1) pre-symptomatic[6],(2) early ambulatory (approx. age 5–7 years), (3) late ambulatory (approx. age 8–11 years), (4) early non-ambulatory (approx. age 12–15 years), and (5) late non-ambulatory (approx. 16 years of age, or older).[21] Only one patient was seen at stage I of disease progression, whose diagnosis was suspected based on a positive family history and developmental delay. There were 8 patients at stage II, the early ambulatory stage (stage II) which is characterized by a positive Gower's sign, waddling gait, toe walking, but with the ability to climb the stairs. Six patients were at the late ambulatory stage (stage III), where there is increasing labored gait and losing the ability to climb stairs and rise from the floor. Most patients (n=14) were seen at stage IV, where they might be able to self-propel for some time and maintain posture but might also start developing scoliosis. Only one patient was seen at the late non-ambulatory (stage V) is characterized by increasingly

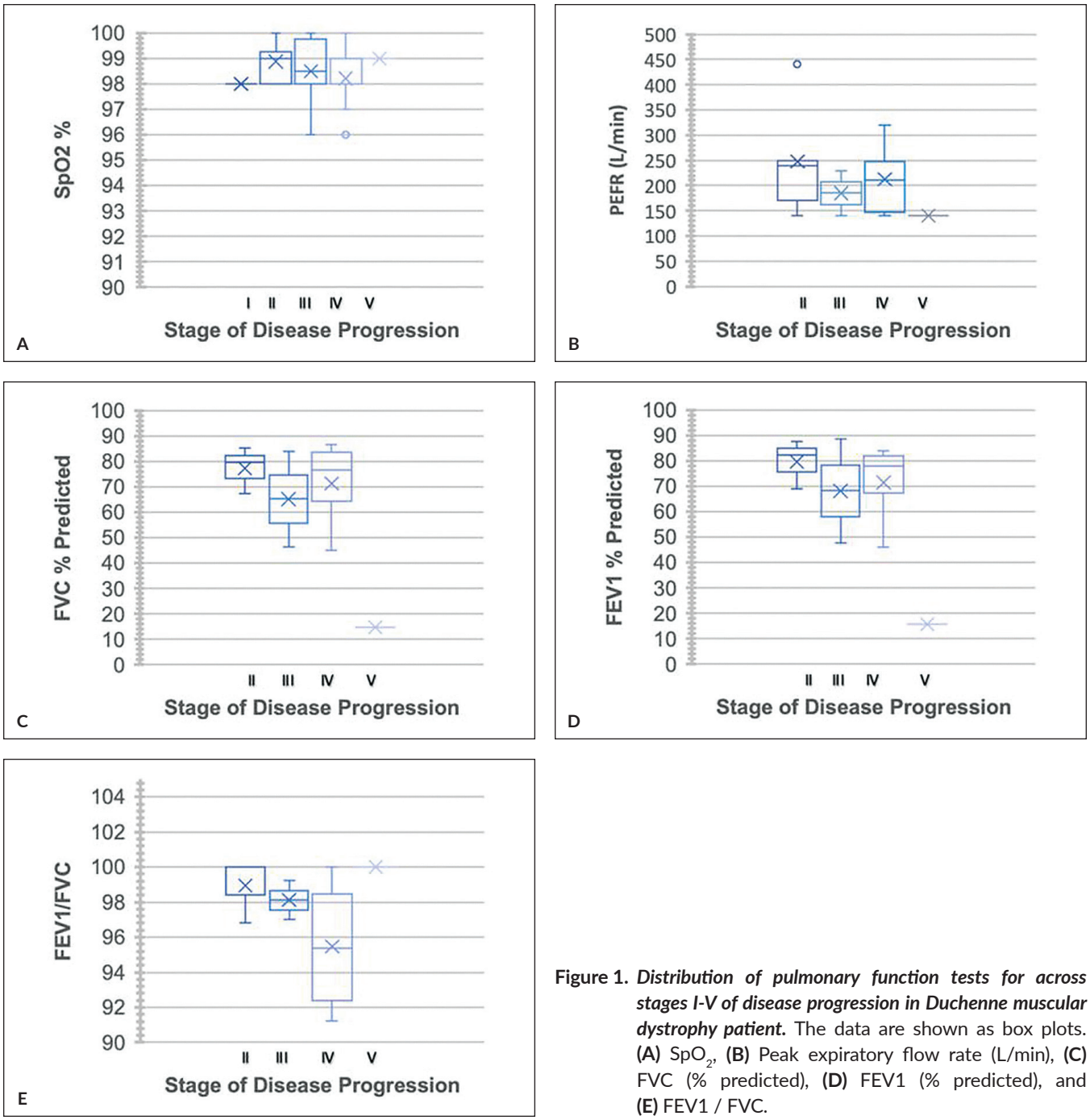

Figure 1. ***Distribution of pulmonary function tests for across stages I-V of disease progression in Duchenne muscular dystrophy patient.*** The data are shown as box plots. **(A)** SpO_2, **(B)** Peak expiratory flow rate (L/min), **(C)** FVC (% predicted), **(D)** FEV1 (% predicted), and **(E)** FEV1 / FVC.

limited upper limb function and postural maintenance hence with a higher risk of respiratory impairment.[6]

The average age at diagnosis and age at enrollment to the multidisciplinary clinic were 8 years old (±2.6) and 9 years old (±3.1), respectively. These findings are similar to the age at diagnosis in a study of Thai boys with DMD, where diagnosis was established by muscle biopsy or multiplex ligation-dependent probe amplification (MLPA).[17] These are also within the approximate age range of patients at stage II, where the early clinical manifestations of proximal muscle weakness are noted.[21] Although females are also affected in rare instances[1], all of the patients at our institution were male. As compared to a study in Taiwan where 43.5% of their patients had positive family history, only 10% had a family history of DMD in our institution, while 33.3% had a family history of progressive muscular weakness. The study in Taiwan, however, considered a positive family history if the mother is a DMD carrier; the maternal uncle or maternal male cousin has DMD; or siblings have DMD, while our institution has yet to test maternal carriage.[29]

Table 4. Respiratory Management and Anticipatory Guidance for Pediatric with Different Stages of Duchenne Muscular Dystrophy

	All (n=30)	StagesI-II (n=9)	Stage III (n=6)	Stages IV-V (n=15)	*p* value
Manually-assisted coughing					
Present	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Absent	30 (100)	9 (100)	6 (100)	15 (100)	
Mechanically-assisted coughing					
Present	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Absent	30 (100)	9 (100)	6 (100)	15 (100)	
Ventilator support					
Present	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Absent	30 (100)	9 (100)	6 (100)	15 (100)	
Corticosteroid use					
Yes	9 (30.0)	3 (33.3)	1 (16.7)	5 (33.3)	0.7664 ns
No	21 (70.0)	6 (66.7)	5 (83.3)	10 (66.7)	
Length (months) of corticosteroids use	13.3 ± 14.9	6.3 ± 5.4	8.0 ±	20.0 ± 19.2	0.410ns
Age of commencement (years) of corticosteroids	9.0 ± 2.5	8.0 ± 2.5	8.3 ± 1.0	9.8 ± 2.9	0.290 ns
Spinal surgery for scoliosis					
No	30 (100)	9 (100)	6 (100)	15 (100)	
Clinic visits					
Yearly	15 (50.0)	5 (55.6)	2 (33.3)	8 (53.5)	0.270 ns
Every 6 months	3 (10.0)	1 (11.1)	2 (33.3)	0 (0.0)	
Every 3 months	12 (40.0)	3 (33.3)	2 (33.3)	7 (46.7)	
Updated vaccination					
Flu vaccine within 1 year	16 (53.3)	4 (44.4)	3 (50.0)	9 (60.0)	0.8885 ns
Pneumococcal vaccine	17 (56.7)	5 (55.6)	4 (66.7)	8 (53.3)	0.8947 ns
Nutrition and dietary counseling					
Yes	30 (100)	9 (100)	6 (100)	15 (100)	-
Referrals to other subspecialty clinic					
Otorhinolaryngology	6 (20.0)	2 (22.2)	2 (33.3)	2 (13.3)	0.6069 ns
Orthosurgery	23 (76.7)	5 (55.6)	5 (83.3)	13 (86.7)	0.2370 ns

**significant, ns not significant*

Pulmonary Function Testing

Respiratory insufficiency in DMD results from respiratory muscle weakness and progressive scoliosis.[11] Baseline and serial pulmonary function tests are recommended to assess restrictive lung disease, to identify those at risk for complications of ineffective airway clearance, those who may benefit from assisted coughing and ventilation, and determine prognosis.[30]

All our ambulatory patients were seen at least once by Pulmonology service for baseline pulmonary function testing as recommended by the American Thoracic Society (ATS) Consensus Statement on Respiratory Care of the Patient with Duchenne Muscular Dystrophy. After confinement to a wheelchair, fall in the vital capacity below 80% predicted, and/or age 12 years, patients should visit a pulmonologist twice yearly.[30] Of the non-ambulatory patients, 46.7% were seen quarterly, while 53.5% were seen annually. It is also recommended that patients who require assisted airway clearance or ventilation should see a pulmonologist every three to six months or as indicated for routine follow-up.[30]

The baseline pulmonary functions of our patients were assessed by measuring oxygen saturation (SpO_2) by pulse oximetry, peak expiratory flow rate (PEFR) via a peak flow meter, and FVC, FEV1, and FVC/FEV1 by spirometry.[20,30] All patients had normal peripheral oxygen saturation on room air. PEFR, which measures maximal expiratory effort, is a surrogate for expiratory muscle strength and is used as a measure of disease progression in DMD.[19] The mean PEFR (L/min) decreased from stages I to II (248 ± 116.9), to stages III, and IV to V (185 ± 63.6, 204.4 ± 69.7). However, no significant difference exists. Spirometry showed restrictive patterns with diminished FVC (less than 80% predicted) with relative preservation of FEV1/FVC (≥ 80%). The mean FVC, FEV1, and FEV1/FVC were 66.2% (±23.7), 67.7% (±23.8), and 97.5 (±3.2), respectively. The maximal inspiratory pressure (cmH_2O), and maximal expiratory pressure (cmH_2O) with a pressure meter to determine respiratory muscle strength and awake carbon dioxide tension (pCO2) through capnography or venous or capillary blood gas were not measured or unavailable hence were not included in our study. None of our patients were documented to have daytime $SpO_2 < 95\%$. Such parameters may identify patients who require daytime ventilatory support.[30]

Nutrition

Loss of ambulation and treatment with corticosteroids[31] increase the risk for being overweight or obese.[10] Consequently, overnutrition in DMD is associated with obstructive sleep apnea.[32] Overweight (26.7%) and obesity (20%) were common among our non-ambulatory patients. Moreover, at least a third were using corticosteroids upon enrollment to the multidisciplinary clinic. In a study where 72% of the patients were currently or previously using steroids, the highest prevalence of obesity was 50% at the age of 10 years.[33] In the same study, BMI was also significantly associated with ambulatory status.

On the other hand, undernutrition may be expected in the later stages of the disease due to swallowing dysfunction and increased energy requirement from respiratory failure.[10] In contrast to the findings of previous studies, where declining BMI was associated with increasing age,[12,33] only 13.3% of our patients had z-scores below the -2 standard deviation (SD), while only one patient was below -3 SD, regardless of the stage of disease progression. All of our patients underwent nutritional and dietary counseling, which are the mainstays of prevention and treatment of overnutrition.[34] The management of undernutrition – evaluation for dysphagia, video-fluoroscopy, and gastrostomy tube placement were not recorded in our study.

Sleep Evaluation

Findings indicating sleep-disordered breathing associated with Duchenne muscular dystrophy[10] were snoring (66.7%) and apnea (6.7%), while the mean apnea-hypopnea index was per 3.0 per hour (±1.6) on patients with polysomnography results. Duchenne muscular dystrophy patients with associated sleep-disordered breathing documented on polysomnography (AHI ≥5 per hour) may require non-invasive nocturnal ventilation through a mouthpiece interface or tracheostomy.[10,13,20,35] Although none of our patients required non-invasive or invasive ventilatory support at the time of the study, at least 20% of our patients were referred to Otorhinolaryngology service for evaluation and management of possible sleep-disordered breathing.

Cardiac Involvement

Evaluation by Cardiology service was also done. 2D echocardiography findings indicating dilated cardiomyopathy and pulmonary hypertension were also observed, with mean left ventricular ejection fraction and pulmonary artery pressure of 62.4 % ± 10.9 and 19.5 ± 37.9 mm Hg, respectively. Specialist referral is also needed for holistic care of these patients.

Airway Clearance

Although only one patient at stage V had pneumonia of two or more per year[10], FVC <50% predicted indicating ineffective airway clearance was also observed in our patients, with the mean of 66.2% ± 23.7. However, none of our patients were instructed how to perform manually- or mechanically-assisted coughing, which may be beneficial in preventing atelectasis and pneumonia.[10,30,36]

Scoliosis

Once the patients become non-ambulatory (stages IV to V), they are increasingly unable to maintain their posture and scoliosis develops.[10,37] A multinational study showed that scoliosis was highest at 77.6% in the late non-ambulatory stage.[38] In our study, 33.3% of non-ambulatory patients had scoliosis. A study involving DMD patients with scoliosis showed that they might benefit from spinal surgery, with notable improvement in functional status and FVC at baseline compared to the non-surgical group.[39] Regardless of the presence of scoliosis, 76.7% were referred to the Orthopedics service. However, none of our patients with scoliosis underwent spinal surgery.

Corticosteroids

Although there is no definitive cure for DMD, the use of corticosteroids has been shown to improve respiratory muscle strength and delay the expected decline in lung function by decreasing inflammation-induced muscle damage.[31,40–42] Thirty percent of our patients had history of taking corticosteroids, while the mean age of commencement of corticosteroids before and upon enrollment to the multidisciplinary clinic was 9 (±2.5) years. Research on the impact of corticosteroids in our patients is recommended in a more extended study period.

Immunizations

Immunizations for pneumonia and influenza should be updated in patients with DMD.[10,20,30] Because only a percentage have immunization with influenza (53%) and pneumococcal (56.7%) vaccines, caregivers should be reminded to update, and patients should have easier access to these vaccines.

Limitations of the Study

Because the UP-PGH Multidisciplinary Neuromuscular Clinic was held six times in 18 months, we anticipated that data gathered were limited to a short study period. Therefore, only 30 pediatric patients with DMD were involved. Our study is also limited by its retrospective design, hence not all the needed clinical data may have been documented, or particular laboratory or radiologic tests may not have been done in all cases.

Another limitation of this study pertains to the assessment of pulmonary function based on spirometry results. In most cases of DMD, baseline spirometry is performed on patients at stage I disease severity and repeated annually by patients with Stage II or III and every six months on patients with Stage IV or V. However, some patients with DMD are very young and uncooperative. Moreover, others had an intellectual disability, hence may not be able

to perform the tests. Furthermore, because the presence of respiratory tract infection may alter spirometry results, spirometry for patients with cough, colds, fever, or respiratory distress may not be feasible during follow-up and postponed to their next clinic visit.

In line with said limitations, we recommend a more extensive prospective study with longer study duration to further characterize the stage of disease progression over time and identify respiratory variables that significantly correlate with the deterioration of pulmonary function.

CONCLUSION

This is the first study on the pulmonary function of Filipino pediatric patients with different stages of DMD seen in a multidisciplinary clinic. Spirometry patterns characteristic of restrictive lung disease were observed. Sleep disordered breathing and pulmonary hypertension were also noted. Prospective studies may help identify respiratory variables that significantly correlate with pulmonary function.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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