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Gain and loss of upper limb abilities in Duchenne muscular dystrophy patients: A 24-month study

Giorgia Coratti[a,b,1], Marika Pane[a,b,1], Claudia Brogna[a], Adele D'Amico[c], Elena Pegoraro[d], Luca Bello[d], Valeria A. Sansone[e], Emilio Albamonte[e], Elisabetta Ferraroli[b], Elena Stacy Mazzone[b], Lavinia Fanelli[a], Sonia Messina[f], Maria Sframeli[f], Michela Catteruccia[c], Gianpaolo Cicala[a,b], Anna Capasso[a,b], Martina Ricci[a,b], Silvia Frosini[g], Giacomo De Luca[c], Enrica Rolle[h], Roberto De Sanctis[a,b], Nicola Forcina[a], Giulia Norcia[a], Luigia Passamano[i], Marianna Scutifero[i], Alice Gardani[j], Antonella Pini[k], Giulia Monaco[k], Maria Grazia D'Angelo[l], Daniela Leone[a], Riccardo Zanin[m], Gian Luca Vita[n], Chiara Panicucci[o], Claudio Bruno[o], Tiziana Mongini[h], Federica Ricci[h], Angela Berardinelli[j], Roberta Battini[g,p], Riccardo Masson[m], Giovanni Baranello[m], Claudia Dosi[m], Enrico Bertini[c], Vincenzo Nigro[q], Luisa Politano[i], Eugenio Mercuri[a,b,*]

[a] Centro Clinico Nemo, IRCCS, Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy
[b] Pediatric Neurology, Università Cattolica del Sacro Cuore, Rome, Italy
[c] Unit of Neuromuscular and Neurodegenerative Disorders, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
[d] Department of Neurosciences, University of Padua, Padua, Italy
[e] The NEMO Clinical Center in Milan, Neurorehabilitation Unit, University of Milan, ASST Niguarda Hospital, Milan, Italy
[f] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[g] Department of Developmental Neuroscience, IRCCS Stella Maris, Pisa, Italy
[h] Neuromuscular Center, AOU Città della Salute e della Scienza, University of Torino, Turin, Italy
[i] Cardiomiology and Medical Genetics, Luigi Vanvitelli University Hospital, Naples, Italy
[j] Child and Adolescence Neurological Unit, National Neurological Institute Casimiro Mondino Foundation, IRCCS, IRCCS Mondino Foundation, Pavia, Italy
[k] Child Neurology and Psychiatry Unit, IRCCS Institute of Neurological Sciences, Bellaria Hospital, Bologna, Italy
[l] NeuroMuscular Unit, IRCCS Eugenio Medea, Bosisio Parini, Italy
[m] Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
[n] Unit of Neurology, IRCCS Centro Neurolesi Bonino-Pulejo - P.O. Piemonte, Messina, Italy
[o] Department of Neuroscience, Rehabilitation, Ophtalmology, Genetics, Maternal and Child Health-DINOGMI, Center of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini IRCCS, University of Genova, Genova, Italy
[p] Department of Clinical and Experimental Medicine, University of Pisa, Italy
[q] Department of Precision Medicine, Luigi Vanvitelli and Telethon Institute of Genetics and Medicine, University of Campania, Italy

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ABSTRACT

Duchenne muscular dystrophy (DMD) is a neuromuscular condition characterized by muscle weakness. The Performance of upper limb (PUL) test is designed to evaluate upper limb function in DMD patients across three domains. The aim of this study is to identify frequently lost or gained PUL 2.0 abilities at distinct functional stages in DMD patients. This retrospective study analyzed prospectively collected data on 24-month PUL 2.0 changes related to ambulatory function. Ambulant patients were categorized based on initial 6MWT distance, non-ambulant patients by time since ambulation loss. Each PUL 2.0 item was classified as shift up, no change, or shift down. The study's cohort incuded 274 patients, with 626 paired evaluations at the 24-month mark. Among these, 55.1 % had activity loss, while 29.1 % had gains. Ambulant patients showed the lowest loss rates, mainly in the shoulder domain. The highest loss rate was in the shoulder domain in the transitioning subgroup and in elbow and distal domains in the

* Corresponding author at: Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo A Gemelli 8, Rome 00152, Italy.
E-mail address: eugeniomaria.mercuri@unicatt.it (E. Mercuri).
[1] These authors contributed equally to this work.

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non-ambulant patients. Younger ambulant patients demonstrated multiple gains, whereas in the other functional subgroups there were fewer gains, mostly tied to singular activities. Our findings highlight divergent upper limb domain progression, partly linked to functional status and baseline function.

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular disease that affects around 1 in 3600 live male births [1]. As part of the disease course, there is a progressive reduction of strength, function, resulting in loss of ambulation and upper limb function [1,2]. Increasing attention has been paid to outcome measures that can assess function across the spectrum of functional abilities, from ambulant to non-ambulant [3–8]. One such outcome is the Performance of upper limb (PUL) test developed by the international Performance of the upper limb Working Group in 2013 to evaluate upper limb function in ambulant and non-ambulant DMD patients [9,10]. The test measures functional abilities in three domains (shoulder, elbow, and distal) and the original version, PUL 1.2, has undergone recent revision. The new version, PUL 2.0, simplifies the scoring system on the basis of Rasch analysis showing the redundancy of some intermediate scores [11]. At variance with the first version of the PUL in which items had a scoring from 0 to 5, in the PUL 2.0 the items receive a score of 0, 1, or 2, with the exception of 1 item scored as 0 and 1. The PUL 2.0 is designed to provide a more hierarchical response system for individual items and is increasingly been used in clinical trials and natural history studies [12–15]. The new three-point scoring system has also the advantage of facilitating the possibility to perform shift analysis that has recently been increasingly used to determine meaningful changes in motor function outcome measures for neuromuscular disorders [16–18].

Over the last few years there has been increasing attention to the use of an alternative methods for assessing gain or loss of functional abilities by using shift analysis that categorise the changes into a binary system (changes from being unable to be able to perform the task with or without compensations, or viceversa). In DMD this analysis has mainly been applied for the North Star Ambulatory assessment (NSAA) [17] and has also been used as an exploratory measure in several clinical trials showing that stratifying patients by their ability to perform or not an individual activity is an alternative effective method of detecting changes in response to an intervention [18,19].

The primary objective of this paper is to describe how often individual PUL 2.0 abilities are lost or gained by using the shift analysis in DMD patients with different functional levels.

2. Materials and methods

The retrospective study was performed by prospectively collecting de-identified data from the Italian DMD study group, that includes 15 national centres (Catholic University, IRCCS, Rome; Centro Clinico Nemo, University of Milano, Milan; IRCCS Eugenio Medea Bosisio-Parini, Bosisio-Parini; IRCCS Istituto Giannina Gaslini, IRCCS, Genoa; University of Messina, Messina; IRCCS Ospedale San Raffaele, Milan; Fondazione IRCCS Istituto Neurologico Besta, Milan; Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan; Luigi Vanvitelli University and University Hospital, Naples; Ospedale Bambino Gesù IRCCS, Rome; University of Padua, Padua; Istituto Mondino, Pavia; University of Turin, Turin; Neuromuscular Pediatric Unit, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna; Department of Developmental Neuroscience, IRCCS Stella Maris, Pisa) . The study included data collected between November 2011 and February 2022.

Individuals with genetically confirmed Duchenne Muscular Dystrophy and a minimum of three assessments, at one-year intervals were eligible for enrolment, irrespective of their ambulatory status. Following the methodology described in our previous study [20], ambulatory status was defined according to the functional status recorded at baseline and during the 24 months of the study. DMD individuals were defined as ambulant if they maintained ambulation throughout the 24 months. Ambulant patients were further subdivided according to meters walked on the 6MWT at baseline (>350, <350, <250). Loss of ambulation was defined as the inability of the patient to walk 10 m independently. Patients who were ambulant at baseline but lost ambulation during the duration of the study (24 months) were defined as transitioning patients. Patients who were already non ambulant at baseline were subdivided as follow: patients losing ambulation within 12 months of baseline, patients who lost ambulation between 12 and 24 months of baseline, patients who lost ambulation between 2 and 5 years of baseline, patients who lost ambulation more than 5 years before baseline.

The analysis was conducted solely on anonymous and de-identified data. Clinical investigations adhered to the Declaration of Helsinki principles, and written informed consent, approved by institutional review boards, was obtained from all participants or their guardians in accordance with ethical requirements. The coordinating center IRB protocol number is 0024731/22.

2.1. PUL 2.0

The primary objective of the PUL 2.0 is to evaluate upper limb performance of those with DMD. It is a functional scale that includes an initial entry item to establish overall upper limb level of function and 22 scorable items. These 22 items are further subdivided into three domains: shoulder level (6 items, maximum score of 12), elbow (9 items, maximum score of 17), and distal level (7 items, maximum score of 13) [11]. Each domain can be scored separately - shoulder, elbow, and distal. The total score can be obtained by summing up the three domain scores, with the maximum global score being 42. Details of the reliability studies and training sessions in both the original PUL version (with an ICC of 0.96) and the PUL 2.0 (with a Person Separation Index of 0.95) have already been reported [9,11]. For this study all evaluators underwent training sessions that yielded a comparable degree of agreement [12]. The PUL 2.0 scoresheet and manual can be obtained from www.opentact.org.

2.2. Statistical analysis

The assessment of gain and losses using the shift analysis was performed taking into consideration pairs of PUL2.0 assessments 24 months apart in patients with different ambulatory status. Each item of the scale was classified as follows:

- Shift up (gain of function): item scores increased from 0 to either 1 or 2;
- No change: item scores remained the same or had changes between 1 and 2 or vice-versa;

- Shift down (loss of function): item scores decreased from 1 or 2 to 0.

Frequency of item distribution and loss progression was calculated on each item/domain

As the aim of this paper was to assess gains and losses in the PUL 2.0 by using the shift analysis in each level of ambulatory status, to maximise participant populations, when patients had multiple assessments performed at different ages and different functional status, each paired assessment was considered according to the ambulatory status at the time the assessments were performed. Therefore, as performed in previous similar studies, every participant's assessment could act as a baseline and assessments from patients with a longer follow-up and different ambulatory status overtime were independently represented in each subgroup [16,17].

Patients in whom one of the two performances was reported as not being reliable by the evaluators, due to transient pain, fractures, recent pneumonia, or other infections, intercurrent surgery, or any other factor that affected temporarily one of the two assessments, were excluded from the analysis. Data from patients participating in clinical trials or open-label studies on investigational drugs were also excluded. Missing data lead to the exclusion of the entire assessment, meaning that no interpolation at an item-level or assessment at 12/24 month was performed if missing data was present.

Quantitative variables were described using the following measures: minimum, maximum, range, mean and standard deviation.

3. Results

The cohort included 626 24-month paired assessments from 274 patients who had at least three assessments at yearly intervals. Table 1 shows patients' characteristics at baseline.

Table 1
Patients' characteristics at baseline.

	All assessments (n = 626)
Age (Mean (SD))	12.1 (5.74)
Total PUL 2.0 (Mean (SD))	31.0 (11.7)
Shoulder PUL 2.0 (Mean (SD))	6.96 (4.89)
Elbow PUL 2.0 (Mean (SD))	12.8 (5.55)
Distal PUL 2.0 (Mean (SD))	11.3 (2.20)
Ambulant (N)	373
>350mt (N)	225
Transitioning (N (%))	5 (2.22 %)
<350mt	101
Transitioning (N (%))	32 (31.7 %)
<250mt	47
Transitioning (N (%))	41 (87.23 %)
Non ambulant	253
<12 months (N)	65
<24 months (N)	31
<5 years (N)	70
>5 years (N)	87

Details of how frequently individual items were already scored as "not able" (score 0) at baseline in relation to ambulatory status are shown in Table 2 and S1 table.

3.1. Shift analysis

From baseline to 24 month follow up, there was a loss of one or more activities in 345 of the 626 paired assessments (55.1 %) and a gain of one or more activities in 182 of the 626 (29.1 %). In 79 of the 626 assessments (12.61 %) there were concomitant gains and losses.

3.1.1. 24-month shift of total scores and PUL2.0 scores at baseline

Fig. 1 shows the mean number of activities lost or gained over 24 months based on total PUL 2.0 score at baseline. S1 Fig shows

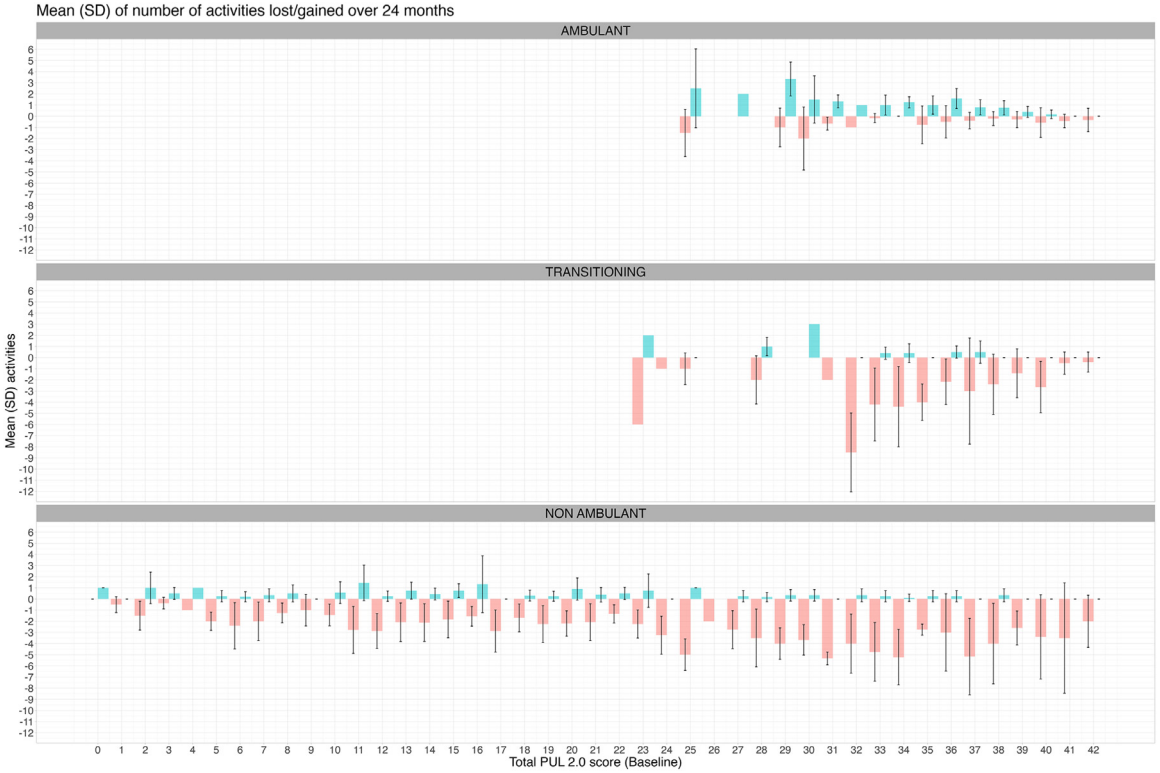

Fig. 1. Mean (SD) number of activities lost or gained at 24-months based on total PUL 2.0 score at baseline in ambulant (top row), transitioning (middle row) and non ambulant (bottom row). Key to figure: Red= mean number of activities lost, Light blue= mean number of activities gained.

Table 2
Frequency distribution of patients "not able" to perform PUL 2.0 items (score=0) by ambulatory status at baseline. The shaded cells indicate increasing number of patients not performing the item.

DOMAIN	ITEM	AMBULANT (N=295)	TRANSITIONING (N=78)	NON AMBULANT (N=253)
SHOULDER	1	0,30%	10,30%	76,70%
	2	0,30%	5,10%	69,20%
	3	0,30%	5,10%	69,60%
	4	0,70%	9,00%	74,70%
	5	9,80%	24,40%	83,40%
	6	39,30%	65,40%	91,70%
ELBOW	7	0%	0%	41,10%
	8	0%	0%	21,70%
	9	0%	0%	16,60%
	10	0,30%	1,30%	58,50%
	11	7,80%	26,90%	73,50%
	12	0%	1,30%	44,70%
	13	0%	0%	41,10%
	14	1,70%	7,70%	70,00%
	15	5,10%	2,60%	31,20%
DISTAL	16	2,70%	1,30%	17,40%
	17	0,30%	0%	6,70%
	18	0%	0%	11,50%
	19	0%	0%	14,20%
	20	0%	0%	4,70%
	21	0%	0%	2,40%
	22	0%	0%	3,20%

the mean number of activities lost or gained over 24 months based on the PUL 2.0 entry item.

3.1.2. Shift of total scores and ambulatory status: individual items

We evaluated gains and losses through shift analysis by examining pairs of PUL2.0 assessments separated by 24 months in patients with varying ambulatory statuses. Fig. 2 displays the results of the frequency analysis, depicting the individual item details that shifted up, down, or remained stable after 12 or 24 months, categorized by ambulatory status (ambulant, transitioning and non ambulant).

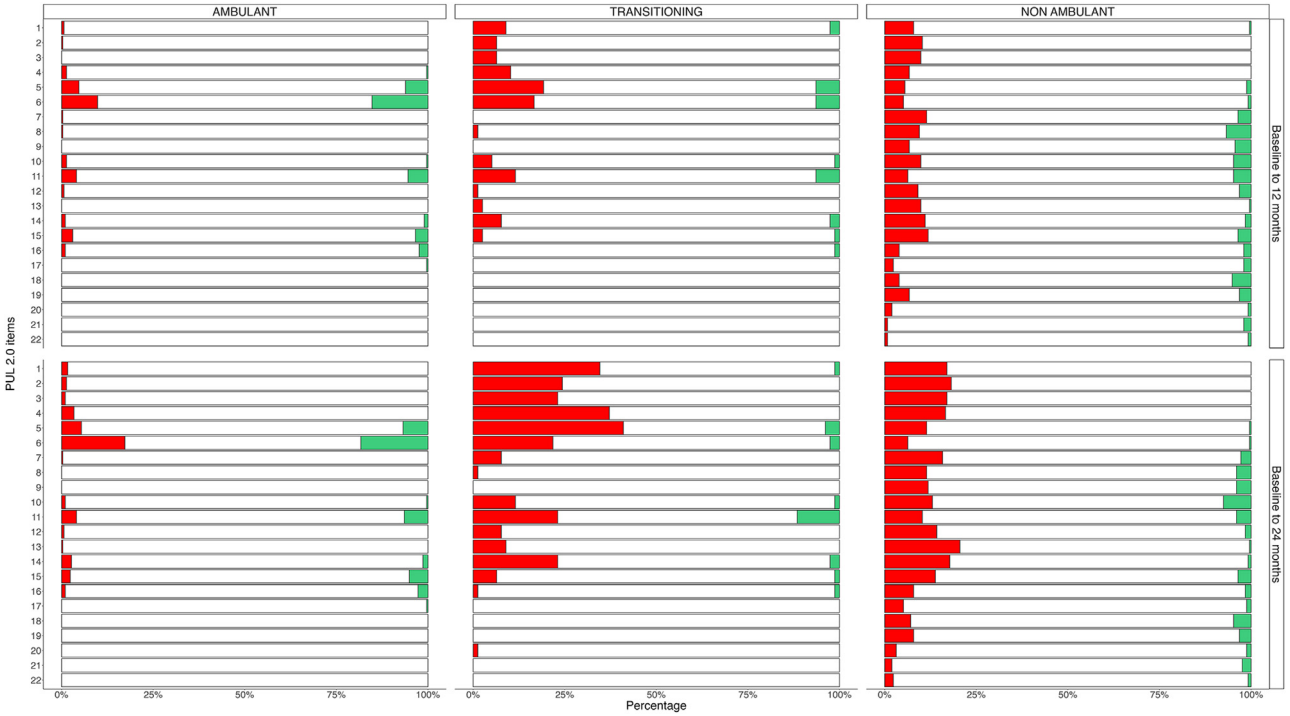

Fig. 2. Details of the frequency analysis at 12-month and 24-month change from baseline for individual items subdivided by ambulatory status. Key to figure: Red columns on the left side represent% of negative shifts (2->0 or 1->0). Green columns on the right side represent% of positive shifts (0->2 or 0->1).

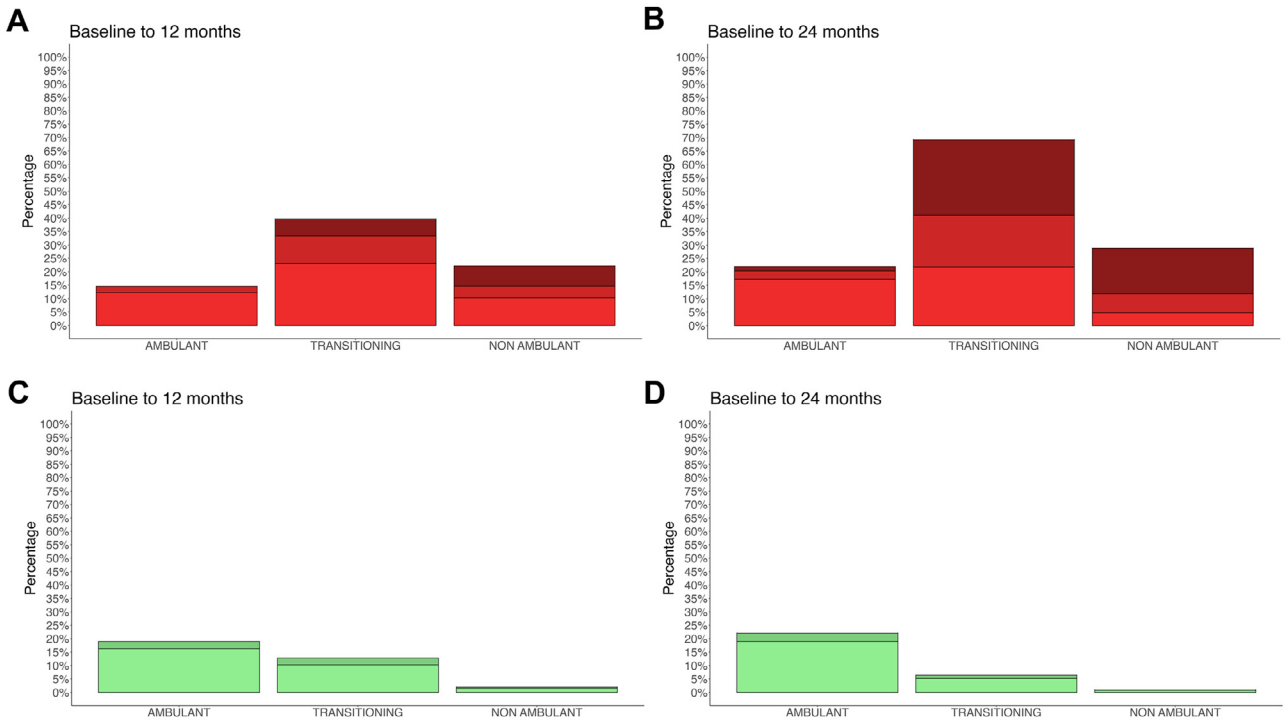

Fig. 3. Details of the frequency analysis on the number of activities lost or gained for the shoulder domain subdivided by ambulatory status. Key to figure: Panel A and B: Percentage of number of activities lost at 12 (A) and at 24 months (B) after baseline. Panel C and D: Percentage of number of activities gained at 12 (C) and at 24 months (D) after baseline. Colour coding: Light red: 1 activity lost; mild red: 2 activities lost; dark red: >2 activities lost, Light green: 1 activity gained; mild green: 2 activities gained; dark green: >2 activities gained.

S2 Fig provides additional details of the results subdividing the ambulant cohort according to meters walked on the 6MWT at baseline (>350, <350, <250) and the non ambulant cohort according to the length of time from loss of ambulation (A) and according to PUL 2.0 entry item (B).

3.1.3. Shift analysis in the individual PUL 2.0 domains

In the examination of the shoulder domain within PUL 2.0, which consists of 6 items with a total score of 12, we conducted a detailed analysis to determine the number of activities gained or lost. To provide a nuanced understanding, we categorized the losses into those involving a single activity and those involving two ore more activities. The percentage of activities lost at both 12 and 24 months post-baseline was calculated. Fig. 3 illustrates the outcomes, with panels a and b depicting the loss of shoulder activities, and panels c and d illustrating the gain of such activities at 12 and 24 months, respectively.

In the examination of the elbow domain within PUL 2.0, which consists of 9 items with a total score of 17, we conducted a detailed analysis to determine the number of activities gained or lost. As done in the shoulder domain, we categorized the losses into those involving a single activity and those involving two ore more activities. The percentage of activities lost at both 12 and 24 months post-baseline was calculated. Fig. 4 illustrates the outcomes, with panels a and b depicting the loss of elbow activities, and panels c and d illustrating the gain of such activities at 12 and 24 months, respectively.

In the examination of the distal domain within PUL 2.0, which consists of 9 items with a total score of 13, we conducted a detailed analysis to determine the number of activities gained or lost. As done in the previous domains, we categorized the losses into those involving a single activity and those involving two ore more activities. The percentage of activities lost at both 12 and 24 months post-baseline was calculated. Fig. 5 illustrates the outcomes, with panels a and b depicting the loss of elbow activities, and panels c and d illustrating the gain of such activities at 12 and 24 months, respectively.

4. Discussion

Over the last few years the PUL has been increasingly used in clinical trials to assess upper limb function across different stages of function in DMD and as the primary measure in studies on non ambulant patients. As the currently used version of the scale, PUL 2.0, is relatively recent, the number of natural history studies reporting changes over time is limited. We recently reported longitudinal data in a large cohort of DMD boys and young adults assessing changes in the raw scores over 12 and 24 months[12]. In this paper we report the use of the shift analysis, a method assessing how frequently abilities are lost or gained that is increasingly used in clinical trials and that has recently been applied to other functional scales in DMD [17] and SMA [16]. While the use of a simplified scoring system with a reduction of the number of scoring options decreases the possibility to detect changes and the sensitivity of the scale, the application of Rasch analysis clearly shows that this is not the case and that the simplified scoring system increases the reliability and the consistency of the scale. This approach is also supported by surveys performed in patients and parents who report to be more interested that an activity is performed irrespective of whether this is performed with (score 1) or without compensation (score 2).

The shift analysis confirmed the decline in upper limb function reported when analysing the changes of total and domain raw scores over time, providing additional information on the patterns of shift changes related to functional status and disease progression [11–13,20].

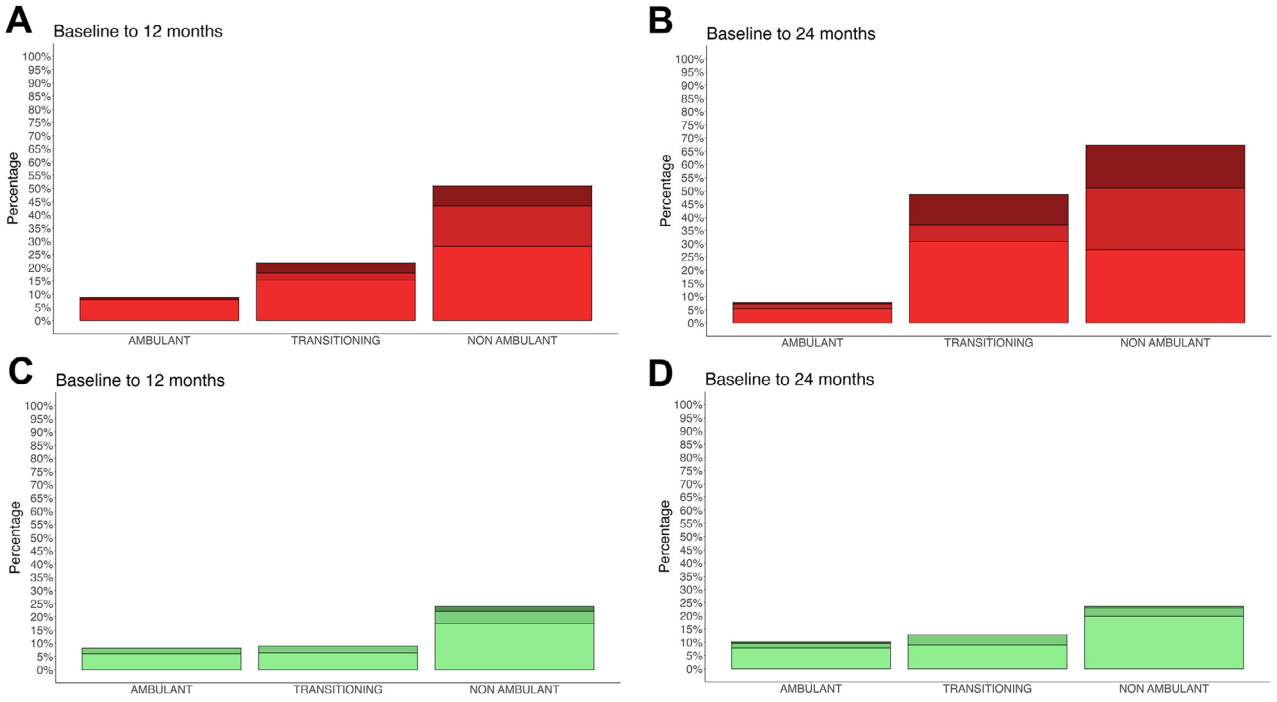

Fig. 4. Details of the frequency analysis on the number of activities lost or gained for the elbow domain subdivided by ambulatory status. Key to figure: Panel A and B: Percentage of number of activities lost at 12 (A) and at 24 months (B) after baseline. Panel C and D: Percentage of number of activities gained at 12 (C) and at 24 months (D) after baseline. Colour coding: Light red: 1 activity lost; mild red: 2 activities lost; dark red: >2 activities lost, Light green: 1 activity gained; mild green: 2 activities gained; dark green: >2 activities gained.

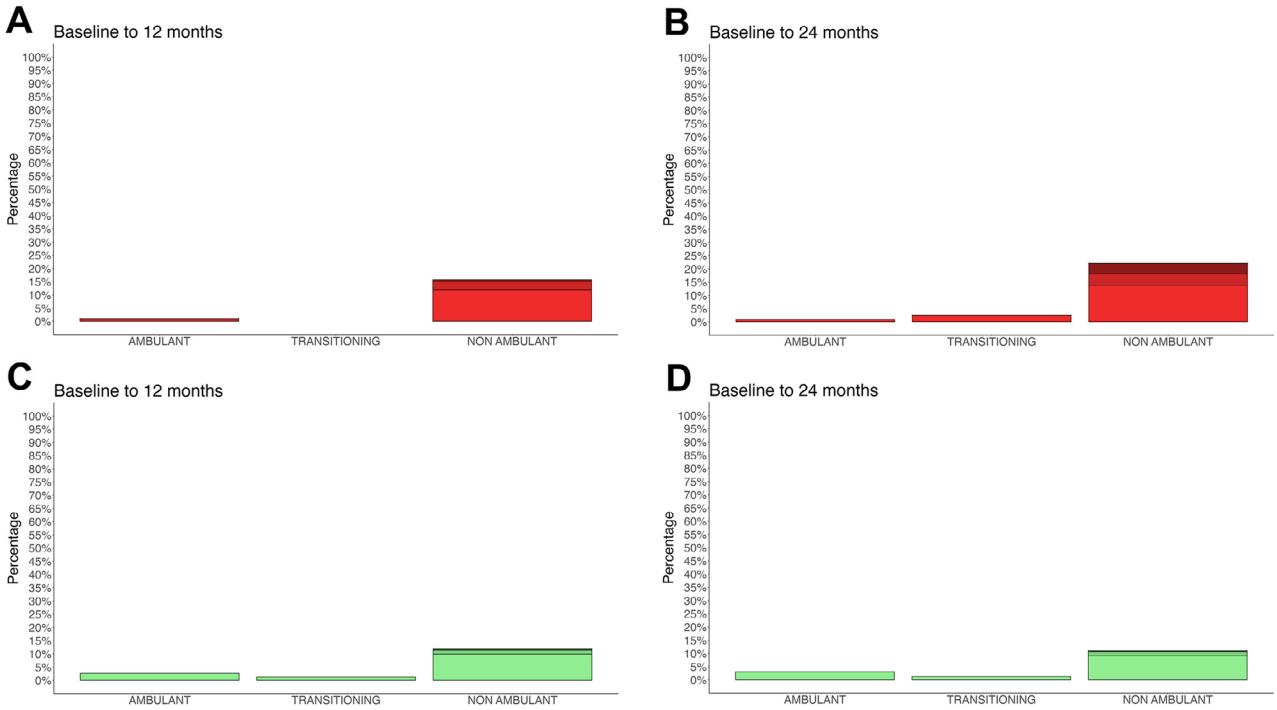

Fig. 5. Details of the frequency analysis on the number of activities lost or gained for the distal domain subdivided by ambulatory status. Key to figure: Panel A and B: Percentage of number of activities lost at 12 (A) and at 24 months (B) after baseline. Panel C and D: Percentage of number of activities gained at 12 (C) and at 24 months (D) after baseline. Colour coding: Light red: 1 activity lost; mild red: 2 activities lost; dark red: >2 activities lost, Light green: 1 activity gained; mild green: 2 activities gained; dark green: >2 activities gained.

Ambulant patients had the lowest rate of loss (shift down) and changes were mainly related to shoulder domain (17 % at 12 months and <30 % at 24 months) with decreasing percentage of loss in elbow and distal domain. The highest rate of loss (shift down) in the shoulder domain was observed in the transitioning subgroup confirming previous observations that shoulder activities are rapidly lost at the time of loss of ambulation and in the following year. The transitioning subgroup also showed a relatively high risk of loss in the elbow domain with relatively preserved distal domain.

The risk of losing elbow activities was highest in the non-ambulatory subgroup, especially in those who had lost ambulation within a few years as most of those with longer loss of ambulation had already lost elbow scores at baseline. Not surprisingly the non ambulant subgroup also had the highest rate of loss in the distal domain. It is of interest that even if we included assessments from patients who had lost ambulation for more than 5 years, the changes in the distal domain were relatively low. These findings confirm previous observations from clinical and MRI studies that the progression in the distal domain is slower than in the other domains and that the PUL 2.0 appears to have a limited value in detecting 12 or 24 month changes in this subgroup [13].

The analysis of the shift at 12 and 24 months did not show a specific pattern of individual items that were more often affected suggesting that the progression within these 2 domains is variable.

Analysing possible patterns of associations with multiple shifts down, the great majority of the individual assessments had loss in one item only with no obvious cluster of items, with the exception of the transitioning subgroup which showed the highest number of multiple losses especially in the shoulder domain where there was concomitant loss in the 6 activities included.

These findings emphasize the importance of monitoring upper limb function in DMD patients, particularly during transition from ambulatory to non ambulatory stage [20].

In non ambulant individuals the possibility to detect multiple item loss was limited by the fact that many items already had a score of 0 at baseline.

The analysis of the gains of activities also showed some variability across the domains. Not surprisingly most of the gains occurred in the younger ambulant patients as part of the variability already reported in the changes using the PUL total score. The gains observed in the other functional subgroups were fewer and mainly isolated to one activity. These findings suggest that despite the shift analysis is likely to reduce the possibility of fluctuations between PUL scores of 2 and 1, i.e. the ability to perform a task with or without compensation, some fluctuations may still occur even with a simplified scoring system. These were however relatively infrequent, isolated to individual items, and were often found in individuals with borderline cognitive or behavioural issues and variable compliance.

In conclusion, our findings confirm that even when using the shift analysis, the progression of changes observed in the different upper limb domains is different in individuals with different functional status and baseline function.

The use of such a method providing a measure of the ability to maintaining functional abilities will help to better contextualize the possible clinical relevance of the changes in response to intervention.

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Declaration of Competing Interest

The authors have nothing to disclose related to the submitted paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2023.11.011.

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