Relationship between loss of ambulation (LoA) and timing of pulmonary outcomes among boys with Duchenne muscular dystrophy (DMD)

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Background:

- Duchenne muscular dystrophy (DMD) is an X-linked disease affecting the dystrophin protein found in muscles.[1]
- DMD often presents in young boys with symptoms of muscle weakness and delays in or inability to achieve physical developmental milestones.[1]
- Disease progression is marked by increasing loss of extremity strength and function, as well as pulmonary and cardiac impairment. Patients eventually require ventilation and feeding tubes. Death typically occurs in young adulthood.[1]
- Pulmonary impairment is an important factor in DMD-related mortality; however, its relationship to other clinical milestones such as loss of ambulation (LoA) is unclear.
  - Previous research has shown that time to reach forced vital capacity (FVC) of 1 liter, a predictor of mortality, differed depending on age at LoA (AaLoA).[2]
- Understanding potential relationships between AaLoA and pulmonary decline, including mortality as a result of pulmonary decline, may inform management strategies for patients with differing disease progression.

Objective: This study sought to describe the relationship between AaLoA and timing of pulmonary outcomes in the CINRG DMD Natural History Study dataset.

Methods:

Data source & study population

- *Data source*: CINRG DNHS (**C**ooperative **I**nternational **N**euromuscular **R**esearch **G**roup **D**uchenne **N**atural **H**istory **S**tudy, NCT00468832) was a prospective, longitudinal study in which patients with DMD were followed up between 2006 and 2016.
  - In total, 440 patients with DMD received standard of care (corticosteroid or palliative therapies) across 20 centers in nine countries.[2,3]
- *Inclusion criteria*: The present observational study identified boys who:
  - Experienced LoA during follow-up or were non-ambulatory at enrollment with a documented date of LoA;
  - Were pulmonary-event free at enrollment (see *Clinical outcomes assessments*).
- LoA was defined as self/parent-reported full-time wheelchair use.

Data analysis

- *Stratification*: Included individuals were divided into three AaLoA groups:
  - <10 years
  - 10-13 years
  - >13 years.
- *Clinical outcomes assessments*:
  - Any severe pulmonary event or pulmonary-related mortality,[a] defined as:
    - Hospitalization for pneumonia or respiratory failure, full-time ventilatory assistance, continuous positive airway pressure (CPAP) use, mouthpiece intermittent ventilation, supplemental oxygen use, nocturnal or full-time bilevel positive airway pressure (BiPAP) use, negative pressure ventilation, ventilation via tracheostomy, or respiratory-related death.
  - FVC < 1L
  - Predicted (p) FVC ≤ 30%
  - pFVC ≤ 50%
  - pFVC ≤ 60%
- The following estimates were derived for each clinical outcome, stratified by AaLoA group:
  - Event-free survival probability (95% confidence interval [CI])
  - Median (95% CI) time to event in years
  - Total number of patients at risk. Patients at risk at baseline were defined as patients who were free of the specified event at visit 1, since the date of the event could not be ascertained for events at or prior to baseline.
  - Total number of events.

[a]Based on the "severe" and "critical" items within the pulmonary domain of the Major Adverse Dystrophinopathy Events (MADE) score. The MADE score was developed by clinical experts to capture disease burden across body systems and severities, and comprises cardiac, myopathy, nutrition status, and respiratory domains.[4]

Results:

Data availability

- Number of patients identified for each analysis was as follows:
  - Time to severe pulmonary event or pulmonary death: 191
  - Time to FVC <1L or pulmonary death analysis: 246
  - Time to pFVC ≤30% or pulmonary death analysis: 236
  - Time to pFVC ≤50% or pulmonary death analysis: 200
  - Time to pFVC ≤60% or pulmonary death analysis: 178

Severe pulmonary event or pulmonary death (Figure 1)

- **Patients with AaLoA <10 years (n=41)**
  - Event-free survival probability was 100% at age 5, 92% at age 10, and 32% at age 15 years.
  - Median time-to-event was 14.2 (95% CI: 13.0; 17.7) years among 25/41 patients (61%).
- **Patients with AaLoA 10-13 years (n=77)**
  - Event-free survival probability was 100% at age 10, 68% at age 15, and 12% at age 20 years.
  - Median time-to-event was 16.1 (95% CI: 15.3; 17.1) years among 51/77 patients (66%).
- **Patients with AaLoA >13 years (n=73)**
  - Event-free survival probability was 100% at age 5, 94% at age 15, and 44% at age 20 years.
  - Median time-to-event was 19.7 (95% CI: 18.1; NA) years among 25/73 patients (34%).
- Median time-to-severe pulmonary event or pulmonary death was significantly longer among patients with later AaLoA (p<0.0001).

FVC <1L or pulmonary death (Figure 2)

- **Patients with AaLoA <10 years (n=54)**
  - Event-free survival probability was 100% at age 5, 81% at age 15, and 25% at age 25 years.
  - Median time-to-event was 19.0 (95% CI: 18.2; NA) years among 20/54 patients (37%).
- **Patients with AaLoA 10-13 years (n=108)**
  - Event-free survival probability was 100% at age 5, 92% at age 15, 44% at age 25, and 19% at age 30 years.
  - Median time-to-event was 22.6 (95% CI: 21.9; 26.2) years among 39/108 patients (36%).
- **Patients with AaLoA >13 years (n=84)**
  - Event-free survival probability was 100% at age 5, 96% at age 15, and 80% at age 25 years.
  - Median time-to-event was 28.3 (95% CI: 26.0; NA) years among 12/84 patients (14%).
- Median time-to-FVC <1L or pulmonary death was significantly longer among patients with later AaLoA (p<0.0001).

pFVC ≤30% or pulmonary death (Figure 3)

- **Patients with AaLoA <10 years (n=53)**
  - Event-free survival probability was 100% at age 5, 82% at age 15, and 18% at age 25 years.
  - Median time-to-event was 18.1 (95% CI: 17.0; NA) years among 20/53 patients (38%).
- **Patients with AaLoA 10-13 years (n=100)**
  - Event-free survival probability was 100% at age 10, 60% at age 20, and 12% at age 30 years.
  - Median time-to-event was 20.8 (95% CI: 19.6; 24.4) years among 38/100 patients (38%).
- **Patients with AaLoA >13 years (n=83)**
  - Event-free survival probability was 100% at age 10, 89% at age 20, and 61% at age 25 years.
  - Median time-to-event was 25.7 (95% CI: 24.0; NA) years among 14/83 patients (17%).
- Median time-to-pFVC ≤30% or pulmonary death was significantly longer among patients with later AaLoA (p<0.0001).

pFVC ≤50% or pulmonary death (Figure 4)

- **Patients with AaLoA <10 years (n=42)**
  - Event-free survival probability was 100% at age 5, 31% at age 15, and 6% at age 20 years.
  - Median time-to-event was 14.2 (95% CI: 13.0; 16.4) years among 28/42 patients (67%).
- **Patients with AaLoA 10-13 years (n=82)**
  - Event-free survival probability was 100% at age 10, 72% at age 15, and 5% at age 30 years.
  - Median time-to-event was 16.5 (95% CI: 15.7; 17.6) years among 52/82 patients (63%).
- **Patients with AaLoA >13 years (n=76)**
  - Event-free survival probability was 100% at age 5, 94% at age 15, and 49% at age 20 years.
  - Median time-to-event was 19.9 (95% CI: 18.5; NA) years among 23/76 patients (30%).
- Median time-to-pFVC ≤50% or pulmonary death was significantly longer among patients with later AaLoA (p<0.0001).

pFVC ≤60% or pulmonary death (figure not shown)

- **Patients with AaLoA <10 years (n=38)**
  - Event-free survival probability was 100% at age 5, 24% at age 15, and 10% at age 20 years.
  - Median time-to-event was 13.5 (95% CI: 12.3; 14.4) years among 27/38 patients (71%).
- **Patients with AaLoA 10-13 years (n=70)**
  - Event-free survival probability was 100% at age 5, 48% at age 15, and 4% at age 30 years.
  - Median time-to-event was 14.6 (95% CI: 14.1; 15.8) years among 54/70 patients (77%).
- **Patients with AaLoA >13 years (n=70)**
  - Event-free survival probability was 100% at age 5, 76% at age 15, and 27% at age 20 years.
  - Median time-to-event was 18.0 (95% CI: 17.5; 19.7) years among 32/70 patients (46%).
- Median time-to-pFVC ≤60% or pulmonary death was significantly longer among patients with later AaLoA (p<0.0001).

Figure 1. Survival probability for time to severe pulmonary event or pulmonary death, stratified by AaLoA*

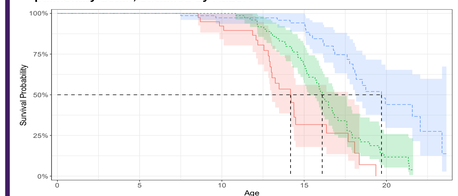


Figure 2. Survival probability for time to FVC <1L or pulmonary death, stratified by AaLoA*

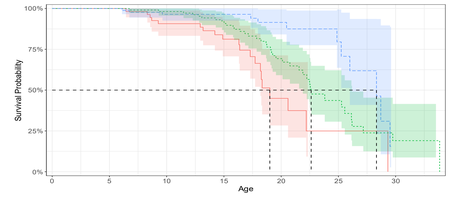


Figure 3. Survival probability for time to pFVC ≤30% or pulmonary death, stratified by AaLoA*

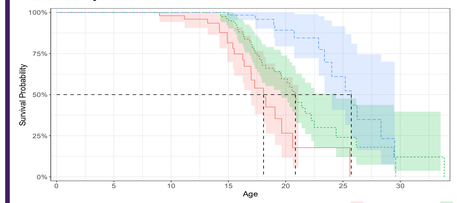
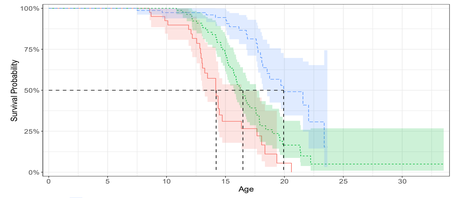


Figure 4. Survival probability for time to pFVC ≤50% or pulmonary death, stratified by AaLoA*



*Among patients at risk at baseline in the CINRG DNHS

Abbreviations: AaLoA=age at loss of ambulation; CINRG DNHS=Cooperative International Neuromuscular Research Group - Duchenne Natural History Study; FVC=forced vital capacity; LoA=loss of ambulation; pFVC=predicted FVC.

Table 1. Number of patients at risk, cumulative number of events, estimated survival (i.e., % event-free) at specified ages, by AaLoA.

AaLoA	Patient age, years	Severe pulmonary event or pulmonary death		FVC <1L or pulmonary death		pFVC ≤30% or pulmonary death		pFVC ≤50% or pulmonary death		pFVC ≤60% or pulmonary death	
		Estimated survival, % (95% CI)	At risk (total events), n	Estimated survival, % (95% CI)	At risk (total events), n	Estimated survival, % (95% CI)	At risk (total events), n	Estimated survival, % (95% CI)	At risk (total events), n	Estimated survival, % (95% CI)	At risk (total events), n
<10 years	5	100.0% (100.0%; 100.0%)	41 (0)	100.0% (100.0%; 100.0%)	54 (0)	100.0% (100.0%; 100.0%)	53 (0)	100.0% (100.0%; 100.0%)	42 (0)	100.0% (100.0%; 100.0%)	38 (0)
	10	92.2% (84.2%; 100.0%)	34 (3)	90.7% (83.3%; 98.8%)	47 (5)	98.0% (94.2%; 100.0%)	47 (1)	92.4% (84.6%; 100.0%)	35 (3)	89.1% (79.6%; 99.8%)	31 (4)
	15	31.7% (17.9%; 56.1%)	7 (20)	81.2% (70.7%; 93.3%)	29 (9)	81.5% (69.8%; 95.2%)	25 (7)	31.0% (18.0%; 53.6%)	8 (22)	24.2% (12.1%; 48.4%)	5 (23)
	20	NA	0 (25)	44.9% (28.3%; 71.3%)	6 (17)	26.6% (11.6%; 60.7%)	3 (18)	5.5% (0.9%; 35.0%)	1 (27)	9.7% (2.7%; 34.7%)	1 (26)
	25	NA	0 (25)	25.0% (9.3%; 67.2%)	1 (19)	17.7% (5.6%; 55.9%)	1 (19)	NA	0 (28)	NA	0 (27)
	30	NA	0 (25)	NA	0 (20)	NA	0 (20)	NA	0 (28)	NA	0 (27)
10-13 years	5	100.0% (100.0%; 100.0%)	77 (0)	100.0% (100.0%; 100.0%)	108 (0)	100.0% (100.0%; 100.0%)	100 (0)	100.0% (100.0%; 100.0%)	82 (0)	100.0% (100.0%; 100.0%)	70 (0)
	10	100.0% (100.0%; 100.0%)	77 (0)	98.1% (95.6%; 100.0%)	106 (2)	100.0% (100.0%; 100.0%)	100 (0)	100.0% (100.0%; 100.0%)	82 (0)	97.1% (93.3%; 100.0%)	68 (2)
	15	67.8% (57.2%; 80.3%)	40 (21)	92.0% (86.8%; 97.5%)	82 (8)	96.2% (92.1%; 100.0%)	76 (3)	71.5% (61.5%; 83.0%)	46 (20)	48.1% (36.9%; 62.6%)	27 (32)
	20	11.7% (5.3%; 25.9%)	5 (49)	69.3% (59.1%; 81.2%)	33 (23)	59.6% (48.1%; 73.8%)	24 (25)	16.5% (8.7%; 31.3%)	7 (49)	13.2% (6.6%; 26.4%)	6 (51)
	25	NA	0 (51)	43.6% (30.7%; 62.1%)	11 (32)	24.0% (12.1%; 47.6%)	4 (35)	5.0% (0.9%; 26.8%)	1 (52)	4.1% (0.8%; 22.3%)	1 (54)
	30	NA	0 (51)	19.0% (8.7%; 41.5%)	3 (38)	12.0% (3.6%; 39.7%)	2 (37)	5.0% (0.9%; 26.8%)	1 (52)	4.1% (0.8%; 22.3%)	1 (54)
>13 years	5	100.0% (100.0%; 100.0%)	73 (0)	100.0% (100.0%; 100.0%)	84 (0)	100.0% (100.0%; 100.0%)	83 (0)	100.0% (100.0%; 100.0%)	76 (0)	100.0% (100.0%; 100.0%)	70 (0)
	10	97.3% (93.6%; 100.0%)	71 (2)	96.4% (92.5%; 100.0%)	81 (3)	100.0% (100.0%; 100.0%)	83 (0)	97.4% (93.8%; 100.0%)	74 (2)	97.1% (93.3%; 100.0%)	68 (2)
	15	94.2% (88.7%; 99.9%)	50 (4)	96.4% (92.5%; 100.0%)	62 (3)	98.4% (95.3%; 100.0%)	60 (1)	94.4% (89.2%; 99.9%)	51 (4)	76.2% (66.2%; 87.6%)	37 (15)
	20	44.0% (29.7%; 65.3%)	11 (22)	91.5% (84.1%; 99.5%)	27 (5)	89.2% (79.4%; 100.0%)	24 (4)	49.1% (34.6%; 69.7%)	13 (20)	27.4% (15.1%; 49.7%)	6 (30)
	25	NA	0 (25)	79.5% (63.7%; 99.4%)	10 (7)	61.0% (40.6%; 91.6%)	7 (8)	NA	0 (23)	NA	0 (32)
	30	NA	0 (25)	NA	0 (12)	NA	0 (14)	NA	0 (23)	NA	0 (32)

Table 2. Estimated median survival time (years), total number of patients, and total number of events by AaLoA.

Age at loss of ambulation	Severe pulmonary event or pulmonary death			FVC <1L or pulmonary death			pFVC ≤30% or pulmonary death			pFVC ≤50% or pulmonary death			pFVC ≤60% or pulmonary death		
	N patients	N events	Median time-to-event, years (95% CI)	N patients	N events	Median time-to-event, years (95% CI)	N patients	N events	Median time-to-event, years (95% CI)	N patients	N events	Median time-to-event, years (95% CI)	N patients	N events	Median time-to-event, years (95% CI)
<10 years	41	25	14.2 (13.0; 17.7)*	54	20	19.0 (18.2; NA)*	53	20	18.1 (17.0; NA)*	42	28	14.2 (13.0; 16.4)*	38	27	13.5 (12.3; 14.4)*
10-13 years	77	51	16.1 (15.3; 17.1)*	108	39	22.6 (21.9; 26.2)*	100	38	20.8 (19.6; 24.4)*	82	52	16.5 (15.7; 17.6)*	70	54	14.6 (14.1; 15.8)*
>13 years	73	25	19.7 (18.1; NA)*	84	12	28.3 (26.0; NA)*	83	14	25.7 (24.0; NA)*	76	23	19.9 (18.5; NA)*	70	32	18.0 (17.5; 19.7)*

*Difference was statistically significant, p<0.0001

Abbreviations: AaLoA=age at loss of ambulation; CI=confidence interval; FVC=forced vital capacity; LoA=loss of ambulation; NA=not applicable; pFVC=predicted FVC.

Discussion:

- In this descriptive analysis, the relationship between time-to-pulmonary-event and AaLoA was explored.
- A pattern of later time-to-event with older AaLoA was observed across all pulmonary outcomes assessed, which could suggest a potential relationship between these outcomes.
- While there was a possibility of bias related to the exclusion of patients with missing LoA information, the inclusion of patients for whom AaLoA >13 years could be inferred based on ambulatory status at last visit was done to limit such bias.

Limitations:

- As non-ambulatory status was defined as full-time wheelchair use, lack of access to wheelchairs may have influenced classification of non-ambulatory status, particularly in low income or developing settings.
- Stratifying by AaLoA, which was ascertained during follow-up, introduces complexity in interpreting the results. By definition, patients need to survive until the AaLoA for that information to be collected, which may manifest as leading to longer survival times in older AaLoA groups.

Conclusions:

Findings from the present analysis lend support to the value of delaying LoA in DMD, particularly as it may relate to slowing pulmonary decline and its consequences. As such, therapies that delay progression to LoA would be valuable for the management of DMD.

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