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Life Expectancy in Duchenne Muscular Dystrophy: Reproduced Individual Patient Data Meta-analysis

Author(s):
Jonathan Broomfield, MSc[1]; Micki Hill, MSc[1]; Michela Guglieri, MD[2]; Michael Crowther, PhD[3]; Keith Abrams, CStat[4]

Equal Author Contributions:
J. Broomfield and M. Hill are co-first authors

Corresponding Author:
Jonathan Broomfield
jb781@le.ac.uk

Affiliation Information for All Authors: 1. Department of Health Sciences, University of Leicester 2. Institute of Human Genetics, Newcastle University3. Department of Medical Epidemiology and Biostatistics, Karolinska Institute 4. Centre for Health Economics, University of York

Contributions:
Jonathan Broomfield: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Micki Hill: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data; Additional contributions: Equal contribution to manuscript as first author (joint first authorship)
Michela Guglieri: Drafting/revision of the manuscript for content, including medical writing for content
Michael Crowther: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Keith Abrams: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

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Statistical Analysis performed by: Jonathan Broomfield, University of Leicester, MSc Micki Hill, University of Leicester, MScMichael Crowther, Karolinska Institutet, PhD Keith Abrams, University of York, CStat

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Abstract

Objective: Duchenne Muscular Dystrophy (DMD) is a rare progressive disease, which is often diagnosed in early childhood, and leads to considerably reduced life-expectancy; due to its rarity, research literature and patient numbers are limited. To fully characterise the natural history, it is crucial to obtain appropriate estimates of the life-expectancy and mortality rates of patients with DMD.

Methods: A systematic review of the published literature on mortality in DMD up until July 2020 was undertaken, specifically focusing on publications in which Kaplan-Meier (KM) survival curves with age as a time-scale were presented. These were digitised and individual patient data (IPD) reconstructed. The pooled IPD were analysed using the Kaplan-Meier estimator and parametric survival analysis models. Estimates were also stratified by birth cohort.

Results: Of 1177 articles identified, 14 publications met the inclusion criteria and provided data on 2283 patients, of whom 1049 had died. Median life-expectancy was 22.0 years (95% CI: 21.2, 22.4). Analyses stratifying by three time-periods in which patients were born showed markedly increased life-expectancy in more recent patient populations; patients born after 1990 have a median life-expectancy of 28.1 years (95% CI 25.1, 30.3).

Conclusions: This paper presents a full overview of mortality across the lifetime of a patient with DMD, and highlights recent improvements in survival. In the absence of large-scale prospective cohort studies or trials reporting mortality data for patients with DMD, extraction of IPD from the literature provides a viable alternative to estimating life-expectancy for this patient population.

Keywords: Duchenne Muscular Dystrophy, DMD, life-expectancy, survival, mortality, rare diseases

1. Introduction

Duchenne Muscular Dystrophy (DMD) is an X-linked, muscle degeneration disease nearly exclusively affecting males. It is a rare disease with a global prevalence of 1 in 3,500-5,000 male births.[1] Although corticosteroids are the mainstay treatment, there is currently no cure. In order to be reimbursed by health agencies, companies that develop new treatments need to show cost-effectiveness, which requires accurate modelling of the disease's natural history, including mortality.

DMD mortality has been published in isolation across different countries, sources and time periods, typically representing the experience of a single practice or selective population. Previous estimates of life-expectancy have been reported in the literature as 25 years,[2,3] while in more recent years this has increased to 31.7 (95% confidence interval (CI): 27.4, 36.0)[4]. Many studies report trends of increasing life-expectancy with time.[1,5-7]

A systematic review was recently conducted to obtain a single estimate of life-expectancy of 29.9 years (95% CI: 26.5, 30.8) in ventilated patients with DMD.[8] While the review provides an excellent summary of the published literature, survival across the whole disease pathway, rather than just the median, is needed to appropriately characterise a natural history model.

This paper therefore aims to extend beyond these single summary estimates of life-expectancy and provide comprehensive survival probabilities/mortality rates at different ages. This was achieved by performing a systematic review of the published literature on DMD life-expectancy, reconstructing individual patient data (IPD) and calculating pooled estimates. These can be used in future natural history or economic modelling of DMD.

2. Methods

2.1. Systematic review

A systematic review was performed on PubMed on 31 July 2020 and publications on DMD mortality prior to this date were identified. The following search terms were used:

1. “Duchenne Muscular Dystrophy” OR “DMD”

2. “Survival” OR “Mortality” OR “Death” OR “Life Expectancy”

3. 1. AND 2.

The citations of a subset of the results, which represented systematic reviews and/or meta-analyses, were also reviewed for inclusion. The additional search terms were included for this review:

4. “Systematic review” OR “Meta-analysis”

5. 3. AND 4.

Searches 3 and 5 were used to conduct the review. There were no exclusions based on region, language or time. Only full texts which were freely available to the Universities of Leicester and Sheffield were included in the review. The publications were required to report at least one Kaplan-Meier (KM) curve for survival in patients with DMD, which was generally confirmed by papers reporting genetic diagnosis. The KM curve had to be calculated as all-cause survival, with age as a timescale. Finally, the reported KM curve had to be able to be digitised, requiring the number of patients at risk to be reported as well as being of suitable digital quality. Where KM curves were stratified by a covariate, the number of patients in each stratum had to be reported, since these curves must be digitised separately.

The review was restricted to all-cause mortality, in order to ensure the outcome was comparable across studies and it was assumed that most deaths in these patients would be related to DMD. Age was chosen as the timescale as this provided clinically meaningful survival estimates and, for example, did not require knowledge of age of diagnosis.

If multiple KM curves were presented in a single paper relating to the same DMD population, all were digitised for comparison, and a joint decision was made by the authors as to which data to include in the analysis, prioritising curves including the highest number of patients and curves of higher digital quality.

The review was carried out according to PRISMA guidelines for conducting a systematic review.[9] Two authors conducted the review separately and discussed any discrepancies. The quality of the papers included was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal tool for case series, since the population consists exclusively of patients with DMD;[10] if studies were assessed by the tool as being at risk of bias, the methods were repeated with these studies excluded as a sensitivity analysis.

2.2. IPD extraction

The KM curves for each strata were digitised using WebPlotDigitizer.[11] The IPD were reconstructed using the approach of Guyot et al,[12] which was developed and implemented using the ipdfc command[13] in Stata. Many studies reported KM curves split by levels of a discrete covariate. In these instances, each curve was digitised separately and the data from the curves were pooled. Digitisation of curves was also conducted by two authors, with summary statistics (medians or earlier quantiles if not reached and survival probabilities) and reproduced graphs being compared to the original study graph to ensure a suitable degree of accuracy. If the digitised number of patients or deaths was greater or less than

the original number by 10% for both authors, the study was deemed insufficiently digitised and excluded from analysis.

2.3. Pooled data analysis

Two approaches to the data analysis were adopted; a non-parametric overview of DMD mortality and a parametric calculation of mortality rates. The data were analysed firstly as a combined cohort and secondly by stratifying the pooled IPD into three cohorts based on the period of birth for each study: pre 1970, 1970-1990 and post 1990. If period of birth for each group of patients was not explicitly reported then it was approximated as the average age at recruitment subtracted from the midpoint of the period of recruitment. The birth cohorts were defined to evenly split patients and investigate trends in life-expectancy over time. The most recent birth cohort is likely to contain only steroid-using patients, as steroid use has been the mainstay of treatment since the 1990s. The cohort analysis is also likely to represent a comparison of ventilated and non-ventilated patients, since ventilation was only introduced in many clinical settings in the 1990s.[8]

A non-parametric KM curve was used to summarise the survival estimates of the pooled sources. Median survival was compared in the pooled dataset and across birth cohorts.

A parametric survival model with a piecewise-constant hazard function was estimated with cut-points first every five years and then every year, from age 0 to the maximum observed death. This covered follow-up from possible diagnosis at birth to a time horizon of the oldest observed death in the dataset. This model assumes that the rate of death of patients is the same for all ages within a time-period, while allowing rates of death to differ across time-periods. Since the rate of death in young patients is likely to be very different to the rate of death in older patients, this model choice is preferred to, for example, an exponential model which assumes the same rate of death across all ages. Rates for patients

older than 40 were grouped and averaged, since patient numbers were small after this time. A normally distributed frailty term for study was incorporated into the model on the log-hazard scale to account for potential between-study variability.[14] The frailty term allows the precise estimates of mortality within each study to differ, by introducing unobserved variation between studies. It is included because the studies cover a range of global populations with follow-up over different calendar periods. The choice of parametric model enables smoother results with interval-specific mortality, which are directly applicable to health economic analysis. Proportional hazards were assumed in secondary analysis between birth cohorts; the assumption was assessed using log-log plots of survival in each cohort against log time. Stata 16 was used for statistical analysis.

2.4 Data availability

The data used in this review are reconstructed IPD and so do not directly correspond to real patients. The full reconstructed dataset is available upon request.

2.5 Standard Protocol Approvals, Registrations, and Patient Consents

No protocol or ethical approval was required for this work, as the data are already anonymised and in the public domain.

3. Results

3.1. Systematic review

The flowchart of the systematic review is shown in Figure 1. Of 1177 results from the initial search described in Section 2.1, 21 papers contained at least one appropriate KM curve. 2 were excluded for not being able to be digitised. 2 more were excluded for a potential overlap of patients - in both instances, a larger study was conducted by the same author in

the same location that was eligible for inclusion and so the smaller study was excluded. Thus, 17 papers remained eligible for digitisation. Following the supplementary review of references in systematic reviews of DMD mortality, a further paper was identified as appropriate for inclusion from Landfeldt et al's review.[8] This brought the final total number of papers to 18.

18 papers were eligible for digitising,[1-7, 15-25] contributing 3131 total patients and 1250 total deaths. Table 1 contains the key details of these papers. The studies were performed worldwide including Europe, USA, Chile and Japan and covered a range of birth, clinic admittance and death cohorts, with the earliest being born in 1954 and the latest in the late 2000s. Table 2 details how studies were assigned to each birth cohort.

The results of the JBI tool are displayed in Table 3. Overall, papers were of fairly high quality; the most common issue was with papers' exclusion criteria (criteria C5). Two papers performed slightly more poorly than the rest; one due to poor reporting of methods of diagnosis and analysis[19] and the other due to the paper being an editorial letter and providing insufficient detail.[25]

3.2. IPD extraction

Of the KM curves from the 18 papers, 4 were not adequately reproduced by either of the two authors.[2,6,15,20] This was because the number of deaths in each level of the curve were not reported, and so the algorithm was much less accurate in data reconstruction. These studies were excluded from the analysis. In addition, one paper only contained information on the number of deaths for some of the covariate levels;[17] IPD from these curves were included, but not from the other curves in this paper as deaths were again overestimated by both authors.

The digitised data from the remaining 14 studies yielded 2283 patients and 1050 deaths (compared to 1049 in the original - one paper produced one more digitised death than was reported[16]). The digitised data gave broadly very similar KM curves to those presented in the publications. The algorithm is least accurate when reproducing ages at death at the end of follow-up, so KM curve replication was poorest in the tails of some studies[1,5,22]. In these studies a small percentage of deaths were observed at late follow-up. Median survival was also compared between original and reproduced curves, and was consistently reproduced and is presented in Table 4.

3.3. Pooled data analysis

The total follow-up time was 40274 patient years with a maximum age of 44.4 years old. Median survival age, calculated using the Kaplan-Meier estimator, was 22.0 years (95% CI: 21.2, 22.4). Survival probabilities at 10, 20, 30 and 40 years were 99.8% (95% CI: 99.4%, 99.9%), 59.5% (95% CI: 56.9%, 61.9%), 26.1% (95% CI: 23.5%, 28.8%) and 13.3% (95% CI: 9.8%, 17.3%), respectively. Figure 2A illustrates the survival probabilities from the digitised data. The at-risk table shows the number of patients at risk at the beginning of the interval and the number in parentheses is the number of deaths that occur within the interval.

Secondary analysis suggested an improvement in life-expectancy over time. The median survival age from the pre 1970 birth cohort was 18.3 years (95% CI: 18.0, 18.9) compared to 24.0 years in the 1970-1990 birth cohort (95% 22.8, 25.0) and 28.1 years in the post 1990 birth cohort (95% 25.1, 30.3). Survival split by birth cohort is presented in Figure 2B. Log-log plots of survival in each cohort were approximately parallel indicating that proportional hazards was an appropriate assumption.

5-year mortality rates per 1,000 person-years (PYs) with CIs from the piecewise exponential model are given in Table 5, adjusted for between study variability by including a shared frailty term. Mortality is averaged over patients older than 40 as data are sparse.

Mortality is very low in patients with DMD aged between 0-10, and increases with age - in the combined analysis it was estimated that for every 1,000 patients aged 20-25, 86 would die each year, increasing to 336 each year for those aged over 40. Uncertainty increases as patients age, as more patients die or are censored so there are fewer patients from which to estimate mortality rates. Mortality rates were much higher in the birth cohort from before 1970 compared to the later cohorts; 265 of every 1000 patients with DMD aged 25-30 that were born before 1970 died every year, compared to just 27.6 a year for every 1000 born after 1990.

As a sensitivity analysis, the studies that performed more poorly in the JBI tool[19,25] were removed and non-parametric analysis was re-run. This yielded an overall median survival of 21.4 years (95% CI: 20.8, 22.2), and median survival estimates of 18.1 years (95% CI: 17.8, 18.7), 22.9 years (95% CI: 22.0, 24.0) and 28.1 years (95% CI: 25.1, 30.3) for patients born before 1970, between 1970-1990 and after 1990 respectively. These estimates are very similar to the original analysis.

4. Discussion

Our work has provided a set of accessible age-specific all-cause mortality rates that can be incorporated into the natural history modelling of DMD. This is particularly important for economic decision modelling evaluating future health technologies/treatments, not just in

DMD but also as a framework for other rare diseases.[26] Natural history models rely on reliable estimates of mortality throughout the disease pathway, and while the analysis is not without limitation, the only previous meta-analytic work of this nature provides a median estimate of survival[8] which while useful is not sufficiently granular for natural history modelling.

Early mortality is negligible, both in the overall dataset and in each birth cohort. Median survival in the overall dataset was 22.0 years (95% CI: 21.2, 22.4), but survival rates have increased over time, with a median survival of 28.1 years (95% CI: 25.1, 30.3) in patients born after 1990. These results are consistent with other recent work.[8] Moreover, these estimates may slightly underestimate median survival in more recently diagnosed patients, as some of the papers that were excluded from the final analysis at the data reconstruction phase had KM curves of patients that either had not reached median survival by age 30[15] or had median estimates greater than 30 years of age.[6,17]

Our work is comparable to Landfeldt et al's review.[8] The search terms were almost identical, and all papers included in their study were identified by our search. However, 6 of our 18 papers identified by the systematic review were not included in their review, which could be due to slightly differing search terms[2] or differing exclusion criteria of DMD diagnosis[18]. While our paper relied only upon a clinical, rather than genetic, diagnosis, the two studies produced very similar results, as did a sub-analysis of our cohort excluding studies that were not included in Landfeldt et al's review. Median survival was comparable between the reviews, with both identifying a marked improvement in life-expectancy over time. However, our paper also provides age-specific estimates of survival and mortality rates over the whole trajectory of a patient with DMD, allowing natural history models to incorporate mortality representative of the global population of patients with DMD.

This study highlights the importance of making the most of available data, an issue particularly pertinent to rare diseases such as DMD. Appropriate estimates of life expectancies are also important for other reasons; for instance, a better understanding of life-expectancies and estimates of age-specific mortality for patients with DMD could help with disease management and planning of service provision, as well as counselling for parents and carers.

However, there are limitations with our work. Firstly, access to the full IPD in the studies would be most desirable, to avoid unnecessary study exclusion caused by a lack of knowledge of strata sample sizes and eliminate any errors caused by data extraction. This study does provide generalisable methodology for situations where IPD are unavailable. We were also limited by restricted literature access and could not review 86 of the 1177 identified articles. Additionally, the assignment of patients to birth cohorts was not always straightforward, and knowledge of the exact period of birth of patients in each study would have been preferable.

A further complication from the lack of IPD is that all patients are assumed to have been followed up from birth. This introduces the possibility of immortal time bias in studies, since it is an unintentional condition to survive beyond a certain point in order to be included in these studies – in other words, the sickest patients that die before being recruited to a study are ignored, and so the population analysed may be slightly healthier than the true underlying DMD population. The impact of this is probably minimal, since studies that did report average ages at recruitment generally reported fairly young (<10 years of age) recruitment ages, but it is difficult to assess what impact, if any, this possible bias may have on the final results.

Further work could be undertaken investigating the impact of other covariates, such as geographic location (which could affect standard of care), information on steroid treatment

(such as type, duration of treatment, age at initiation) and ventilator use. Although interesting and pertinent questions, this would require a high level of harmonisation between studies. Our birth cohort assignment should stratify between patient populations before and after steroid use became mainstay (following the publication of a number of trials in the late 1980s and early 1990s reporting beneficial effects of corticosteroid therapy[27]), but this obviously does not guarantee a clear comparison of steroid and non-steroid users. The study populations vary globally and ethnically, with studies from North and South America, Europe and Asia. Whilst an in-depth sub-analysis by region would be desirable, it is a reflection of the rarity of the disease that these sources must be pooled together to obtain more precise estimates of survival rates and probabilities.

Extensions of the work could be to supplement with, and compare to, results from the Cooperative International Neuromuscular Research Group (CINRG). CINRG have conducted an international natural history study on 440 patients.[28] This included prospectively collecting mortality data,[29] but to date no mortality analysis has been published. Comparison with this study would enable validation of these results in a US population, as only 5 of the 14 included studies contained patients from the USA. Similar work could be completed in the UK by linking to large scale population linked electronic health record data, for example the Clinical Practice Research Datalink (CPRD). This would have the additional advantage of minimising selection effects due to cohorts often being established at specialist centres.

We make several recommendations based on our findings. This work highlights improvements in survival for patients with DMD over time, as standards of care have increased. We emphasise the need for mortality collection to be considered in the design stage, especially in natural history/registry studies. We strongly advocate the need to include mortality data in any natural history model, in order to accurately represent the

whole natural history, whether IPD are available or not. When they are not available, we recommend using the DMD mortality statistics provided here, or obtaining them through other means (such as a review of relevant records or similar systematic review of mortality rates).

Appendix 1: Authors

Name	Location	Contribution
Jonathan Broomfield	Department of Health Sciences, University of Leicester, Leicester, UK	Joint first author of manuscript. Conducted the systematic review and data reconstruction, and analysis and data interpretation. Corresponding author.
Micki Hill	Department of Health Sciences, University of Leicester, Leicester, UK	Joint first author of manuscript. Conducted the systematic review and data reconstruction, and analysis and data interpretation.
Michela Guglieri, MD	Institute of Human Genetics, Newcastle University, Newcastle, UK	Reviewed and edited final manuscript.
Michael Crowther, PhD	Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden	Contributed to analysis and data interpretation. Reviewed and edited final manuscript.
Keith Abrams, CStat	Centre for Health Economics, University of York, York, UK	Contributed to analysis and data interpretation. Reviewed and edited final manuscript.

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Legend

Table 1: Description of the 18 studies eligible for digitisation.

Table 2: Assignment of KM curves to birth cohorts.

Table 3: Results from the JBI tool for assessing bias.

Table 4: Original and reproduced statistics from each study

Table 5: 5-year mortality rates per 1,000 PYs, combined and stratified, with 95% CIs.

Figure 1: Flow of identified DMD mortality articles on PubMed.

*One paper's KM curve did not use age as a timescale, but the age of patients could be calculated.

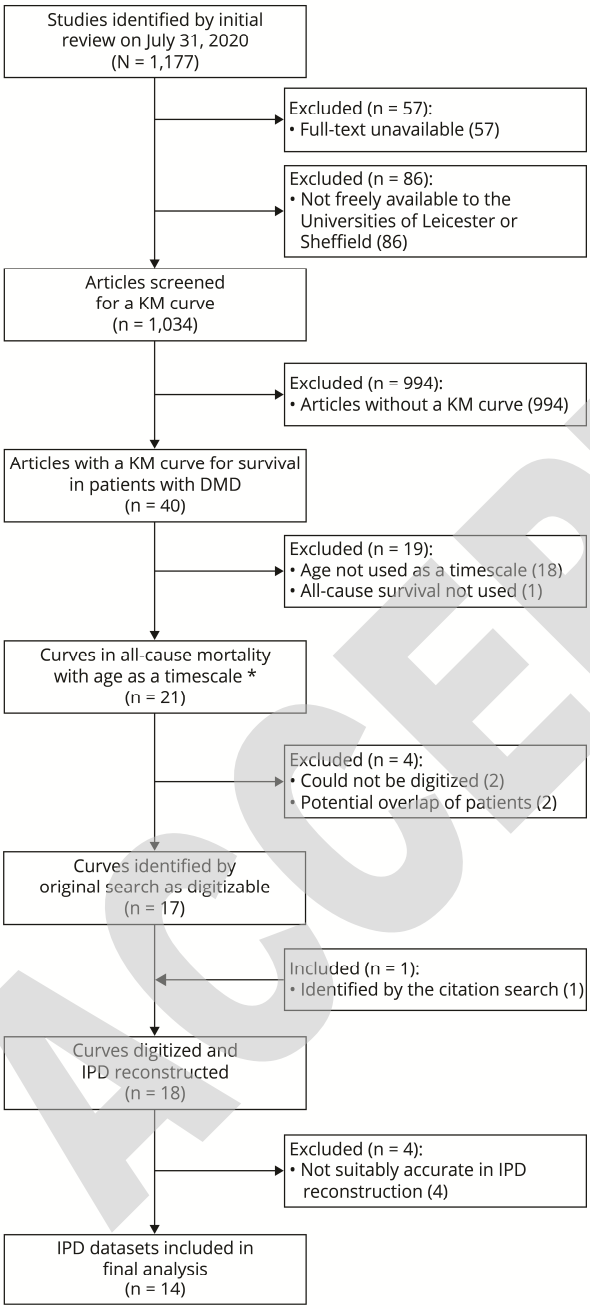

Figure 2: Kaplan-Meier estimates, pooled and split by birth cohort, from the digitized data.

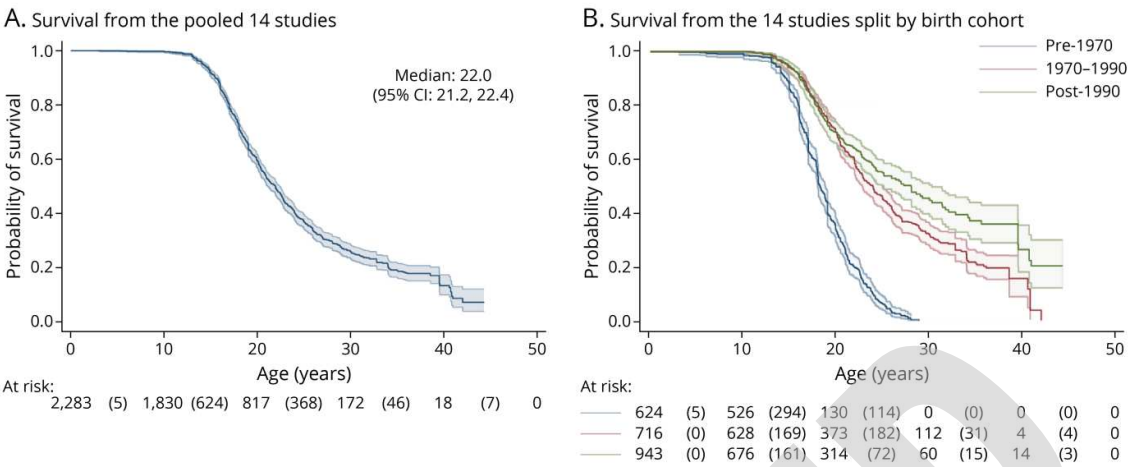

Table 1: Description of the 18 studies eligible for digitisation.

Author	Year	Region	Time Period	N	Deaths	Covariate(s)	Birth Cohort
Wittlieb-Weber[15]*	2020	USA and Canada	Admitted 2005-2015	407	27	None	Post 1990
San Martin[1]	2018	Santiago, Chile	Admitted 1993-2013	462	166	None; Admittance period; Socioeconomic status	Post 1990
Wang[4]	2018	Greater Cleveland, USA	Visited clinic 2003-2015	57	27	Genetic mutation	Post 1990
van den Bergen[5]	2014	Netherlands	Born 1961-2006	629	139	Birth cohort	Pre 1970, Post 1990
Kieny[6]*	2012	Nantes, France	Visited clinic 1981-2011	119	55	Ventilation; Birth cohort	Pre 1970, 1970-1990
Rall[16]	2012	Wuerzburg, Germany	Born 1970-1980	66	45	Ventilation	1970-1990
Matsumura[17†]	2011	Osaka, Japan	Visited clinic 1977-2010	286	177	Period/ventilation	Pre 1970, 1970-1990, Post 1990
Fraser[18]	2011	Leeds, UK	Visited clinic 1987-2010	192	93	None	1970-1990
Bach[19]	2011	New Jersey, USA	Visited clinic 2002-2011	101	45	None	1970-1990
Gordon[20]*	2011	Nova Scotia, Canada	Visited clinic 1977-2006	44	13	Bisphosphonate use	Pre 1970, 1970-1990
Ishikawa[7]	2010	Yakumo, Japan	Visited clinic 1964-2010	187	113	Period/ventilation	Pre 1970, 1970-1990, Post 1990
Kohler[21]	2009	Zurich, Switzerland	Enrolled 1999-2006	43	3	None	1970-1990
Mochizuki[2]*	2008	Hasuda, Japan	Admitted 1995-2007	74	11	Mental difficulty	1970-1990
Eagle[3]	2002	Newcastle, UK	Visited clinic 1967-2002	183	168	Period/ventilation	Pre 1970, 1970-1990
Gomez-Merino[22]	2002	New Jersey, USA	Visited clinic 1983-2002	91	34	Protocol access	1970-1990
Phillips[23]	2001	Liverpool, UK	Visited clinic 1986-1999	58	37	None	1970-1990
Boland[24]	1996	Minnesota, USA	Born 1953-1983	33	17	None	Pre 1970
Yasuma[25]	1996	Suzuka, Japan	Visited clinic 1980-1995	99	80	Ventilation	Pre 1970, 1970-1990

*Study was entirely excluded from final analysis for insufficiently accurate IPD.

†Study was partly excluded from final analysis for insufficiently accurate IPD.

Table 2: Assignment of KM curves to birth cohorts.

Study	Year	Covariate	Birth Period	Recruitment Period	Recruitment Age	Birth Cohort
Wittlieb-Weber[15]*	2020	-	Not reported	2005-2015	Mean = 10.2	Post 1990
San Martin[1]	2018	-	Not reported	1993-2013	Mean = 6.1	Post 1990
Wang[4]	2018	Pooled	Not reported	2003-2015	Mean = 18.1	Post 1990
van den Bergen[5]	2014	Birth 1	1961-1974			Pre 1970
		Birth 2	1980-2006			Post 1990
Kieny[6]*	2012	Birth 1	1955-1970			Pre 1970
		Birth 2	1970-1994			1970-1990
Rall[16]	2012	Pooled	1970-1980			1970-1990
Matsumura[17]	2011	No vent 1	Not reported	1977-1984	Not reported	Pre 1970
		No vent 2	Not reported	1984-2010	Not reported	1970-1990
		Vent 1*	Not reported	1984-1993	Not reported	1970-1990
		Vent 2*	Not reported	1994-2003	Not reported	1970-1990
		Vent 3*	Not reported	2004-2010	Not reported	Post 1990
Fraser[18]	2011	-	Not reported	1987-2010	Mean = 11.8	1970-1990
Bach[19]	2011	-	Not reported	2002-2011	Not reported	1970-1990
Gordon[20]*	2011	No bisphos	Not reported	1977-1997	Not reported	1970-1990
		Bisphos	Not reported	1997-2007	Median = 12	Post 1990
Ishikawa[7]	2010	NIV	Not reported	1991-2010	Not reported	Post 1990
		Tracheotomy	Not reported	1984-1991	Not reported	1970-1990
		No vent 1	Not reported	1991-2010	Not reported	1970-1990
		No vent 2	Not reported	1984-1991	Not reported	Pre 1970
		No vent 3	Not reported	1964-1984	Not reported	Pre 1970
Kohler[21]	2009	-	Not reported	1999-2006	Mean = 15.3	1970-1990
Mochizuki[2]*	2008	Pooled	Not reported	1995-2007	Not reported	1970-1990
Eagle[3]	2002	Ventilation	Not reported	1990-2002	Not reported	1970-1990
		No vent 1	Not reported	1990-2002	Not reported	1970-1990
		No vent 2	Not reported	1980-1989	Not reported	Pre 1970
		No vent 3	Not reported	1970-1979	Not reported	Pre 1970
		No vent 4	Not reported	1960-1969	Not reported	Pre 1970
Gomez-Merino[22]	2002	Pooled	Not reported	1983-2002	Not reported	1970-1990
Phillips[23]	2001	-	Not reported	1986-1999	Mean = 12	1970-1990
Boland[24]	1996	-	1954-1982			Pre 1970
Yasuma[25]	1996	No vent	Not reported	1980-1987	Not reported	Pre 1970
		CR vent	Not reported	1987-1991	Not reported	Pre 1970
		NIPPV vent	Not reported	1992-1995	Not reported	1970-1990

*Study or curve was excluded from final analysis for insufficiently accurate IPD.

Table 3: Results from the JBI tool for assessing bias.

Paper	Year	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Wittlieb-Weber[15]*	2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
San Martin[1]	2018	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang[4]	2018	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
van den Bergen[5]	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kieny[6]*	2012	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Rall[16]	2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Matsumura[17†]	2011	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Fraser[18]	2011	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bach[19]	2011	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Yes	Yes	No
Gordon[20]*	2011	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Ishikawa[7]	2010	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Kohler[21]	2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mochizuki[2]*	2008	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
Eagle[3]	2002	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Gomez-Merino[22]	2002	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Phillips[23]	2001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Boland[24]	1996	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Yasuma[25]	1996	Yes	Unclear	Unclear	Yes	Yes	No	No	Yes	No	Yes

*Study was entirely excluded from final analysis for insufficiently accurate IPD.
†Study was partly excluded from final analysis for insufficiently accurate IPD.
C1: Were there clear criteria for inclusion in the case series?
C2: Was the condition measured in a standard, reliable way for all participants included in the case series?
C3: Were valid methods used for identification of the condition for all participants included in the case series?
C4: Did the case series have consecutive inclusion of participants?
C5: Did the case series have complete inclusion of participants?
C6: Was there clear reporting of the demographics of the participants in the study?
C7: Was there clear reporting of clinical information of the participants?
C8: Were the outcomes or follow up results of cases clearly reported?
C9: Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
C10: Was statistical analysis appropriate?

Table 4: Original and reproduced statistics from each study.

Study	Year	Covariate	n (deaths)		Median		S(20)	
			Orig.	Rep.	Orig.	Rep.	Orig.	Rep.
Wittlieb-Weber[15]*	2020	-	407 (28)	406 (39)	27.065†	27.037†	0.887	0.908
San Martin[1]	2018	-	462 (166)	462 (166)	20.271	20.278	0.518	0.519
Wang[4]	2018	Deletion exon 14	9 (3)	9 (3)	24.029†	24.283†	0.918	0.889
		Other mutation	48 (24)	48 (24)	31.919	32.083	0.892	0.948
van den Bergen[5]	2014	Born 1961-1974	293 (98)	293 (98)	17.969	18.087	0.181	0.177
		Born 1980-2006	336 (41)	336 (41)	29.008	29.070	0.832	0.831
Kieny[6]*	2012	Born 1955-1970	119 (55)	119 (84)	25.753	25.743	0.930	0.930
		Born 1970-1994			40.964	40.964	1.000	1.000
Rall[16]	2012	No ventilation	66 (45)	66 (46)	18.943	19.051	0.272	0.273
		Ventilation			26.943	20.057	0.819	0.886
Matsumura[17]	2011	No vent, 1977-1984	33 (33)	33 (33)	17.501	17.575	0.396	0.394
		No vent, 1984-2010	49 (49)	49 (49)	19.261	19.319	0.396	0.408
		Vent, 1984-1993*	204 (95)	204 (148)	32.175	32.343	0.894	0.895
		Vent, 1994-2003*			32.846	33.052	0.949	0.949
		Vent, 2004-2010*			27.458†	27.575†	0.966	0.971
Fraser[18]	2011	-	192 (93)	192 (93)	21.443	21.550	0.593	0.607
Bach[19]	2011	-	101 (45)	101 (45)	28.000	28.094	0.894	0.895
Gordon[20]*	2011	No bisphosphonates	44 (13)	39 (39)	20.948	20.996	0.608	0.607
		Bisphosphonates			26.942	24.013	0.850	0.818
Ishikawa[7]	2010	NIV, 1991-2010	88 (17)	88 (17)	39.603	39.561	0.972	0.966
		Tracheo, 1984-1991	24 (21)	24 (21)	28.808	29.693	0.834	0.826
		No vent, 1991-2010	8 (8)	8 (8)	21.939	20.132	0.665	0.625
		No vent, 1984-1991	11 (11)	11 (11)	17.173	17.149	0.352	0.357
		No vent, 1964-1984	56 (56)	56 (56)	18.084	18.036	0.088	0.091
Kohler[21]	2009	-	43 (3)	43 (3)	35.044	35.010	1.000	1.000
Mochizuki[2]*	2008	Mental retardation	74 (11)	74 (22)	25.925	25.877	0.915	0.913
		No retardation			32.870‡	32.913‡	1.000	1.000
Eagle[3]	2002	Vent, 1990-2002	24 (9)	24 (9)	26.206	26.165	0.892	0.830
		No vent, 1990-2002	33 (33)	33 (33)	19.025	18.961	0.338	0.333
		No vent, 1980-1989	68 (68)	68 (68)	18.678	18.710	0.385	0.382
		No vent, 1970-1979	49 (49)	49 (49)	17.983	17.849	0.216	0.245
		No vent, 1960-1969	9 (9)	9 (9)	14.334	14.337	0.000	0.000
Gomez-Merino[22]	2002	No protocol access	57 (31)	57 (31)	24.729‡	25.002‡	1.000	1.000
		Access to protocol	34 (3)	34 (3)	28.778	28.912	0.802	0.803
Phillips[23]	2001	-	58 (37)	58 (37)	21.500	21.454	0.727	0.732
Boland[24]	1996	-	33 (17)	33 (17)	22.698	22.573	0.515	0.546
Yasuma[25]	1996	No vent, 1980-1987	65 (65)	65 (65)	20.092	20.122	0.507	0.508
		CR, 1987-1991	7 (7)	7 (7)	21.034	21.007	0.710	0.714
		NIPPV, 1992-1995	27 (8)	27 (8)	30.422	30.478	0.916	0.944

*Study or curve was excluded from final analysis for insufficiently accurate IPD.

[†]Median not reached so compared p(25).

[‡]Median and p(25) not reached so compared p(10).

Table 5: 5-year mortality rates per 1,000 PYs, combined and stratified, with 95% CIs.

Age	Combined	Pre 1970	1970-1990	Post 1990
0-5	0.07	0.141	0.061	0.0148
	(0.00955, 0.513)	*(0.019, 1.05)*	*(0.00814, 0.449)*	*(0.00195, 0.111)*
5-10	0.324	0.649	0.278	0.0678
	(0.115, 0.918)	*(0.223, 1.89)*	*(0.0956, 0.808)*	*(0.0226, 0.203)*
10-15	11.9	24.2	10.4	2.53
	(8.09. 17.6)	*(15.4, 38.2)*	*(6.57, 16.4)*	*(1.50, 4.26)*
15-20	66.9	148	63.4	15.5
	(46.7, 95.9)	*(96.2, 228)*	*(41.2, 97.5)*	*(9.43, 25.4)*
20-25	85.5	232	99.5	24.3
	(59.3, 123)	*(149, 362)*	*(64.4, 154)*	*(14.9, 39.6)*
25-30	87.7	275	118	28.7
	(58.7, 131)	*(171, 444)*	*(74.2, 187)*	*(17.2, 48.0)*
30-35	84.4	265	113	27.6
	(51.9, 137)	*(152, 459)*	*(66.2, 194)*	*(15.4, 49.4)*
35-40	71	244	104	25.5
	(35.5, 142)	*(116, 514)*	*(50.3, 217)*	*(11.9, 54.7)*
40+	336	1250	536	131
	(146, 773)	*(518, 3020)*	*(225, 1280)*	*(53.4, 318)*
Variance between studies = 0.442 (0.180, 0.991) in combined analysis.				
Variance between studies = 0.557 (0.246, 1.35) in stratified analysis.				

Life Expectancy in Duchenne Muscular Dystrophy: Reproduced Individual Patient Data Meta-analysis

Jonathan Broomfield, Micki Hill, Michela Guglieri, et al.

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