

Prognostic factors, disease course, and treatment efficacy in Duchenne muscular dystrophy: A systematic review and meta-analysis

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Abstract

Introduction/Aims: Prognostic factors in Duchenne muscular dystrophy (DMD) predict the disease course and may help individualize patient care. The aim was to summarize the evidence on prognostic factors that may support treatment decisions.

Methods: We searched six databases for prospective studies that each included ≥ 50 DMD patients with a minimum follow-up of 1 y. Primary outcomes were age at loss of ambulation (LoA), pulmonary function (forced vital capacity percent of predicted, FVC%p), and heart failure.

Results: Out of 5074 references, 59 studies were analyzed. Corticosteroid use was associated with a delayed LoA (pooled effect hazard ratio [HR] 0.42, 95% confidence interval [CI] 0.23–0.75, I² 94%), better pulmonary function tests (higher peak FVC%, prolonged time with FVC%p > 50%, and reduced need for assisted ventilation) and delayed cardiomyopathy. Longer corticosteroid treatment was associated with later LoA (>1 y compared to <1 y; pooled HR: 0.50, 95% CI 0.27–0.90) and early treatment start (aged <5 y) may be associated with early cardiomyopathy and higher fracture risk. Genotype appeared to be an independent driver of LoA in some studies. Higher baseline physical function tests (e.g., 6-minute walk test) were associated with delayed LoA. Left ventricular dysfunction and FVC <1 L increased and the use of angiotensin-converting enzyme (ACE) inhibitors reduced the risk of heart failure and death. Fusion surgery in scoliosis may potentially preserve pulmonary function.

Discussion: Prognostic factors that may inform clinical decisions include age at corticosteroid treatment initiation and treatment duration, ACE-inhibitor use, baseline physical function tests, pulmonary function, and cardiac dysfunction.

Abbreviations: 6MWT, 6-minute walk test; ACE, angiotensin-converting enzyme; CI, confidence interval; CS, corticosteroid; DMD, Duchenne muscular dystrophy; e.g., for example; FF, fat fraction; FVC, forced vital capacity; HR, hazard ratio; i.e., id est; LoA, loss of ambulation; LVEF, left ventricular ejection fraction; MeSH, medical subject headings; MRI, magnetic resonance imaging; NIV, non-invasive ventilation; NIPPV, nasal intermittent positive-pressure ventilation; NSAA, North Star Ambulatory Assessment; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analyses; RCT, randomized controlled trial; SIGN, Scottish Intercollegiate Guidelines Network; SNP, single nucleotide polymorphism; VL, vastus lateralis.

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KEYWORDS

Duchenne muscular dystrophy, Morbus Duchenne, mortality, outcome, prognostic factor

1 | INTRODUCTION

In Duchenne muscular dystrophy (DMD) disease progression and the complications associated with muscle weakness influence the overall prognosis. On average, untreated patients lose their ability to walk independently between 8 and 12 y,¹ and with the progression of the disease scoliosis and breathing difficulties occur.^{2,3} Whereas before 1970 patients life expectancy was 14.4 y,⁴ recent improvements in mechanical ventilation, corticosteroid treatment, and improved medical therapy for cardiomyopathy have resulted in a median life expectancy of 30 y with a range between 21 and 40.⁵

The current management of DMD patients requires the coordinated care of various specialists and allied health providers that enables improvements in overall survival and quality of life.^{6,7} Multidisciplinary care includes rehabilitation, the initiation of corticosteroids and the management of side effects, the prevention of respiratory and heart failure, and psychosocial support.⁶⁻⁸

The main causes of death are heart related complications such as heart failure and arrhythmia followed by respiratory failure and infections.^{9,10} Oral corticosteroid treatment is recommended before substantial physical decline has occurred.⁶ Physical therapy is used to prevent contractures, help to maintain motor function,¹¹ and to optimize lung volume recruitment techniques and to learn assisted coughing. Spinal surgery is recommended for scoliosis >20–30 degrees, in non-ambulatory boys who are pre-pubertal and not on corticosteroids.⁷ Treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers may delay the onset of left ventricular dysfunction and reduce mortality.^{7,12} Multiple studies have shown a substantial improvement in survival when non-invasive ventilation (NIV) or invasive assisted ventilation is initiated.^{5,13,14} More recently, treatments that result in skipping of the affected exon in specific mutations^{15,16} may modify progression in a subgroup of patients and result in a milder phenotype/disease progression.¹⁷

Whereas several factors have been associated with an increased risk of death such as underweight and a poor lung function,^{18,19} additional factors may predict the course of the disease and guide the treatment in DMD patients, improve quality of life, and prolong their survival. Prognostic factors may help in the decision process on when and how to initiate treatments. The aim of this systematic review and meta-analysis was to summarize the current evidence on prognostic factors that influence disease progression and may have an impact on treatment efficacy in patients with DMD.

2 | METHODS

In this systematic review and meta-analysis, we followed the recommendations of the Preferred Reporting Items for Systematic Review

and Meta-analyses Statement.²⁰ The methods used for this systematic review have been previously described.²¹

2.1 | Literature search

We searched the following six databases on July 30, 2021: Pubmed, Medline, Embase, Scopus, Cochrane, and Pedro. The search strategy was defined with the help of an experienced information specialist (M.G.) and by discussing the relevant literature within the research team. We used the medical subject headings (MeSH) and Embase subject headings (Emtree) terms for Duchenne muscular dystrophy. Furthermore, the subject headings “Duchenne”, “Dystrophy”, “Morbus” and “Syndrome” were applied. The search terms “Becker” and “Duchenne Becker” were excluded. Two full electronic search strategies are summarized in Supporting Information Tables S1 and S2, which are available online. We excluded conference proceedings and abstracts. To identify additional relevant studies, we screened the bibliographies of the included studies, review articles, guidelines, the gray literature (literature not peer-reviewed, including reports, government documents, dissertations), and other relevant literature.

2.2 | Eligibility criteria

Included were prospective cohort studies, prospective observational studies, registry or database studies based on prospectively collected data, and randomized controlled trials (RCTs) in patients with a confirmed diagnosis of DMD. Because the sample size and number of events influence the robustness of prediction models,²² we included studies with a minimum sample size of 50 patients and a follow-up duration of ≥ 1 y. No language restrictions were applied and all studies for which there were individuals with sufficient language proficiency (English, German, French, Spanish, Italian, Swedish, Danish, and Dutch) within the research team were considered. For studies published in another language (e.g., Polish, Croatian) we contacted researchers in our network who were able to translate the study and assist with the data extraction. Studies were excluded if no researcher with sufficient language proficiency to read and understand a study was available.

Excluded were cross-sectional studies, case reports, case series, retrospective chart reviews, and epidemiological studies.

2.3 | Study selection, data extraction and synthesis

Two reviewers (T.D.L., F.J.W.) independently screened the titles and abstracts of all references, and potentially relevant references were assessed in full text for in- or exclusion. Disagreements were

discussed and resolved by consensus or by third party arbitration (MMW).

A predefined form was used to extract relevant data of each study and to operationalize outcome measures and predictors. The extracted data included author, year, number of participants, and factors assessed as potential prognostic factors and endpoints. Data was extracted by one reviewer (F.J.W.) and confirmed by a second reviewer (T.D.L.). Discrepancies or inconsistencies were discussed with a third reviewer (M.M.W.). In case of several publications for the same study, we included the publication(s) analyzing relevant outcomes to answer the research question. If details for extracting the relevant information were missing, the corresponding author was contacted.

2.4 | Quality assessment

The methodical quality of the studies was evaluated by two reviewers (T.D.L., F.J.W.) using the guidelines of the Scottish Intercollegiate Guidelines Network (SIGN) quality checklist for RCTs and cohort studies.²³ Each domain to assess the internal validity was rated (yes/no/cannot say/does not apply). The overall methodical quality was defined²³ as high (++ , majority of criteria were met with little or no risk of bias), acceptable (+ , most criteria were met, with some flaws in the study associated with a risk of bias), or low (0 , most criteria or key aspects of the study design were not fulfilled). Registry, database, and cohort studies were rated no higher than (+) due to their weaker study design. In order to provide an exhaustive overview of the currently available literature, we decided against the exclusion of studies based on their quality ratings. However, we did not include studies of low quality into meta-analyses.

2.5 | Outcomes of interest

The primary outcomes of interest were the time of loss of ambulation (LoA), pulmonary function, and heart failure. LoA was defined in most studies as full-time/continuous wheelchair use (see Supporting Information Table S3 for an overview of the outcome definitions used in the included studies). For pulmonary function tests, forced vital capacity percent of predicted (FVC% predicted) and FVC absolute values were mostly used. Heart failure or cardiomyopathy was mainly defined as a left ventricular ejection fraction of <55 or <45%. Secondary outcomes were mortality (mainly all-cause mortality) and total number of adverse events as defined by the original studies. Additional outcomes included physical function tests, and the development of scoliosis. All outcomes were extracted as described in the primary studies and operationalized.

2.6 | Statistical analysis

Continuous variables are shown as mean and standard deviation or median and interquartile range. Data synthesis was performed when

three or more studies assessed the same predictor for one outcome. We used random-effects models in case I² was $\geq 25\%$ and results are reported in hazard ratios (HRs) with 95% confidence interval (95% CI). The statistical analyses were conducted using the statistical software R (<https://stat.ethz.ch/CRAN/>).

3 | RESULTS

3.1 | Study selection

Of 5074 references screened, 199 references were read in full text, and 59 studies (in total 100 publications) were included in the final synthesis (Figure 1). The main reasons for exclusion were other study design, no predictor analysis, or case series including less than 50 patients.

3.2 | Baseline characteristics

Study design was observational in 45 studies (23 (51%) prospective cohort studies, 10 (22%) database or registries, and 12 (27%) observational studies, Supporting Information Table S4) and 14 were RCTs. Studies were conducted in the USA (n = 14), Italy (n = 3), United Kingdom (n = 4), France (n = 6), Japan (n = 4), Canada (n = 2), China (n = 2), Germany (n = 2), the Netherlands (n = 1), Turkey (n = 1), and the Republic of Korea (n = 1). The remaining 19 studies included patients from several countries. The sample size ranged from 51²⁴ to 5345²⁵ DMD patients and the mean follow-up duration from 1²⁶ to 15.2²⁷ y. The age of the included patients at baseline was between <1²⁵ and 39²⁸ y.

3.3 | Study quality

In total, five RCTs (35.7%) were rated to be of high quality and nine RCTs (64.3%) of acceptable quality. The quality of observational studies was moderate in 27 (60%) and low in 18 (40%).

3.4 | Predictors for ambulation

Studies consistently found a longer time to LoA in patients with corticosteroid treatments (Supporting Information Table S5). The pooled overall effect of five studies showed a HR for corticosteroid treatment of 0.42 (95% CI 0.23 to 0.75, I² 94%) compared to no corticosteroid treatment (Figure 2). The finding was consistent in a sensitivity analysis excluding multiple arms for individual trials (Figure 3). More (continuous) or a longer (>1 y) corticosteroid treatment was more effective than intermittent or <1 y corticosteroid use (pooled HR of four studies: 0.50, 95% CI 0.27 to 0.90). The finding was mainly driven by studies that compared corticosteroid treatment of >1 to <1 y (Supporting Information Table S5 and Figure 2). In one study, treatment

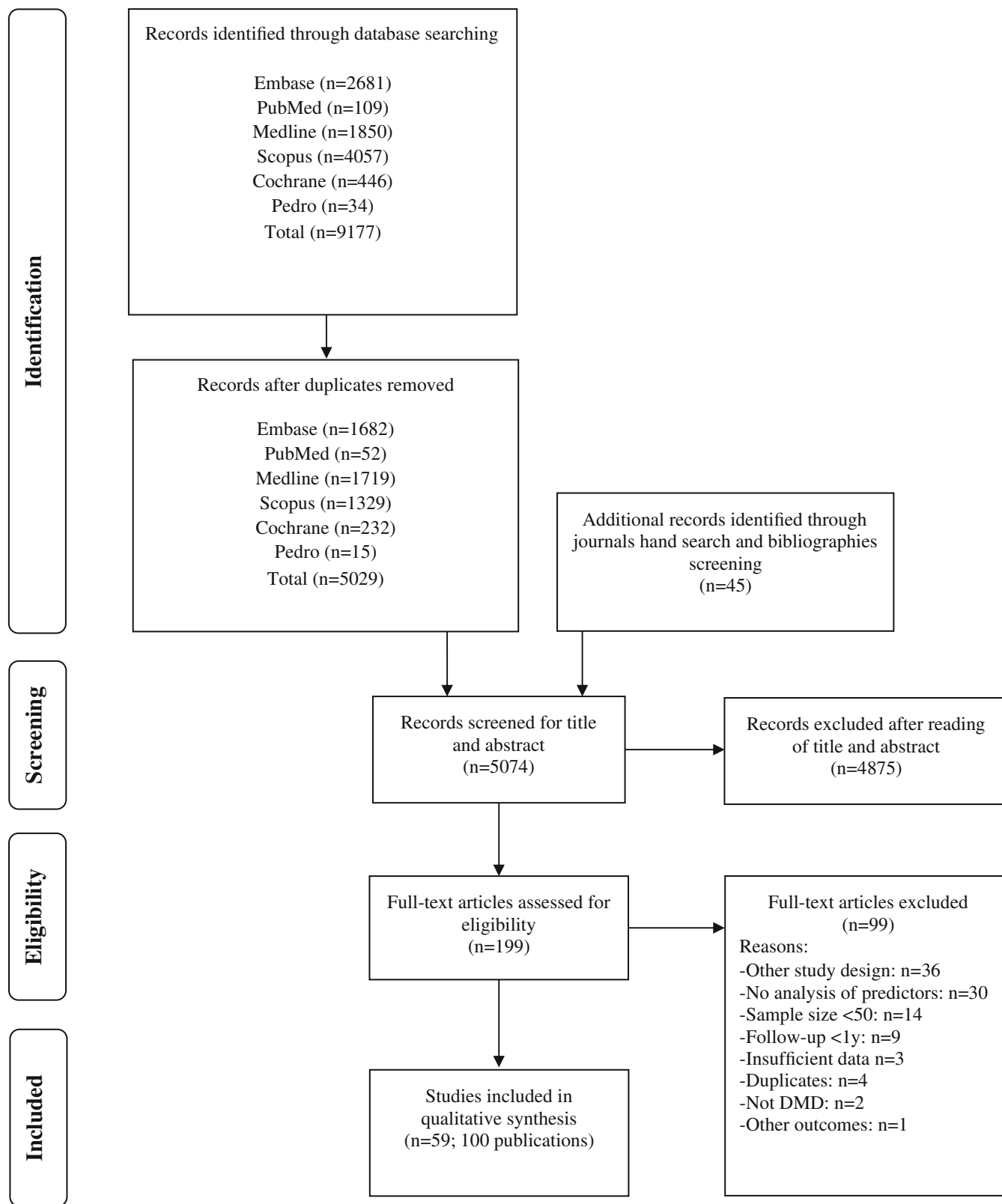


FIGURE 1 Study flow

duration of >3 y was associated with later LoA compared to no CS treatment and a treatment duration of <3 y.²⁹ Although initiating corticosteroid treatment is recommended before LoA,⁶ two studies failed

to show an influence of the age when the corticosteroid treatments was started. Corticosteroid treatment was associated with a higher body weight, delayed growth, and a higher incidence for cataracts.

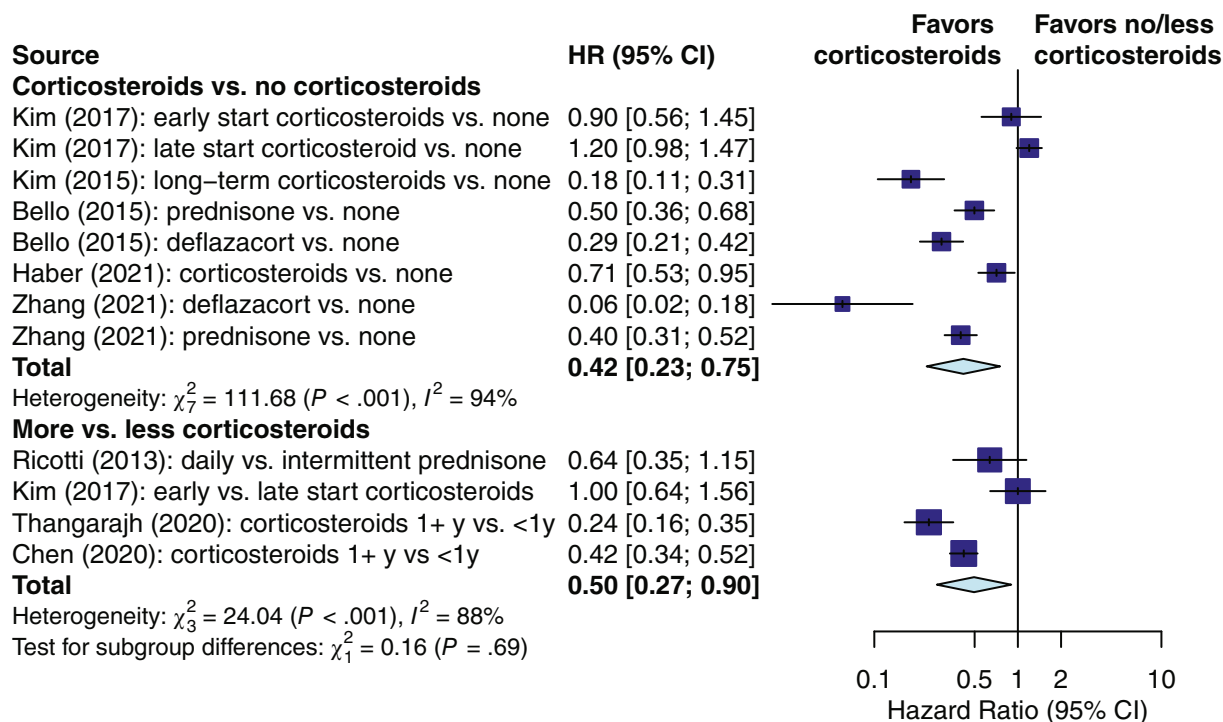


FIGURE 2 Influence of corticosteroid treatment and dosing regimen on loss of ambulation main plot (Bello⁴³).

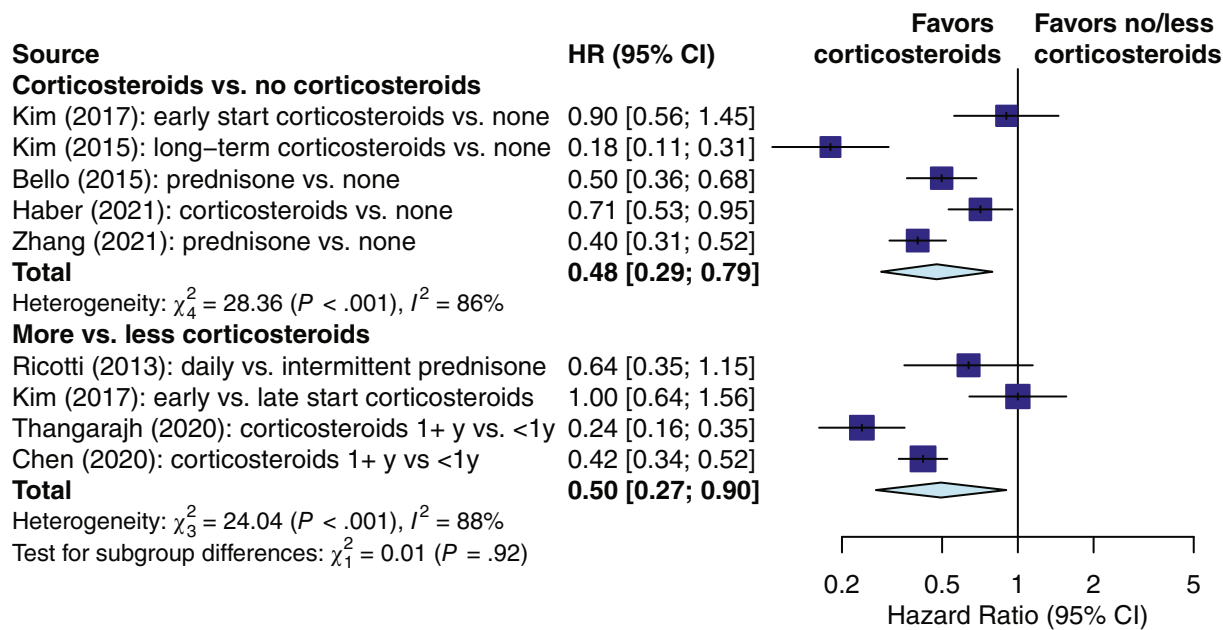


FIGURE 3 Sensitivity analysis of influence of corticosteroid treatment and dosing regimen on loss of ambulation. Sensitivity analysis excluding multiple arms in individual studies (Kim³³ late corticosteroid start, Bello⁴³ and Zhang⁴⁴ deflazacort arm).

Intermittent corticosteroid use versus daily use was not associated with fewer adverse effects. Two observational studies found a longer time to LoA in patients treated with deflazacort compared to prednisone. However, deflazacort use was also associated with more delayed growth, higher fracture risk and increased risk for cataracts compared to prednisone. The differences between deflazacort and

prednisone for weight gain were conflicting (Supporting Information Table S6).

Better performance in baseline physical function tests was associated with later LoA (>350 m, >319 m, or > 330 m in the 6MWT; >22 points in the NSAA, <7 s in the 10meter walk/run tests). Early surgery of muscles (resection of the muscoli sartorius, tensor fasciae latae,

and rectus femoris) and incision of the proximal iliotibial band before LoA was associated with longer time to LoA compared to late surgery.

Blood biomarkers (i.e., MYL3, ETFA, MDH2, and TNNT3) decreased with decrease in ambulation and may differentiate between ambulant and non-ambulant patients.³⁰ However, findings from this study need to be validated in other studies. Several gene mutations were associated with longer time until LoA (Supporting Information Table S5). Most evidence was available for deletions amenable to exon 44 skipping (six studies), deletions amenable to exon 8 skipping (two studies), deletion of exons 3–7 (one study), and single exon 45 deletion (two studies). Baseline MRI and MRI spectroscopy may be helpful to identify patients at risk for earlier LoA. In the spectroscopy, the fat fraction (FF) of the vastus lateralis (VL) muscle showed good predictive ability for ambulation. While patients with an FF of <0.2 were able to ambulate at 2 y, a VL FF >0.3 was associated with >50% LoA. The increase of the muscle MRI transverse magnetization relaxation time constant (T2) of the VL or the long head of the biceps femoris was associated with earlier LoA.³¹

3.5 | Predictors of pulmonary function

Corticosteroid treatment was consistently associated with higher FVC or FVC% predicted (four studies) and FVC% predicted <50% occurred with increasing age (one study, Supporting Information Table S5). The decline in FVC% predicted was not influenced by corticosteroid use in three studies. In patients with corticosteroid treatment start before the age of 5 y, age adjusted FVC values were lower compared to patients with treatment start aged 5 y and older. Corticosteroid use was associated with a later need for ventilator assistance in one study.²⁵ Intermittent corticosteroid use was inferior in one study compared to continuous use, and higher doses (≥ 0.65 mg/kg/d) did not influence FVC compared to doses <0.65 mg/kg/d. Patients taking prednisone had a higher FVC% predicted than those taking deflazacort. Fusion surgery in scoliosis delayed FVC decline in three studies.

3.6 | Predictors for heart failure

Corticosteroid treatment was also associated with a delayed onset of heart failure in four studies, and the annual decline in functional shortening was smaller in two studies (Supporting Information Table S5). A longer corticosteroid treatment duration was associated with a delayed onset of cardiomyopathy in two studies. Intermittent versus continuous use of corticosteroids had no effect on the onset of cardiomyopathy.³² Early corticosteroid treatment (start aged <5 y) was associated with an increased risk for early onset of cardiomyopathy in one study.³³ Although this finding was based on one large registry study (726 patients), the finding is observational and may be confounded by other factors. ACE-inhibitor use was associated with a lower proportion of heart failure over a 5-y treatment period.

Gene mutations/polymorphism: On the gene locus TCTEX1D1 of chromosome 1, single nucleotide polymorphisms (SNPs) rs1060575 and rs3816989 were associated with early/severe cardiomyopathy (LVEF <40% or fraction shortening <15% before age 13 y) compared to patients with no or mild heart involvement at the age of 28 y (defined as LVEF between 45% and 54% or fraction shortening between 20% and 27%).

3.7 | Predictors for mortality

Corticosteroid use was associated with a reduced mortality (two studies) and fewer heart failure-related deaths (one study, Supporting Information Table S6). Longer ACE-inhibitor use was associated with a lower mortality after 10 y of follow-up in one study. Carvedilol use was not associated with mortality. Preventive NIV in non-hypercapnic patients resulted in a higher mortality compared to no NIV. Swallowing disorders were associated with a higher risk of death during a 12-y follow-up.³⁴ Left ventricular dysfunction predicted mortality in four studies. An increased risk of death was observed for those with FVC <1 L. Furthermore, a greater annual decrease in FVC% predicted was associated with an increased mortality.

4 | DISCUSSION

4.1 | Results in the Context of the Literature

This analysis identified important prognostic factors that may inform clinical decisions, including the age at initiation and the duration of corticosteroid treatment, ACE-inhibitor use, baseline physical function tests, left ventricular dysfunction, and pulmonary function tests. A recently published systematic review identified a set of 23 prognostic indicators of disease progression in DMD.³⁵ The review concluded that a cardiac medication, DMD genetic modifiers, DMD mutation type, and glucocorticoid exposure were the core prognostic indicators. However, the systematic review included case series with very small number of patients and did not assess follow-up duration.

A Cochrane systematic review³⁶ found moderate quality evidence from RCTs that corticosteroid therapy in DMD improves muscle strength and function in the short term (1 y). In the current analysis corticosteroid treatment improved lung function and a treatment duration of at least 1 y (most likely more than 3 y) prolonged ambulation and delayed the onset of cardiomyopathy. Adverse effects of corticosteroid treatments included a higher body weight, delayed growth, and a higher incidence of cataracts. Furthermore, early initiation of corticosteroid treatment (aged <5 y) may be associated with early cardiomyopathy and lower FVC values. Although most studies were observational in design and other confounding factors may influence the findings, this may indicate that there is an optimal time range when corticosteroid treatment should be initiated. In a recently published individual patient data meta-analysis including only the placebo

arm patients of an RCT, deflazacort was superior to prednisone in slowing disease progression as measured by the 6-minute walk test at 48 weeks.³⁷ Although our analysis showed that deflazacort may be inferior in preventing decline in pulmonary function and was associated with more adverse events, a recently published large prospective RCT found daily deflazacort to be equally effective to daily prednisone for motor function, pulmonary function, and satisfaction with treatment.³⁸ Both were superior to intermittent prednisone alternating 10 days on and 10 days off over a 3-y follow-up when assessed by composite outcome comprising measures of motor function, pulmonary function, and satisfaction with treatment.³⁸ Other prognostic factors included baseline function tests for LoA, ACE-inhibitor use for heart failure and mortality, fusion surgery in scoliosis to preserve pulmonary function and delay LoA. Left ventricular dysfunction and FVC <1 L was associated with an increased risk of death.

For several recommendations, we found no or insufficient evidence, thus indicating a need for further studies. For example, fusion surgery in scoliosis may have preserved pulmonary function in uncontrolled trials but no RCTs are available.³⁹ Furthermore, we found no study with sufficient follow-up that assessed nocturnal mechanical ventilation in chronic hypoventilation, which has been found to result in short-term alleviation of symptoms.⁴⁰ MRI screening and genetic testing may be helpful to individualize treatment in the future. For example, ataluren improved dystrophin expression in the skeletal muscle of patients with nonsense DMD mutations. In a randomized placebo-controlled trial, ataluren was only effective in patients with a baseline δ MWT between 300 and 400 m.⁴¹ This subgroup is believed to represent a stage of the disease at which a response to dystrophin restoration therapy is possible. In a propensity matched cohort study, ataluren was associated with later LoA compared to no ataluren treatment.¹⁵ Although efforts are underway to identify blood biomarkers of disease progression,⁴² the evidence is insufficient to recommend specific biomarkers to inform clinical practice. Based on the current systematic review additional prospective studies are needed in light of the many unresolved questions in DMD.

4.2 | Implications for research

We identified numerous questions in DMD patients should be addressed with future high-quality studies:

- Although ACE-inhibitor use seems to be promising, the evidence found in the current study is weak and additional studies should assess the appropriate age to initiate treatment and the optimal treatment duration.
- Studies suggest that there may be an optimal age when corticosteroids should be started. However, these findings may be influenced by other factors such as disease severity or progression. Therefore, studies should assess the optimal age at which corticosteroids should be started to prolong LoA without unacceptable adverse effects. Promising results indicate that blood biomarkers and MRI

studies may help to identify DMD patients at risk for early LoA. These findings need to be validated and their usefulness in clinical practice assessed in additional studies.

- Ataluren aims to improve dystrophin expression in the skeletal muscle of patients with nonsense DMD mutations. Studies showed no convincing overall efficacy on patient relevant outcomes.^{15,41} There is a need for randomized studies to assess whether a subgroup of patients may be susceptible to dystrophin restoration therapy.
- Post-marketing studies should evaluate the long-term and prescribing patterns of exon skipping compounds. There also is a need for additional human studies on experimental molecular therapies such as gene therapy.

4.3 | Implications for practice

Clinical care in DMD patients includes a coordinated and multidisciplinary approach to optimize treatment and prevent complications.⁶⁻⁸ When initiating corticosteroid treatment, optimal treatment duration seems to be more than 3 y to delay LoA. Furthermore, early initiation of corticosteroid treatment (aged <5 y) may be associated with early cardiomyopathy, lower FVC values, and a higher risk for adverse events such as fractures. ACE-inhibitor use may result in delayed onset of heart failure and reduced mortality and should thus be considered. Genetic mutations/polymorphism may be an independent driver of LoA, and treatments that result in skipping of the affected exon in specific mutations^{15,16} may modify progression in a subgroup of patients with milder phenotype/disease progression.¹⁷

4.4 | Limitations

There are several limitations. First, although we used up-to-date methods to identify all potentially relevant references, we may have missed important studies that should have been included. Second, many studies included in this review were of moderate methodological quality. Although we included studies with at least 50 patients, we cannot exclude that we included studies with insufficient power. For many factors and outcomes, insufficient studies were available to conduct quantitative analyses. Furthermore, many studies had other research questions and did not specifically address the impact of prognostic factors. Therefore, statistical analysis to minimize bias was not always applied. Many studies were observational, and we cannot exclude that other confounding factor may have influenced the results. In particular, corticosteroid use may be more readily administered in patients with fast progression and therefore, the influence of corticosteroids on disease progression may be underestimated. Third, studies used different case definitions and outcome measures, and this may result in variation across studies. Therefore, the findings of this review should be confirmed by high quality clinical studies that assess prognostic factors and outcome measures in a standardized fashion.

5 | CONCLUSIONS

Important prognostic factors that may inform clinical decisions include the age at initiating corticosteroid treatment and the treatment duration, ACE-inhibitor use, baseline physical function tests, left ventricular dysfunction, and pulmonary function tests. Prospective studies should validate prognostic factors and stratified treatments based on prognostic factors. Numerous questions in DMD remain unanswered and additional prospective studies are needed.

AUTHORS CONTRIBUTIONS

M.M.W., T.D.L., F.J.W. designed and conceived the study. T.D.L. and F.J.W. were responsible for the independent literature screening, data extraction and quality assessment. M.M.W., T.D.L., F.J.W., M.R.B., analyzed the data. The first draft of the article was written by M.M.W., F.J.W., and revised by T.D.L., M.R.B., and M.K. All authors approved the final version of the manuscript. T.D.L. and F.J.W. contributed equally to this work.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article. Extracted data and quality assessments for individual studies are available from the corresponding author upon reasonable request.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

- Sienko Thomas S, Buckcon CE, Nicorici A, Bagley A, McDonald CM, Sussman MD. Classification of the gait patterns of boys with Duchenne muscular dystrophy and their relationship to function. *J Child Neurol*. 2010;25(9):1103-1109.
- Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol*. 2010;9(1):77-93.
- Verma S, Anziska Y, Cracco J. Review of Duchenne muscular dystrophy (DMD) for the pediatricians in the community. *Clin Pediatr*. 2010;49(11):1011-1017.
- Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscul Disord*. 2002;12(10):926-929.
- Landfeldt E, Thompson R, Sejersen T, McMillan HJ, Kirschner J, Lochmüller H. Life expectancy at birth in Duchenne muscular dystrophy: a systematic review and meta-analysis. *Eur J Epidemiol*. 2020;35(7):643-653.
- Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. 2018;17(3):251-267.
- Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol*. 2018;17(4):347-361.
- Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. *Lancet Neurol*. 2018;17(5):445-455.
- Saito T, Tataru K, Kawai M. [changes in clinical condition and causes of death of inpatients with Duchenne muscular dystrophy in Japan from 1999 to 2012]. *Rinsho shinkeigaku = Clin Neurol*. 2014;54(10):783-790.
- D'Amario D, Amodeo A, Adorisio R, et al. A current approach to heart failure in Duchenne muscular dystrophy. *Heart*. 2017;103(22):1770-1779.
- Case LE, Apkon SD, Eagle M, et al. Rehabilitation Management of the Patient with Duchenne Muscular Dystrophy. *Pediatrics*. 2018;142-(Supplement 2):S17-S33.
- McNally EM, Kaltman JR, Benson DW, et al. Contemporary cardiac issues in Duchenne muscular dystrophy. Working Group of the National Heart, lung, and blood institute in collaboration with Parent Project Muscular Dystrophy. *Circulation*. 2015;131(18):1590-1598.
- Villanova M, Brancalion B, Mehta AD. Duchenne muscular dystrophy: life prolongation by noninvasive ventilatory support. *Am J Phys Med Rehabil*. 2014;93(7):595-599.
- Toussaint M, Chatwin M, Soudon P. Mechanical ventilation in Duchenne patients with chronic respiratory insufficiency: clinical implications of 20 years published experience. *Chron Respir Dis*. 2007;4(3):167-177.
- Mercuri E, Muntoni F, Osorio AN, et al. Safety and effectiveness of ataluren: comparison of results from the STRIDE registry and CINRG DMD natural history study. *J Comp Eff Res*. 2020;9(5):341-360.
- Shimizu-Motohashi Y, Komaki H, Motohashi N, Takeda S, Yokota T, Aoki Y. Restoring dystrophin expression in duchenne muscular dystrophy: current status of therapeutic approaches. *J Pers Med*. 2019;9(1):1.
- Lim KRQ, Maruyama R, Yokota T. Eteplirsen in the treatment of Duchenne muscular dystrophy. *Drug des Devel Ther*. 2017;11:533-545.
- Cheeran D, Khan S, Khera R, et al. Predictors of death in adults with Duchenne muscular dystrophy-associated cardiomyopathy. *J Am Heart Assoc*. 2017;6(10):e006340.
- Phillips MF, Quinlivan RC, Edwards RH, Calverley PM. Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. *Am J Respir Crit Care Med*. 2001;164(12):2191-2194.
- Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
- Weber F. Prognosefaktoren zur Stratifizierung und Behandlung der Duchenne-Muskeldystrophy. *Studienprotokoll Eines Systematischen Literaturreviews*. Unpublished. University of Zurich. 2017.

22. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ*. 2020;368:m441.
23. Scottish Intercollegiate Guidelines Network (SIGN). *A guideline developer's handbook*.: SIGN; 2019. (SIGN publication no. 50). <https://www.sign.ac.uk/our-guidelines/sign-50-a-guideline-developers-handbook/>. Accessed November 12, 2019.
24. Stern LZ, Ringel SP, Ziter FA. Drug trial of superoxide dismutase in Duchenne's muscular dystrophy. *Arch Neurol*. 1982;39(6):342-346.
25. Koeks Z, Bladen CL, Salgado D, et al. Clinical outcomes in Duchenne muscular dystrophy: a study of 5345 patients from the TREAT-NMD DMD global database. *J Neuromuscul Dis*. 2017;4(4):293-306.
26. Escolar DM, Hache LP, Clemens PR, et al. Randomized, blinded trial of weekend vs daily prednisone in Duchenne muscular dystrophy. *Neurology*. 2011;77(5):444-452.
27. Lebel DE, Corston JA, McAdam LC, Biggar WD, Alman BA. Glucocorticoid treatment for the prevention of scoliosis in children with Duchenne muscular dystrophy: long-term follow-up. *J Bone Joint Surg Am*. 2013;95(12):1057-1061.
28. Segawa K, Sugawara N, Maruo K, et al. Left ventricular end-diastolic diameter and cardiac mortality in duchenne muscular dystrophy. *Neuropsychiatr Dis Treat*. 2020;16:171-178.
29. Kim S, Campbell KA, Fox DJ, Matthews DJ, Valdez R. Corticosteroid treatments in males with Duchenne muscular dystrophy: treatment duration and time to loss of ambulation. *J Child Neurol*. 2015;30(10):1275-1280.
30. Strandberg K, Ayoglu B, Roos A, et al. Blood-derived biomarkers correlate with clinical progression in Duchenne muscular dystrophy. *J Neuromuscul Dis*. 2020;7(3):231-246.
31. Barnard AM, Willcocks RJ, Triplett WT, et al. MR biomarkers predict clinical function in Duchenne muscular dystrophy. *Neurology*. 2020;94(9):e897-e909.
32. Trucco F, Domingos J, Tay CG, et al. Cardiorespiratory progression over 5 years and role of corticosteroids in DMD: a single site retrospective longitudinal study. *Chest*. 2020;158:1606-1616.
33. Kim S, Zhu Y, Romitti PA, et al. Associations between timing of corticosteroid treatment initiation and clinical outcomes in Duchenne muscular dystrophy. *Neuromuscul Disord*. 2017;27(8):730-737.
34. Boussaid G, Lofaso F, Santos DB, et al. Impact of invasive ventilation on survival when non-invasive ventilation is ineffective in patients with Duchenne muscular dystrophy: a prospective cohort. *Respir Med*. 2016;115:26-32.
35. Ferizovic N, Summers J, de Zárte IBO, et al. Prognostic indicators of disease progression in Duchenne muscular dystrophy: a literature review and evidence synthesis. *PLoS One*. 2022;17(3):e0265879.
36. Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database Syst Rev*. 2016;5:CD003725.
37. McDonald CM, Sajeev G, Yao Z, et al. Deflazacort vs prednisone treatment for Duchenne muscular dystrophy: a meta-analysis of disease progression rates in recent multicenter clinical trials. *Muscle Nerve*. 2020;61(1):26-35.
38. Guglieri M, Bushby K, McDermott MP, et al. Effect of different corticosteroid dosing regimens on clinical outcomes in boys with Duchenne muscular dystrophy: a randomized clinical trial. *JAMA*. 2022;327(15):1456-1468.
39. Cheuk DKL, Wong V, Wraige E, Baxter P, Cole A. Surgery for scoliosis in Duchenne muscular dystrophy. *Cochrane Database Syst Rev*. 2015;10:CD005375.
40. Annane D, Orlikowski D, Chevret S. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. *Cochrane Database Syst Rev*. 2014;12:CD001941.
41. McDonald CM, Campbell C, Torricelli RE, et al. Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;390(10101):1489-1498.
42. Signorelli M, Ayoglu B, Johansson C, et al. Longitudinal serum biomarker screening identifies malate dehydrogenase 2 as candidate prognostic biomarker for Duchenne muscular dystrophy. *J Cachexia Sarcopenia Muscle*. 2020;11(2):505-517.
43. Bello L, Gordish-Dressman H, Morgenroth LP, et al. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne natural history study. *Neurology*. 2015;85(12):1048-1055.
44. Zhang S, Qin D, Wu L, et al. Genotype characterization and delayed loss of ambulation by glucocorticoids in a large cohort of patients with Duchenne muscular dystrophy. *Orphanet J Rare Dis*. 2021;16(1):188.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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