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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 one year. 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 HR 0.42, 95% CI 0.23 to 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 year compared to <1 year; pooled HR: 0.50, 95% CI 0.27 to 0.90) and early treatment start (aged <5 years) 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 liter 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.

Keywords

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

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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 eight and twelve years,[1] and with the progression of the disease scoliosis and breathing difficulties occur.[2,3] Whereas before 1970 patients life expectancy was 14.4 years,[4] recent improvements in mechanical ventilation, corticosteroid treatment, and improved medical therapy for cardiomyopathy have resulted in a median life expectancy of 30 years 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. [8,6,7]

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.[12,7] Multiple studies have shown a substantial improvement in survival when non-invasive ventilation (NIV) or invasive assisted ventilation (IV) is initiated.[13-15] More recently, treatments that result in skipping of the affected exon in specific mutations[16,17] may modify progression in a subgroup of patients and result in a milder phenotype/disease progression.[18]

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Whereas several factors have been associated with an increased risk of death such as underweight and a poor lung function,[19,20] 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.

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2. Methods

In this systematic review and meta-analysis we followed the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) Statement.[21] The methods used for this systematic review have been previously described.[22]

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 (MG) 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 **Supplemental Tables 1 and 2**. We excluded conference proceedings and abstracts. To identify additional relevant studies, we screened the bibliographies of the included studies, review articles, guidelines, the grey 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,[23] we included studies with a minimum sample size of 50 patients and a follow-up duration of ≥1 year. 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

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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 (TDL, FJW) 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 (FJW) and confirmed by a second reviewer (TDL). Discrepancies or inconsistencies were discussed with a third reviewer (MMW). 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 (TDL, FJW) using the guidelines of the Scottish intercollegiate Guidelines Network (SIGN) quality checklist for RCTs and cohort studies.[24] Each domain to assess the internal validity was rated (yes/no/can't say/does not apply). The overall methodical quality was defined[24] as high (++, majority of criteria were met with little or no risk of bias), acceptable (+, most criteria were met, with some

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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 rated 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 LoA, pulmonary function, and heart failure. LoA was defined in most studies as full-time/continuous wheelchair use (see **Supplemental Table 3** for an overview of the outcome definitions used in the included studies). For pulmonary function tests, 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 ≥25% and results are reported in hazard ratios (HR) with 95% confidence interval (95% CI). The statistical analyses were conducted using the statistical software R (https://stat.ethz.ch/CRAN/).

3. Results

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3.1 Study selection

Out 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, **Supplemental Table 4**) 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 51[25] to 5,345[26] DMD patients and the mean follow-up duration from 1[27] to 15.2[28] years. The age of the included patients at baseline was between <1[26] and 39[29] years.

3.3 Study quality

In total, 5 RCTs (35.7%) were rated to be of high quality and 9 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

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Studies consistently found a longer time to LoA in patients with corticosteroid treatments (**Supplemental Table 5)**. The pooled overall effect of 5 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 year) corticosteroid treatment was more effective than intermittent or <1 year corticosteroid use (pooled HR of 4 studies: 0.50, 95% CI 0.27 to 0.90). The finding was mainly driven by studies that compared corticosteroid treatment of >1 year to <1 year **(Supplemental Table 5 and Figure 2**). In one study, treatment duration of >3 years was associated with later LoA compared to no CS treatment and a treatment duration of <3 years.[30] Although initiating corticosteroid treatment is recommended before LoA,[6] 2 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. 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 **(Supplemental Table 6)**.

Better performance in baseline physical function tests was associated with later LoA (>350m, >319m, or >330m in the 6MWT; >22 points in the NSAA, <7 seconds in the 10meter walk/run tests). Early surgery of muscles (resection of the musculi sartorius, tensor fasciae lateae, 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.[31] However,

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findings from this study need to be validated in other studies. Several gene mutations were associated with longer time until LoA (**Supplemental Table 5**). Most evidence was available for deletions amenable to exon 44 skipping (6 studies), deletions amenable to exon 8 skipping (2 studies), deletion of exons 3-7 (1 study), and single exon 45 deletion (2 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 years, 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.[32]

3.5 Predictors of pulmonary function

Corticosteroid treatment was consistently associated with higher FVC or FVC% predicted (4 studies) and FVC% predicted <50% occurred with increasing age (1 study, **Supplemental Table 5**). The decline in FVC% predicted was not influenced by corticosteroid use in 3 studies. In patients with corticosteroid treatment start before the age of 5 years, age adjusted FVC values were lower compared to patients with treatment start aged 5 years and older. Corticosteroid use was associated with a later need for ventilator assistance in 1 study.[26] Intermittent corticosteroid use was inferior in 1 study compared to continuous use, and higher doses (≥0.65mg/kg/day) did not influence FVC compared to doses <0.65mg/kg/day. Patients taking prednisone had a higher FVC% predicted than those taking deflazacort. Fusion surgery in scoliosis delayed FVC decline in 3 studies.

3.6 Predictors for heart failure

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Corticosteroid treatment was also associated with a delayed onset of heart failure in 4 studies, and the annual decline in functional shortening was smaller in 2 studies (**Supplemental Table 5**). A longer corticosteroid treatment duration was associated with a delayed onset of cardiomyopathy in 2 studies. Intermittent versus continuous use of corticosteroids had no effect on the onset of cardiomyopathy.[33] Early corticosteroid treatment (start aged <5 years) was associated with an increased risk for early onset of cardiomyopathy in 1 study.[34] 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-year treatment period.

Gene mutations/polymorphism: On the gene locus TCTEX1D1 of chromosome 1, SNPs rs1060575 and rs3816989 were associated with early/severe cardiomyopathy (LVEF <40% or fraction shortening <15% before age 13 years) compared to patients with no or mild heart involvement at the age of 28 years (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 (2 studies) and fewer heart failure-related deaths (1 study, **Supplemental Table 6**). Longer ACE-inhibitor use was associated with a lower mortality after 10 years of follow-up in 1 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-year follow-up.[35] Left ventricular dysfunction predicted mortality in 4 studies. An increased risk of death was observed for those with FVC <1 liter. Further, a greater annual decrease in FVC% predicted was associated with an increased mortality.

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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.[36] 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 review[37] found moderate quality evidence from RCTs that corticosteroid therapy in DMD improves muscle strength and function in the short term (1 year). In the current analysis corticosteroid treatment improved lung function and a treatment duration of at least one year (most likely more than three years) 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. Further, early initiation of corticosteroid treatment (aged <5 years) 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.[38] 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

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function, pulmonary function, and satisfaction with treatment.[39] Both were superior to intermittent prednisone alternating 10 days on and 10 days off over a 3-year follow-up when assessed by composite outcome comprising measures of motor function, pulmonary function, and satisfaction with treatment.[39] Other prognostic factors included baseline function tests for loss of ambulation, ACE-inhibitor use for heart failure and mortality, fusion surgery in scoliosis to preserve pulmonary function and delay loss of ambulation. Left ventricular dysfunction and FVC <1 liter 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.[40] Further, we found no study with sufficient follow-up that assessed nocturnal mechanical ventilation in chronic hypoventilation, which has been found to results in short-term alleviation of symptoms.[41] 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 6MWT between 300 and 400 meters.[42] 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 loss of ambulation compared to no ataluren treatment.[16] Although efforts are underway to identify blood biomarkers of disease progression,[43] 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

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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 loss of ambulation without unacceptable adverse effects. Promising results indicate that blood biomarkers and MRI studies may help to identify DMD patients at risk for early loss of ambulation. 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.[16,42] 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.[7,6,8] When initiating corticosteroid treatment, optimal treatment duration seems to be more than three years to delay loss of ambulation.

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Further, early initiation of corticosteroid treatment (aged <5 years) 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 loss of ambulation, and treatments that result in skipping of the affected exon in specific mutations[16,17] may modify progression in a subgroup of patients with milder phenotype/disease progression.[18]

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. Further, 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.

4.5 Conclusion

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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.

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Authors contributions

MMW, TDL, FJW designed and conceived the study. TDL and FJW were responsible for the independent literature screening, data extraction and quality assessment. MMW, TDL, FJW, MRB analyzed the data. The first draft of the article was written by MMW, FJW and revised by TDL, MRB and MK. All authors approved the final version of the manuscript. TDL and FJW contributed equally to this work.

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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

IV, invasive assisted ventilation

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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FIGURE Titles and LEGENDS

Figure 1 Study flow

Figure 2 Influence of corticosteroid treatment and dosing regimen on loss of ambulation main plot

Legend: HR, Hazard ratios for outcome Loss of ambulation (LoA); 95% CI, 95% confidence interval; Bello[56]

Figure 3 Sensitivity analysis of influence of corticosteroid treatment and dosing regimen on loss of ambulation

Legend: Sensitivity analysis excluding multiple arms in individual studies (Kim[34] late corticosteroid start, Bello[56] and Zhang[126] deflazacort arm).

HR, Hazard ratios for outcome Loss of ambulation (LoA); 95% CI, 95% confidence interval

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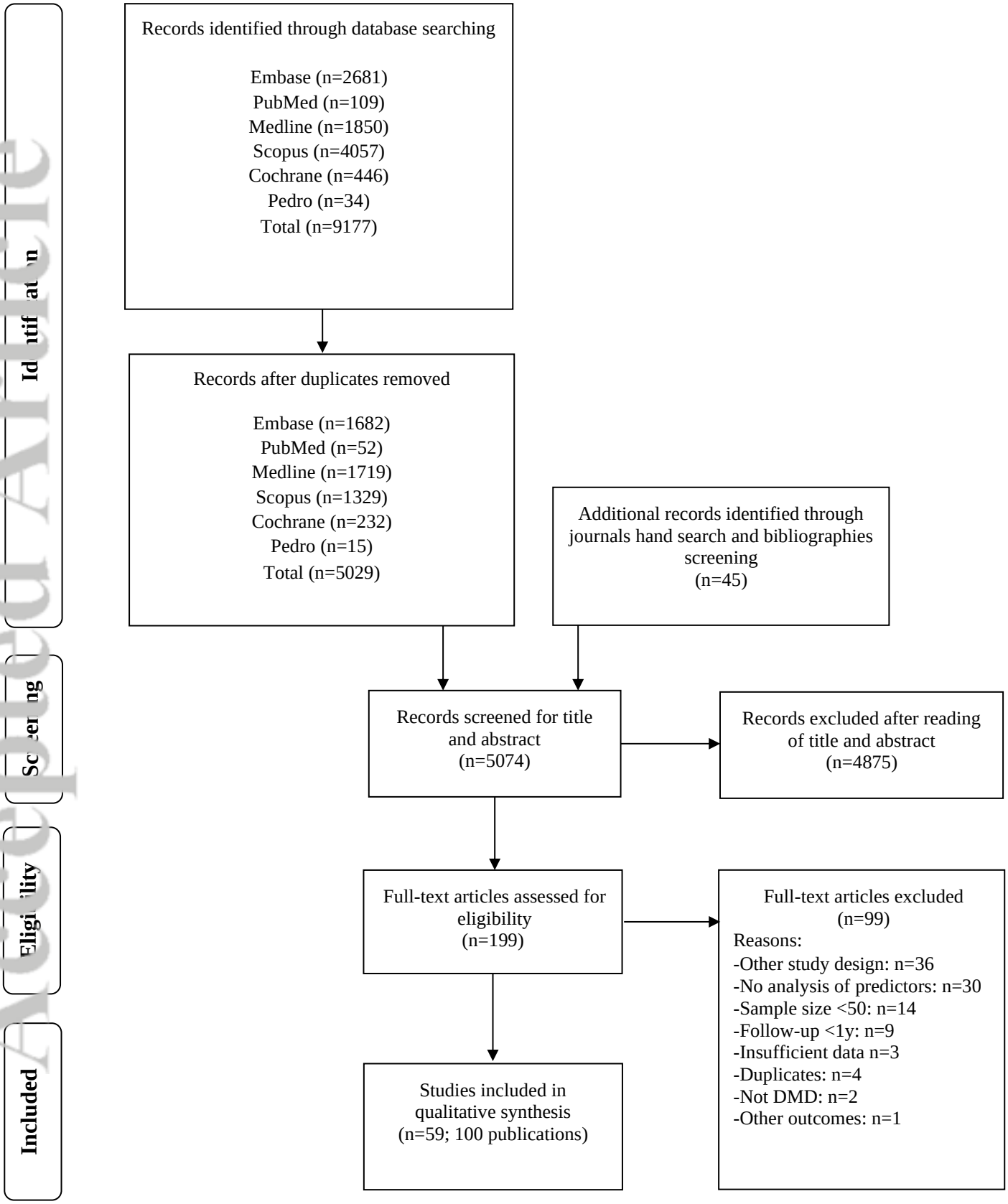

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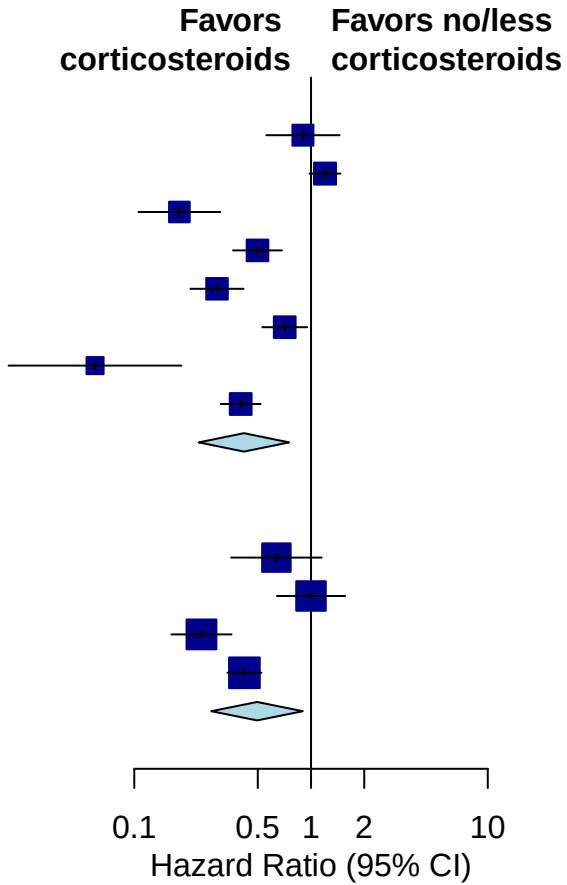
Source	HR (95% CI)
Corticosteroids vs. no corticosteroids	
Kim (2017): early start corticosteroids vs. none	0.90 [0.56; 1.45]
Kim (2017): late start corticosteroid vs. none	1.20 [0.98; 1.47]
Kim (2015): long−term corticosteroids vs. none	0.18 [0.11; 0.31]
Bello (2015): prednisone vs. none	0.50 [0.36; 0.68]
Bello (2015): deflazacort vs. none	0.29 [0.21; 0.42]
Haber (2021): corticosteroids vs. none	0.71 [0.53; 0.95]
Zhang (2021): deflazacort vs. none	0.06 [0.02; 0.18]
Zhang (2021): prednisone vs. none	0.40 [0.31; 0.52]
Total	**0.42 [0.23; 0.75]**
Heterogeneity: $\chi^2_7 = 111.68$ ($P < .001$), $I^2 = 94\%$	
More vs. less corticosteroids	
Ricotti (2013): daily vs. intermittent prednisone	0.64 [0.35; 1.15]
Kim (2017): early vs. late start corticosteroids	1.00 [0.64; 1.56]
Thangarajh (2020): corticosteroids 1+ y vs. <1y	0.24 [0.16; 0.35]
Chen (2020): corticosteroids 1+ y vs <1y	0.42 [0.34; 0.52]
Total	**0.50 [0.27; 0.90]**
Heterogeneity: $\chi^2_3 = 24.04$ ($P < .001$), $I^2 = 88\%$	
Test for subgroup differences: $\chi^2_1 = 0.16$ ($P = .69$)	



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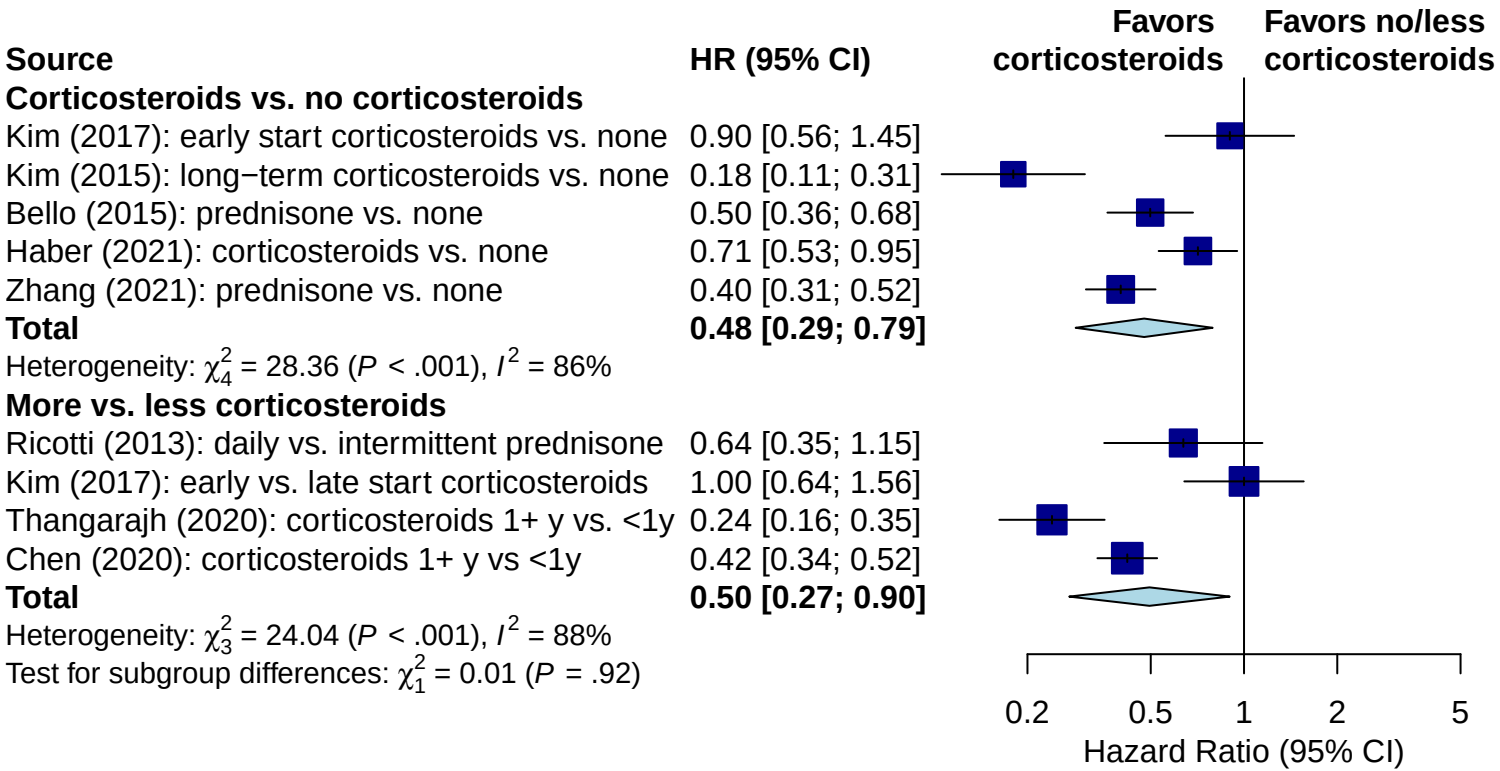

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