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Evaluation of effects of continued corticosteroid treatment on cardiac and pulmonary function in non-ambulatory males with Duchenne Muscular Dystrophy from MD STAR*net*

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Abstract

Introduction/Aims: Corticosteroids have been shown to improve muscle strength and delay loss of ambulation (LOA) in Duchenne muscular dystrophy (DMD) and are considered standard of care despite significant side-effects. The objective of this study is to evaluate whether corticosteroid treatment after LOA is beneficial for cardiac or pulmonary functions among boys with DMD.

Methods: We used the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*) to characterize associations between corticosteroid use and onset of abnormal left ventricular (LV) function or abnormal percent predicted forced vital capacity (ppFVC) among 398 non-ambulatory boys with DMD. Kaplan-Meier curve estimation was used to compare time to onset by corticosteroid use groups; Cox proportional hazards modeling was used to estimate hazards ratios (HR)s and corresponding 95% confidence intervals.

Results: We found no differences in time to onset of abnormal LV function by corticosteroid use groups. We observed a longer time from LOA to first abnormal ppFVC in boys that were treated

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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.

with corticosteroid ≥1 year beyond LOA compared to those with no corticosteroid use or those who stopped corticosteroid use within 1 year of LOA.

Discussion: Our findings show no association of corticosteroid use beyond LOA with the onset of abnormal LV function, but a significant association with a delay in onset of abnormal ppFVC. Prospective studies of corticosteroid use in boys with DMD who have lost ambulation may identify benefits and can better elucidate risks, allowing for more effective counseling of patients on continuing treatment after LOA.

Keywords

Duchenne muscular dystrophy; corticosteroid; cardiomyopathy

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a severe neuromuscular disorder resulting in progressive muscle weakness, cardiac failure, and respiratory compromise. Patients suffer progressive loss of motor function resulting in loss of ambulation (LOA) early in their 2nd decade of life. Both genetic and non-genetic factors are known to influence the rate of progression.[1–3] As muscle weakness progresses, patients are increasingly at risk for orthopedic complications, such as fractures and scoliosis, and respiratory complications, such as hypoventilation and pneumonia.[4, 5] Respiratory complications have long been recognized as the most significant contributor to morbidity and mortality in DMD patients, but complications due to cardiac dysfunction are becoming an increasingly significant as patients with DMD survive longer.[6]

Corticosteroids have been shown to improve muscle strength and delay LOA and are considered standard of care in ambulatory boys with DMD.[5, 7–9] Even with wide agreement that corticosteroids have significant benefit on strength and ambulation, there is widespread variation in clinical practice regarding timing of initiation of treatment, dosing schedule, and management of side-effects.[10] Care guidelines updated in 2018 recommend initiation of treatment with corticosteroids soon after diagnosis and continuing treatment with dose reductions as necessary to manage side-effects.[9] While the benefits of corticosteroids in DMD are increasingly clear, there remains uncertainty about the balance of benefits and side-effects that arise with long-term treatment. As patients with DMD progress beyond LOA, the relative importance of side-effects that were well-tolerated at earlier stages of disease increases, and management becomes more complex. Side effects such as weight gain, hypertension, and glucose intolerance, and effects on growth and bone density are compounded in non-ambulatory patients with active declines in heart and lung function.

Studies in relatively small cohorts have suggested therapeutic benefit from corticosteroid use after LOA, including the prevention of scoliosis and preservation of cardiac and pulmonary functions.[11–16] However, these benefits have not been sufficiently evaluated in relation to risk for complications due to side-effects such as weight gain and fractures. An earlier study by the Muscular Dystrophy Surveillance, Tracking and Research network (MD STAR*net*), reported delayed onset of cardiomyopathy among ambulatory and non-ambulatory boys with DMD using corticosteroids, with an expected 20% decreased risk over 5 years of use.[13] The

overall objective of this study was to expand on earlier MD STAR*net* findings and determine whether corticosteroid treatment beyond LOA was associated with delayed progression of abnormal cardiac and pulmonary function among boys with DMD.

METHODS

Study Cohort

We used data from the MD STAR*net*, which conducts population-based surveillance of individuals with DMD and Becker muscular dystrophy (BMD), to identify non-ambulatory boys with DMD. As described previously, surveillance began in 2004 and retrospectively identified and prospectively followed all individuals with suspected DMD or BMD born between January 1982 – December 2011 at 4 participating sites: Arizona, Colorado, Iowa, and western New York.[17] Georgia and Hawaii were added in 2006 and 2008, respectively. Abstracted data for each case was collected from the medical record by trained abstractors. Annual medical record abstraction continued through December 2011 for most cases. For cases identified between September 2011 and December 2011, abstraction of data was extended through the end of 2012. A committee of neuromuscular clinicians reviewed each case and assigned a definition of definite, probable, possible, manifesting female, or asymptomatic based on clinical trajectory, and laboratory and genetic results.[18] Phenotype (DMD, BMD, female, non-classifiable) was assigned using an algorithm based on abstracted clinical and diagnostic information.[19] Only cases classified as “definite” and “probable” DMD were included in the study cohort. LOA was defined as the age at which the subject was first reported in the medical record as having stopped walking or being a fulltime wheelchair user. Individuals that had not met LOA were excluded. Individuals that had undefined corticosteroid exposure or had stopped treatment with corticosteroid >1 year prior to LOA were also excluded.

Standard protocol approvals, registrations, and patient consents

This study was approved by the relevant institutional review boards (IRB). In Colorado, Georgia, Iowa and western New York, public health authorities permitted medical record abstraction. In Arizona and Hawaii, IRB approval was obtained from the University of Arizona and the Hawaii Department of Health, respectively, and when needed, from other health care facilities where data collection occurred.

Corticosteroid Exposure

Use of corticosteroids was determined from the medical record and included both prednisone and deflazacort with a variety of dosing regimens. To distinguish groups of boys with longer term vs shorter term exposure to corticosteroid, we classified boys with DMD into three groups based on corticosteroid exposure: 1) never used corticosteroid, 2) were treated with corticosteroid but discontinued use within one year (before or after) LOA, and 3) started use of corticosteroid before LOA and continued use ≥1 year beyond LOA. Historically, many boys with DMD discontinue use of corticosteroids around the time of LOA, and our grouping allowed comparison of groups with no corticosteroid exposure (group 1) to those with corticosteroid exposures commonly seen in clinical practice (groups 2 and 3). The mean total duration of corticosteroid treatment and mean age at LOA were

calculated for each group. Treatment with other disease modifying therapies such as FDA approved exon skipping therapies were not considered in our analysis since these treatments were not available during the study period.

Cardiac Function

Left ventricular (LV) heart function was determined from medical records based on echocardiographic measurements for ejection fraction (EF) and, if EF was not available, shortening fraction (SF). If neither EF nor SF were available in the record (n=32), SF was calculated from left ventricle internal diameter in diastole (LVID) and left ventricle internal diameter in systole (LVIS) using the formula, SF = ((LVID-LVIS)/LVID)*100. Abnormal LV function was defined as EF less than 55% or SF/calculated SF less than 28%.

Pulmonary Function

Pulmonary function was determined from medical records based on measurement of the percent predicted forced vital capacity (ppFVC). Typically, ppFVC is considered abnormal if between 50% and 80%, and clinically significantly abnormal if <50%. For our analyses, we considered ppFCV <50% as having met the endpoint of clinically significant abnormal pulmonary function since interventions are recommended at this point.[20] If ppFVC was missing from the record, but absolute FVC was available (n=40), ppFVC was calculated using the method proposed by Hankinson *et al.*, which used absolute forced vital capacity, sex, race, age and height.[21] For individuals where height was unavailable but arm span was measured (n=38), we calculated height (height= arm span* 0.945).[22]

Statistical Analysis

We assessed the distribution of age, years exposure to corticosteroid, and normal or abnormal cardiac function or pulmonary function between corticosteroid use groups using the chi-square statistic. To compare the observed mean ages at onset of abnormal LV function or abnormal ppFVC by corticosteroid use groups, we used pairwise two-tailed t-tests to assess differences between all groups. We used Kaplan-Meier curves to estimate survival time by corticosteroid use and Cox proportional hazard ratio (HR point estimate with 95% confidence limits [CI]), which accounts for the expected number of events (abnormal echocardiogram or pulmonary function test) over time, to estimate the hazards of abnormal LV function or abnormal ppFVC by corticosteroid use groups, including all pairwise comparisons. We tested the assumption that the ratio of hazards were constant over time (time to event) for all Cox proportional hazard models. Assumptions were met for all models. Two time-scales were used for the survival analyses: 1) time from birth to abnormal LV function or abnormal ppFVC and 2) time from LOA to abnormal LV function or abnormal ppFVC. Since scoliosis can have an effect on cardiac and pulmonary function, we determined whether the proportion of individuals with clinically significant scoliosis (≥ 20 degrees)[20] differed between the corticosteroid exposure groups using a χ^2 test. Statistical analysis was conducted at University of Utah using SAS software, Version 9.4 (SAS Institute, Cary NC) and independently replicated at the University of Iowa.

RESULTS

Sample and Corticosteroid Exposure Groups

A total of 1054 individuals with DMD or BMD were identified by the MD STAR*net* (Figure 1). We excluded 304 individuals that did not meet inclusion criteria for DMD leaving 750 confirmed individuals with DMD. An additional 352 individuals were excluded, including those who did not have a recorded age at LOA, used corticosteroid but stopped >1 year prior to LOA, or had undefined steroid exposure. The final sample was comprised of 398 non-ambulatory males with DMD with 193 that never used corticosteroids, 104 that discontinued use within one year (before or after) LOA, and 101 that started use before LOA and continued use ≥1 year beyond LOA (Table 1). The mean total duration of corticosteroid treatment was 3.69 years for individuals treated with corticosteroid but stopping within 1 year of LOA and 8.73 years for boys treated for at least 1 year beyond LOA. Individuals treated with corticosteroid for >1 year beyond LOA, walked longer than boys stopping corticosteroid within 1 year of LOA or those never treated with corticosteroid (Table 1).

Association between corticosteroid use and cardiac function

To determine whether corticosteroid use beyond one year after LOA delayed abnormal LV function, we compared time from birth to abnormal LV function and time from LOA to abnormal LV function in the three steroid exposure groups. Of the 398 subjects available for analysis, 48 were excluded due to absent data on cardiac function, and 16 with abnormal cardiac function prior to LOA, leaving 334 available for analysis (Table 2). In the 334 individuals studied for LV function, those who used corticosteroids >1 year beyond LOA had slightly longer cardiac follow-up and number of echocardiograms performed, however, the number of cardiac studies per year was similar in all groups. (Table 3). The proportion of individuals with scoliosis ≥ 20 degrees were balanced in the three corticosteroid groups (χ^2=1.92, p=0.37). No statistically significant difference in frequency of abnormal LV function was identified between the three corticosteroid groups (Table 2).

Time from birth to abnormal LV function.—Observed mean ages at onset of abnormal LV function were not statistically different between corticosteroid use groups (Figure 2A), which is consistent with the findings from the K-M curve estimation (Figure 2B). Cox proportional hazard modeling showed no difference in risk of abnormal LV function by corticosteroid use group for all pairwise comparisons (Table 4).

Time from LOA to abnormal LV function.—Pairwise comparisons of the observed means across corticosteroid use groups showed that the time from LOA to abnormal LV function appeared to be shorter for those who continued corticosteroid use more than one year beyond LOA than the other two groups (Figure 2C). K-M curve estimation showed no significant overall group differences for time from LOA to onset of abnormal LV function (Figure 2D). The results for the Cox proportional hazards model showed reduced hazards of abnormal LV function among those who were never treated with corticosteroid or stopped treatment within 1 year of LOA compared to those who continued use at least 1 year beyond LOA; although the confidence intervals for all pairwise comparisons contained the null (Table 4).

Effect of prolonged steroid use on pulmonary function

To evaluate corticosteroid use beyond LOA and pulmonary function, we compared the times from birth to the first abnormal ppFVC and time from LOA to first abnormal ppFVC in the three steroid exposure groups. Of the 398 subjects available for analysis, 48 were excluded due to absent ppFVC data, and 25 with abnormal ppFVC prior to LOA, leaving 325 available for analysis (Table 2). In the 325 individuals studied for pulmonary function, those who used corticosteroids >1 year beyond LOA had longer pulmonary follow-up and more PFT's available, however, the number of pulmonary studies per year was similar in all groups (Table 3). The proportion of individuals with scoliosis ≥20 degrees were similar between the three corticosteroid groups (χ^2=0.44, p=0.80). The frequency of abnormal ppFVC was not statistically different between the three corticosteroid groups (Table 2).

Time from birth to first abnormal ppFVC.—Pairwise t-test comparisons of observed means showed a significantly later onset of abnormal ppFVC among boys who continued corticosteroid use at least one year beyond LOA compared to boys who were never treated or those who discontinued within one year of LOA (Figure 3A). No statistically significant difference was found between boys who were never treated with corticosteroid and those who discontinued within one year of LOA. K-M curve estimation showed no statistically significant differences between groups for time from birth to first abnormal ppFVC (Figure 3B). Risk of abnormal ppFVC was increased in boys who were never treated with corticosteroid and those who discontinued within 1 year of LOA compared to those who continued use ≥1 year after LOA, although the difference was only significant for the group stopping treatment within 1 year of LOA compared to continuing treatment beyond 1 year of LOA. (Table 4).

Time from LOA to first abnormal ppFVC.—Analyses of the observed mean time from LOA to abnormal ppFVC showed no statistically significant pairwise differences (Figure 3C); K-M curve estimation was consistent with the observed mean comparisons (Figure 3D). Finally, Cox proportional hazard modeling showed no statistically significant difference in risk of abnormal ppFVC for all pairwise comparisons (Table 4).

DISCUSSION

In our cohort, we found that non-ambulatory boys with DMD who were treated with corticosteroid for at least one year beyond LOA had no statistically significant difference in the age of onset of abnormal LV function compared to those who stopped treatment within 1 year of LOA or those were never treated with corticosteroid. While the age at first abnormal LV function was not different between groups, the time from LOA to the first abnormal LV function was decreased in boys with treatment ≥1 year after LOA compared to those who stopped within a year of LOA or were never treated. This effect was not statistically significant for the whole cohort (Figure 3B). Taken together, the shorter time from LOA to onset of abnormal LV function in boys for whom steroid treatment continued beyond LOA likely reflects prolonged ambulation in those individuals, thereby creating a shorter interval between LOA and onset of abnormal LV function, rather than a detrimental effect of corticosteroids on cardiac function. A more significant impact of corticosteroid on cardiac

function might have been seen with better imaging tools such as cardiac MRI that can more directly measure fibrosis and other aspects of DMD related cardiomyopathy.

In terms of pulmonary function, we observed a delay in the average age at which the ppFVC reached below 50% predicted in boys who continued treatment for >1 year after LOA (15.98 years) compared to those that were never treated (14.96 years) or stopped treatment within 1 year of LOA (14.67 years). The time from LOA to the first ppFVC <50% was no different between groups. Similarly, in a large DMD natural history cohort, the ppFVC increased up to age 7 in patients not treated with corticosteroids and to age 10 in patients treated with corticosteroid and then declined in both groups in linear fashion over time.[25] Treatment with corticosteroids delayed the decline phase but did not alter the rate of decline. Our results are consistent with this finding, suggesting that there is a benefit of delaying decline in lung function with corticosteroids, but this benefit may not persist beyond LOA.

Studies highlighting the benefits from long-term treatment with corticosteroid are emerging. A single center retrospective study showed decreased all-cause mortality of 76% in subjects treated with corticosteroid vs those who did not receive corticosteroid, with most of that effect attributed to decreased heart failure related deaths in treated individuals.[24] A larger, multicenter, prospective study showed decreased rate of decline in motor and heart function in subjects treated with >1 year of corticosteroid compared to those treated for <1 month.[23] A previous study from the MD STAR*net* showed delayed onset of cardiomyopathy in boys with DMD treated with at least 1 month of corticosteroid.[13] In each case, consistent benefit was shown for treatment with corticosteroid vs no (or little) treatment. In contrast, our study considers the effects of prolonged treatment with corticosteroid, beyond LOA, on the onset of abnormal LV function and pulmonary function.

Limitations of the study are inherent to the retrospective/observational design of the MD STAR*net* project. Measurements for cardiac and pulmonary function were ascertained from the medical record and are dependent on the quality and timing in a clinical setting rather than a controlled clinical trial setting. Based on care guidelines that were published near the end of this study,[26, 27] assessment of cardiac and pulmonary function should be obtained at least annually beyond 10 years of age, but not all centers followed these guidelines uniformly, and not all patients are followed at specialty centers. Furthermore, it could be postulated that patients receiving treatment with corticosteroid for a longer interval may be seen more regularly and may be more apt to adopt new care guidelines, and this might lead to earlier detection of abnormal cardiac or lung function. Indeed, in our study, the group treated with corticosteroid for at least 1 year beyond LOA had relatively longer follow-up and more echocardiogram and PFT studies than the other groups, however, the number of studies per year was similar between groups. Other factors, such as the development of scoliosis, can be responsive to treatment with corticosteroid and might alter the progression of cardiac or pulmonary function. In our cohort, the three different corticosteroid exposure groups are balanced for the number of individuals with scoliosis ≥ 20 degrees suggesting that scoliosis is not a confounding factor.

Other limitations to the study include variability in the measurement of cardiac and pulmonary function which are technically demanding and techniques for performing these

tests can be variable between centers. Our analysis was limited to EF/SF and ppFVC measurements since more detailed measurements of cardiac and pulmonary function were not widely collected. Wide variability in practice relating to corticosteroids, including changing practice parameters over time, may result in confounding due to differences in the type of steroid used (deflazacort vs prednisone), duration of use, different dosing regimens, and different adaptations to side-effects. The strength of the study is in its long-term follow-up and population-based ascertainment. While there is variability in care for patients across different centers, records were abstracted systematically and represent experience in common clinical care settings for patients with DMD including patients seen at specialty centers and those seen outside of specialty centers. Results from this study may not be generalizable to DMD individuals living outside the surveillance area.

Our findings highlight the complexity of treatment with corticosteroids for DMD and the importance of additional studies to determine the benefits and risks of prolonged treatment. Current care guidelines recommend continued treatment of non-ambulatory DMD patients with corticosteroids with dose adjustments to mitigate side-effects.[9] However, there is little guidance about how to balance risks and benefits in non-ambulatory patients for whom worsening side-effects may have a more significant impact. The recommendation to continue treatment after LOA is based on presumed benefits to upper limb motor function, and cardiac and pulmonary function. However, the evidence supporting these benefits is limited mostly to studies comparing groups with minimal to no corticosteroid exposure to groups with longer exposure. Consistent with previous studies, boys with longer corticosteroid exposure in our study have a prolonged time to LOA compared to boys with less exposure to corticosteroid. Longer steroid use might also be associated with benefits to cardiac and lung function, however, we have shown that corticosteroid use for at least 1 year beyond LOA was not associated with earlier or later onset of abnormal LV function but was associated with a significant delay in the onset of abnormal ppFVC. Prospective studies of the effects of corticosteroids on motor, cardiac, and pulmonary function in non-ambulatory boys with DMD will be important in defining the risks and benefits to allow more effective counseling of patients about how long to continue treatment, and how and when to consider stopping treatment.

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Disclosures:

RJ Butterfield is receiving funding via contracts for clinical trials from Avexis, PTC Therapeutics, Sarepta Therapeutics, Pfizer, Biogen, Carpricor, and Catabasis. He serves on scientific advisory boards for Sarepta Therapeutics, Biogen, Avexis and Pfizer.

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S Thomas has no conflicts to disclose.

ML Feldkamp has no conflicts to disclose.

ABBREVIATIONS

LOA	loss of ambulation
DMD	Duchenne muscular dystrophy
MD STARnet	Muscular Dystrophy Surveillance, Tracking, and Research Network
LV	left ventricular
ppFVC	percent predicted forced vital capacity
BMD	Becker muscular dystrophy
IRB	institutional review board
EF	ejection fraction
SF	shortening fraction
LVID	left ventricle internal diameter in diastole
LVIS	left ventricle internal diameter in systole
HR	hazard ratio
CI	confidence interval

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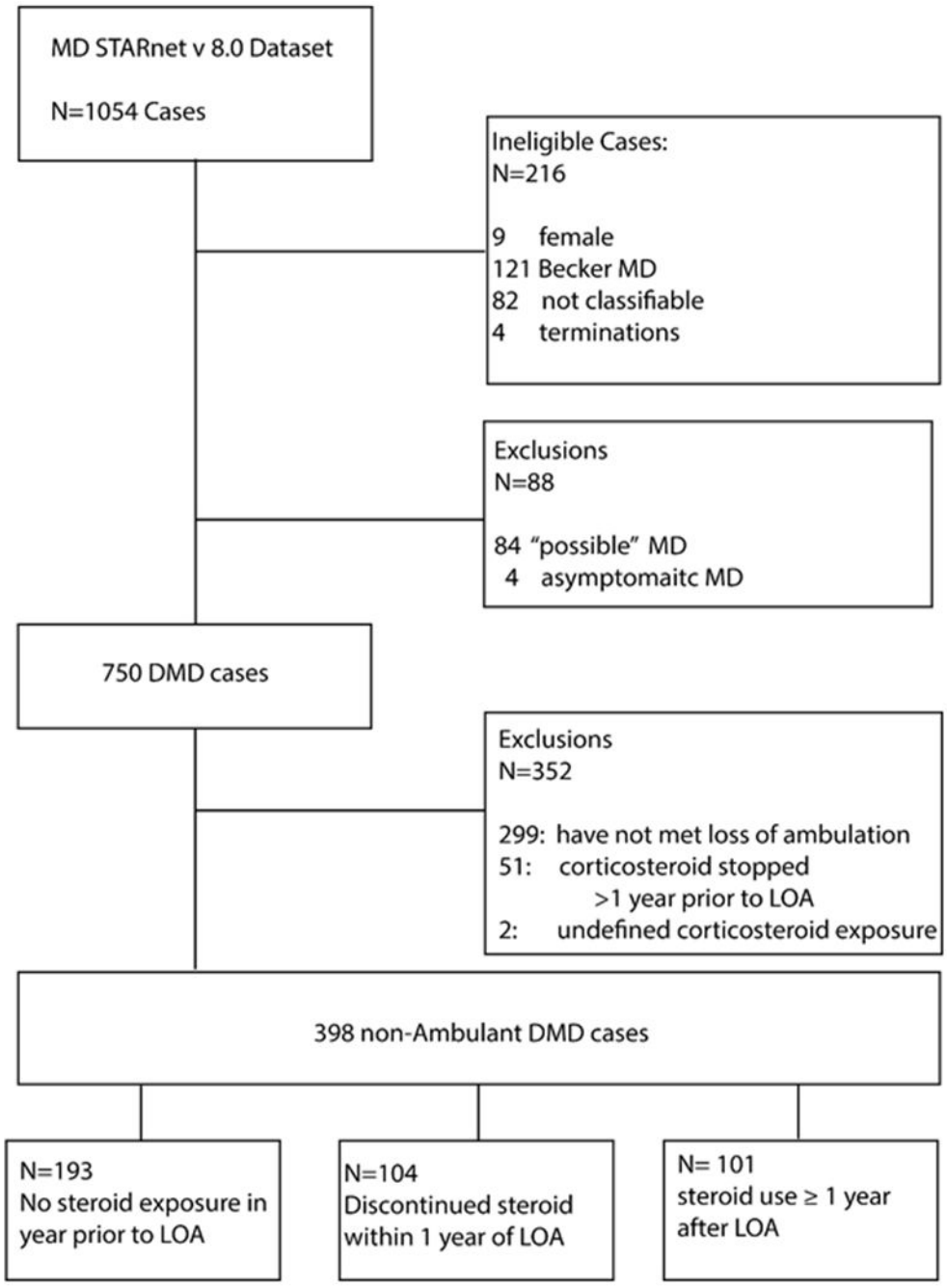

Figure 1.
Case selection to identify non-ambulatory boys with DMD, MD STARnet 1982-2012.

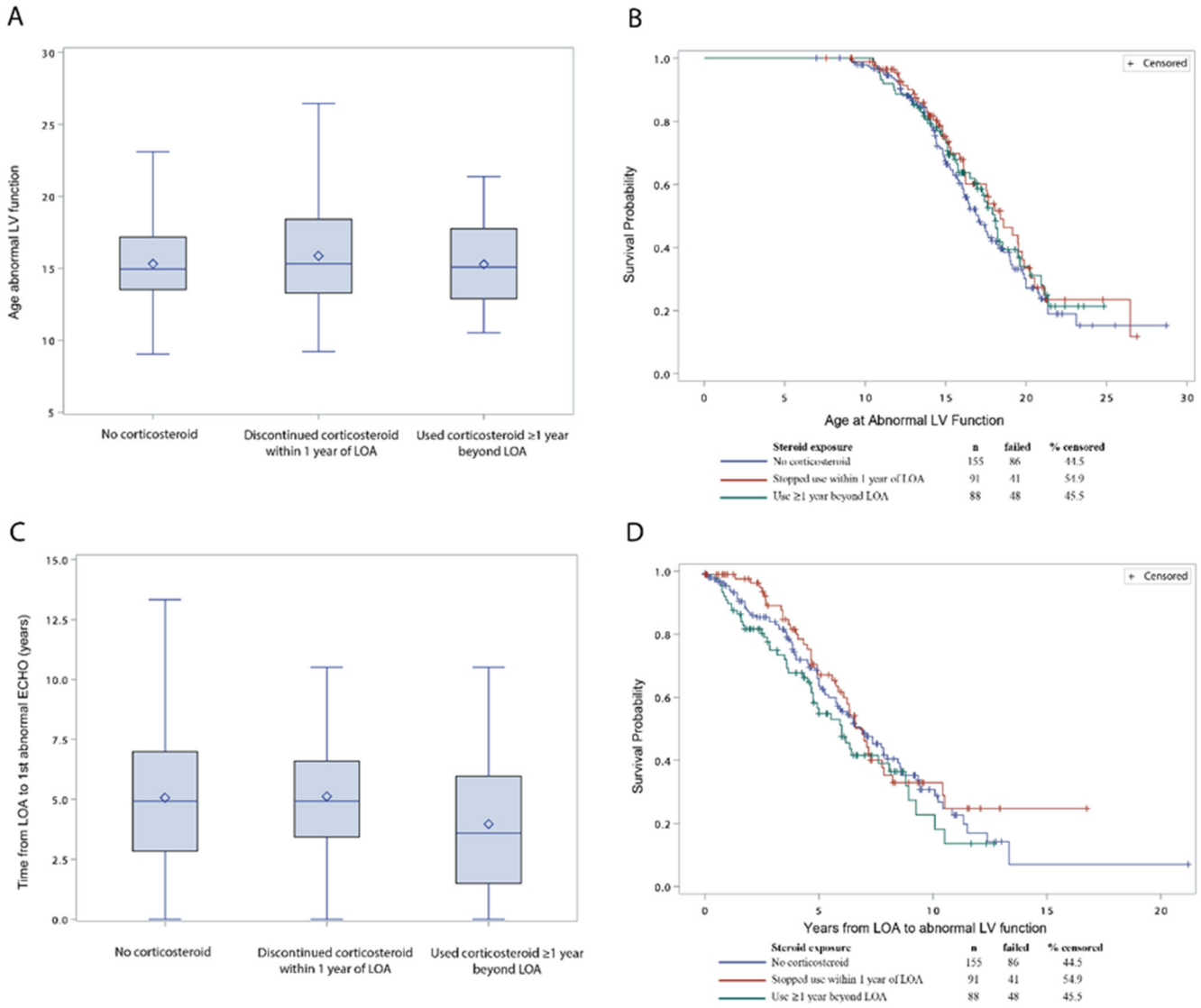

Figure 2. Effect of corticosteroid use beyond LOA on onset of abnormal LV function in non-ambulatory boys with DMD, MD STARnet 1982-2012.

Comparison of corticosteroid exposure in males with DMD not treated with corticosteroid to those stopping corticosteroids within a year of LOA, and those treated for ≥1 year after LOA. A) Observed median age of abnormal LV function. T-tests for pairwise comparisons were not statistically significant. B) Kaplan-Meier curves comparing age at abnormal LV function in the three corticosteroid exposure groups (χ^2=1.27, p=0.53). C) Observed median time from LOA to abnormal LV function in the three corticosteroid exposure groups. Observed mean time from LOA to onset of abnormal LV function for those never on corticosteroids and those who discontinued within 1 year of LOA were longer than for those who continued corticosteroids ≥1 year after LOA, t=2.0 (p=0.047) and t=2.09 (p=0.04) respectively. D) Kaplan-Meier curves comparing time from LOA to abnormal LV function in the three corticosteroid exposure groups (χ^2= 2.48, p=0.29).

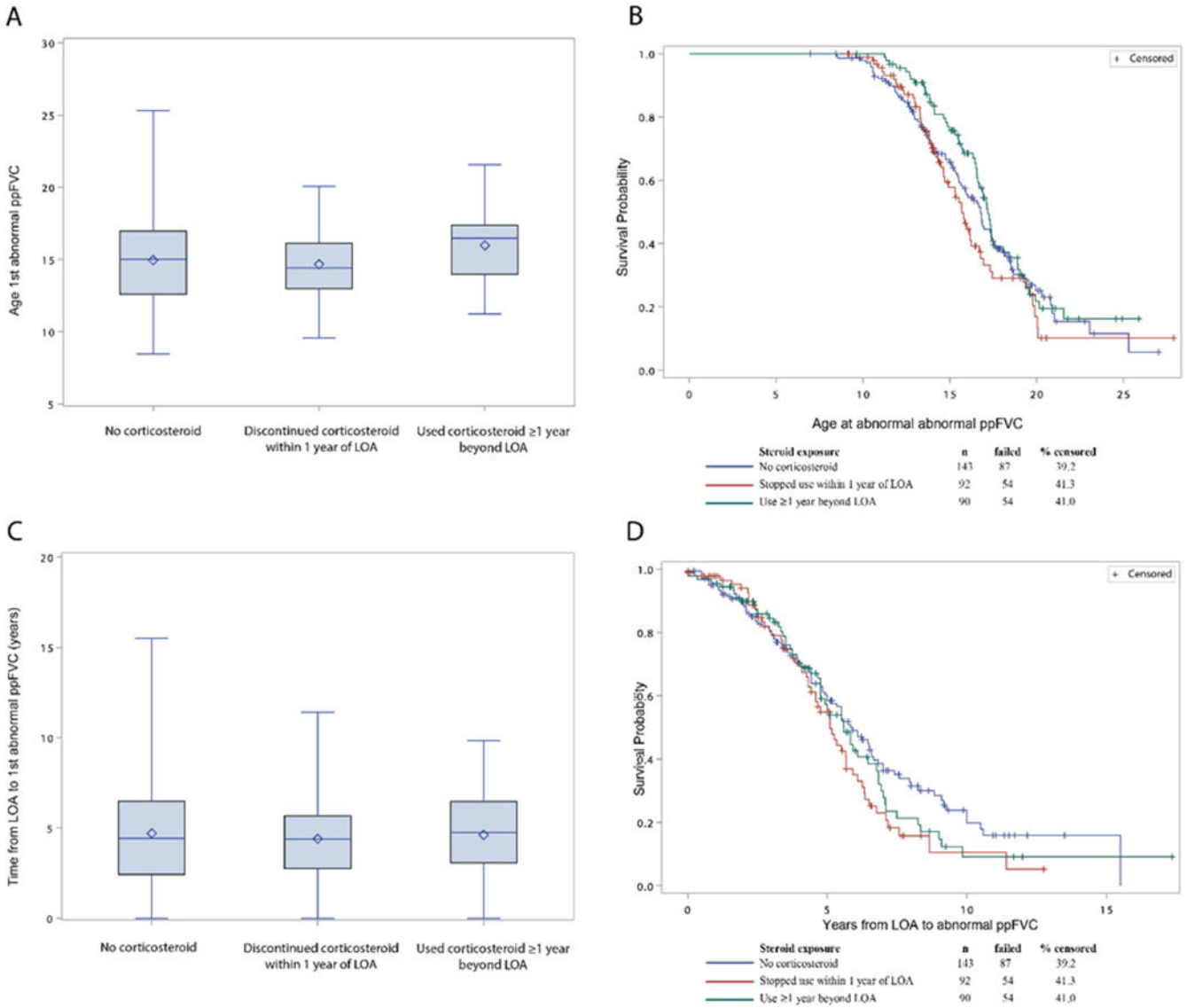

Figure 3. Effect of corticosteroid use beyond LOA on onset of abnormal pulmonary function in non-ambulatory boys with DMD, MD STARnet 1982-2012.

Comparison of corticosteroid exposure in males with DMD not treated with corticosteroid to those stopping corticosteroids within a year of LOA, and those treated for ≥1 year after LOA. A) Median observed age of first abnormal ppFVC. Mean age at first abnormal ppFVC for those not treated with corticosteroids and those who discontinued within 1 year of LOA were younger than for those who continued corticosteroids ≥1 year after LOA, t= −2.1 (p=0.04) and t= −2.68 (p=0.01) respectively. B) Kaplan-Meier curves comparing age at abnormal ppFVC (χ^2=4.03, p=0.13). C) Median time from LOA to abnormal ppFVC. T-tests for pairwise comparisons were not statistically significant. D) Kaplan-Meier curves comparing time from LOA to abnormal ppFVC (χ^2= 3.61, p=0.16)

Table 1.

Years of corticosteroid exposure, and age at LOA by corticosteroid exposure group among males with DMD, MD STAR*net* 1982-2012.

Corticosteroid exposure group	Cases–	Years of Corticosteroid Exposure (mean, SD)	Age at LOA (mean, SD)[a]
None	193	0.00	10.30 (1.78)
Stopped use within 1 year of LOA	104	3.69 (2.95)	10.65 (2.23)
Use >1 year beyond LOA	101	8.73 (4.44)	11.70 (2.04)

DMD: Duchenne muscular dystrophy, LOA: Loss of ambulation, SD: standard deviation

[a]ANOVA, F=17.0, p<0.0001

Table 2.

Cardiac and pulmonary function by corticosteroid exposure group among non-ambulatory males with DMD, MD STAR*net* 1982-2012.

	Abnormal LV Function [a]		Abnormal ppFVC [b]	
Corticosteroid exposure group	**Yes n (%)**	**Total n**	**Yes n (%)**	**Total n**
None	86 (55%)	155	87 (61%)	143
Stopped use within 1 year of LOA	41 (45%)	91	54 (59%)	92
Use >1 year beyond LOA	48 (55%)	88	54 (60%)	90
Total	175 (52%)	334	195 (60%)	325

DMD: Duchenne muscular dystrophy, LOA: Loss of ambulation, LV: left ventricular, ppFVC: Forced vital capacity

[a] Analysis from 398 subjects, excluding 48 with absent echo data and 16 with abnormal echo prior to LOA. χ^2=2.72, p-value=0.26

[b] Analysis from 398 subjects with DMD, excluding 48 with absent FVC data and 25 with abnormal FVC prior to LOA. χ^2=0.11, p-value=0.95

Table 3.

Cardiac and pulmonary function tests performed and age of cases by corticosteroid exposure group among non-ambulatory males with DMD, MD STAR*net* 1982-2012.

	Corticosteroid Exposure Group		
	None	**Stopped use within 1 year of LOA**	**Use >1 year beyond LOA**
Cardiac Function			
Number of cases	155	91	88
Median years between first and last echocardiogram	5.93	6.25	7.16
Median number of echocardiograms per case	5	5	6
Median year of birth	1991	1994	1992
Pulmonary Function			
Number of cases	143	92	90
Median years between first and last PFT	4.91	6.25	7.08
Median number of PFT studies per case	6	7	9
Median year of birth	1990	1992	1992

Table 4.

Pairwise Cox proportional hazards analysis by corticosteroid exposure groups for abnormal cardiac and pulmonary function among non-ambulatory males with DMD, MD STAR*net* 1982-2012.

	HR	95% CL
Time from birth to abnormal LV function		
None vs. Stopped use within 1 year of LOA	1.22	0.84-1.77
None vs. Use ≥1 year beyond LOA	1.14	0.80-1.63
Stopped use within 1 year of LOA vs. Use ≥1 year beyond LOA	0.94	0.62-1.42
Time from LOA to abnormal LV function		
None vs. Stopped use within 1 year of LOA	1.13	0.78-1.63
None vs. Use ≥1 year beyond LOA	0.81	0.57-1.16
Stopped use within 1 year of LOA vs. Use ≥1 year beyond LOA	0.72	0.48-1.10
Time from birth to abnormal ppFVC		
None vs. Stopped use within 1 year of LOA	0.82	0.58-1.16
None vs. Use ≥1 year beyond LOA	1.21	0.86-1.70
Stopped use within 1 year of LOA vs. Use ≥1 year beyond LOA	1.47	1.01-2.15
Time from LOA to abnormal ppFVC		
None vs. Stopped use within 1 year of LOA	0.72	0.51-1.02
None vs. Use ≥1 year beyond LOA	0.85	0.60-1.19
Stopped use within 1 year of LOA vs. Use ≥1 year beyond LOA	1.18	0.81-1.72

DMD: Duchenne muscular dystrophy, HR: hazard ratio, CL: confidence limit, LOA: Loss of ambulation, LV: left ventricular, ppFVC: Forced vital capacity