Original research

Early treatment of type II SMA slows rate of progression of scoliosis

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2023-332084).

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Received 26 June 2023
Accepted 5 September 2023
Published Online First 22 September 2023

ABSTRACT

Background Type II spinal muscular atrophy (SMA) often leads to scoliosis in up to 90% of cases. While pharmacological treatments have shown improvements in motor function, their impact on scoliosis progression remains unclear. This study aims to evaluate potential differences in scoliosis progression between treated and untreated SMA II patients.

Methods Treatment effect on Cobb's angle annual changes and on reaching a 50° Cobb angle was analysed in treated and untreated type II SMA patients with a minimum 1.5-year follow-up. A sliding cut-off approach identified the optimal treatment subpopulation based on age, Cobb angle and Hammersmith Functional Motor Scale Expanded at the initial visit. Mann-Whitney U-test assessed statistical significance.

Results There were no significant differences in baseline characteristics between the untreated (n=46) and treated (n=39) populations. The mean Cobb angle variation did not significantly differ between the two groups (p=0.4). Optimal cut-off values for a better outcome were found to be having a Cobb angle <26° or an age <4.5 years. When using optimal cut-off, the treated group showed a lower mean Cobb variation compared with the untreated group (5.61 (SD 4.72) degrees/year vs 10.05 (SD 6.38) degrees/year; p=0.01). Cox-regression analysis indicated a protective treatment effect in reaching a 50° Cobb angle, significant in patients <4.5 years old (p=0.016).

Conclusion This study highlights that pharmacological treatment, if initiated early, may slow down the progression of scoliosis in type II SMA patients. Larger studies are warranted to further investigate the effectiveness of individual pharmacological treatment on scoliosis progression in this patient population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Type II spinal muscular atrophy (SMA) commonly results in scoliosis, and while pharmacological treatments have shown improvements on motor function, their effect on scoliosis is uncertain. The study sought to compare scoliosis progression between treated and untreated patients, shedding light on the potential benefits of pharmacological treatments in delaying the progression of scoliosis in type II SMA.

WHAT THIS STUDY ADDS

⇒ This study is the first to conduct a comprehensive long-term assessment of scoliosis in treated SMA II. Although overall differences between treated and untreated patients were not observed, subgroup analysis highlighted variations in progression. The study identified specific cut-off values (<26° for Cobb angle and <4.5 years for age) that indicated how pharmacological treatment may slow down scoliosis progression, as the treated group showed lower mean Cobb variation and reduced likelihood of reaching a 50° Cobb angle.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings can guide clinicians in determining the optimal timing for treatment initiation to improve outcomes. The study emphasises the importance of early intervention in slowing scoliosis progression, which can have implications for treatment guidelines and policies for SMA patients. Overall, this research contributes to the existing knowledge in SMA research and has the potential to influence clinical practice and policy decisions related to scoliosis management in this patient group.

To cite: Coratti G, Lenkowicz J, Pera MC, *et al*. *J Neurol Neurosurg Psychiatry* 2024;**95**:235–240.

INTRODUCTION

Spinal muscular atrophy (SMA) is a rare neuromuscular disorder caused by mutations in the *SMN1* gene that affects the motor neurons with subsequent muscle atrophy and weakness.[1] The disease is classically subdivided into different types (0–IV), based on age of onset and maximal motor function achieved.[2 3] Classically, in type II SMA (also called intermediate), the onset is between 6 and 18 months of age and patients achieve the ability to sit unsupported but not to walk. Scoliosis is a common

Table 1 Characteristics of the cohort at baseline and at last visit

	Whole cohort at baseline (N=77)	Whole cohort at last visit (N=77)
Age		
Mean (SD)	5.67 (2.66)	10.3 (3.53)
Median (min, max)	4.68 (1.36, 13.1)	10.2 (4.66, 20.9)
Sex		
Female	35 (45.5%)	35 (45.5%)
Male	42 (54.5%)	42 (54.5%)
SMN2 copy number		
2	12 (15.6%)	12 (15.6%)
3	54 (70.1%)	54 (70.1%)
4+	4 (5.2%)	4 (5.2%)
Missing	7 (9.1%)	7 (9.1%)
SMA function		
Non-sitter	1 (1.3%)	9 (11.7%)
Sitter	76 (98.7%)	68 (88.3%)
HFMSE score		
Mean (SD)	15.2 (8.50)	13.5 (9.65)
Median (min, max)	14.0 (1.00, 44.0)	12.0 (1.00, 47.0)
Treatment status		
Not treated	46 (59.7%)	38 (49.4%)
Treated	31 (40.3%)	39 (50.6%)
Cobb angle		
Mean (SD)	29.0 (24.8)	65.1 (31.6)
Median (min, max)	20.0 (0, 130)	68.3 (8.00, 150)

HFMSE, Hammersmith Functional Motor Scale Expanded; SMA, spinal muscular atrophy; SMN2, survival motor neuron 2.

complication of type II SMA, affecting up to 90% of them.[4] The recent care recommendations published soon before the advent of disease-modifying drugs provides indications on assessments, monitoring and management modalities (eg, bracing), strongly suggesting to perform spinal surgery once the Cobb's angle reaches 50°.[5] In the past, surgery was performed at puberty once the bone maturation was complete.[6–9] As a very high number of type II SMA patients reached this value before puberty, there was consensus to perform surgery before puberty using age appropriate methods such as growing rods or magnetic bars in order to avoid further progression of the scoliosis with subsequent impact on posture and motor and respiratory function.[8 10 11] As a consequence of this, many patients have in the last decade undergone a first intervention with growing rods followed by the definitive spinal surgery when reaching puberty.[12] The availability of disease-modifying treatments (DMT) for SMA since 2017 has shown improved disease progression in type II SMA as proven by several papers reporting efficacy in motor and respiratory function.[13–18] Less has been reported about scoliosis.[19] The follow-up of clinical trials and the first long-term real-world data, however, seem to suggest that scoliosis is often present in treated type II SMA children.[12 20–22] No systematic study has so far investigated the possible impact of the existing drugs on the progression of scoliosis assessing whether the treatment may at least delay scoliosis progression when compared with untreated patients. The lack of information is probably due to the need to establish progression over a relatively long time and to the paucity of data on scoliosis progression in untreated patients. We recently assessed onset and progression of scoliosis in untreated type II SMA showing that 32% of the patients reached a Cobb angle of 50 before puberty.[23] Our results also provided some reference data on the progression in relation to different variables, such as age, function and baseline Cobb's angle.

The aim of this study is to perform a similar analysis on treated SMA II patients and to conduct a comparative study between treated and untreated SMA II patients to assess possible differences on scoliosis progression and need for surgery.

Table 2 Characteristics of the cohort at first assessment subdivided in untreated and treated

	Untreated (N=46)	Treated (N=39)	P value
Age			0.437
Mean (SD)	6.21 (3.05)	5.63 (2.61)	
Median (min, max)	(1.36, 13.06)	(2.06, 15.93)	
Sex			0.255
Female	18 (39.1%)	21 (53.8%)	
Male	28 (60.9%)	18 (46.2%)	
SMN2 copy number			0.509
2	8 (17.4%)	4 (10.2%)	
3	30 (65.2%)	31 (79.6%)	
4+	3 (6.5%)	2 (5.1%)	
Missing	5 (10.9%)	2 (5.1%)	
SMA function			1.000
Non-sitter	1 (2%)	0 (0%)	
Sitter	45 (98 %)	39 (100%)	
HFMSE score			0.192
Mean (SD)	13.91 (8.30)	16.31 (8.45)	
Median (min, max)	(1.0, 35.0)	(4.0, 44.0)	
Cobb angle			0.088
Mean (SD)	33.94 (28.4)	25.3 (17.0)	
Median (min, max)	(0, 130)	(0, 68.5)	

HFMSE, Hammersmith Functional Motor Scale Expanded; SMA, Spinal Muscular Atrophy; SMN, survival motor neuron 2.

MATERIALS AND METHODS

The patients included in this study are part of a prospective study on SMA trajectories of disease progression.

For this study, patients were included if they had a confirmed genetic and clinical diagnosis of type II SMA and had a minimum of 1.5 years of follow-up, during which the scoliosis angle was measured using the Cobb's angle method. These criteria were applicable regardless of whether the patients received any form of disease-modifying therapy. Patients who had already undergone scoliosis surgery at their initial visit were excluded. Patients in whom the X-rays were not performed at one of the participating centres (Fondazione Policlinico Gemelli IRCCS, Catholic University, Rome; IRCCS Istituto Giannina Gaslini, Genoa; IRCCS Ospedale Bambino Gesù, Rome) were also excluded.

All centres shared a similar radiological protocol, with radiographic examinations obtained in the anteroposterior view in the sitting position, consistent with recent care recommendations, and were reviewed by a single operator at each centre. Clinical information, such as sex, age, Hammersmith Functional Motor Scale Expanded (HFMSE) scores, motor function level (sitter, non-sitter) and SMN2 copy number, was also collected during each assessment. Data collection was discontinued at the time of scoliosis surgery.

Statistical analysis

The study presented continuous variables as either mean and SD or median (with range or IQR), depending on appropriateness, and categorical variables as frequencies (and percentage). The population was described using SMN2 copy number (2, 3, 4+

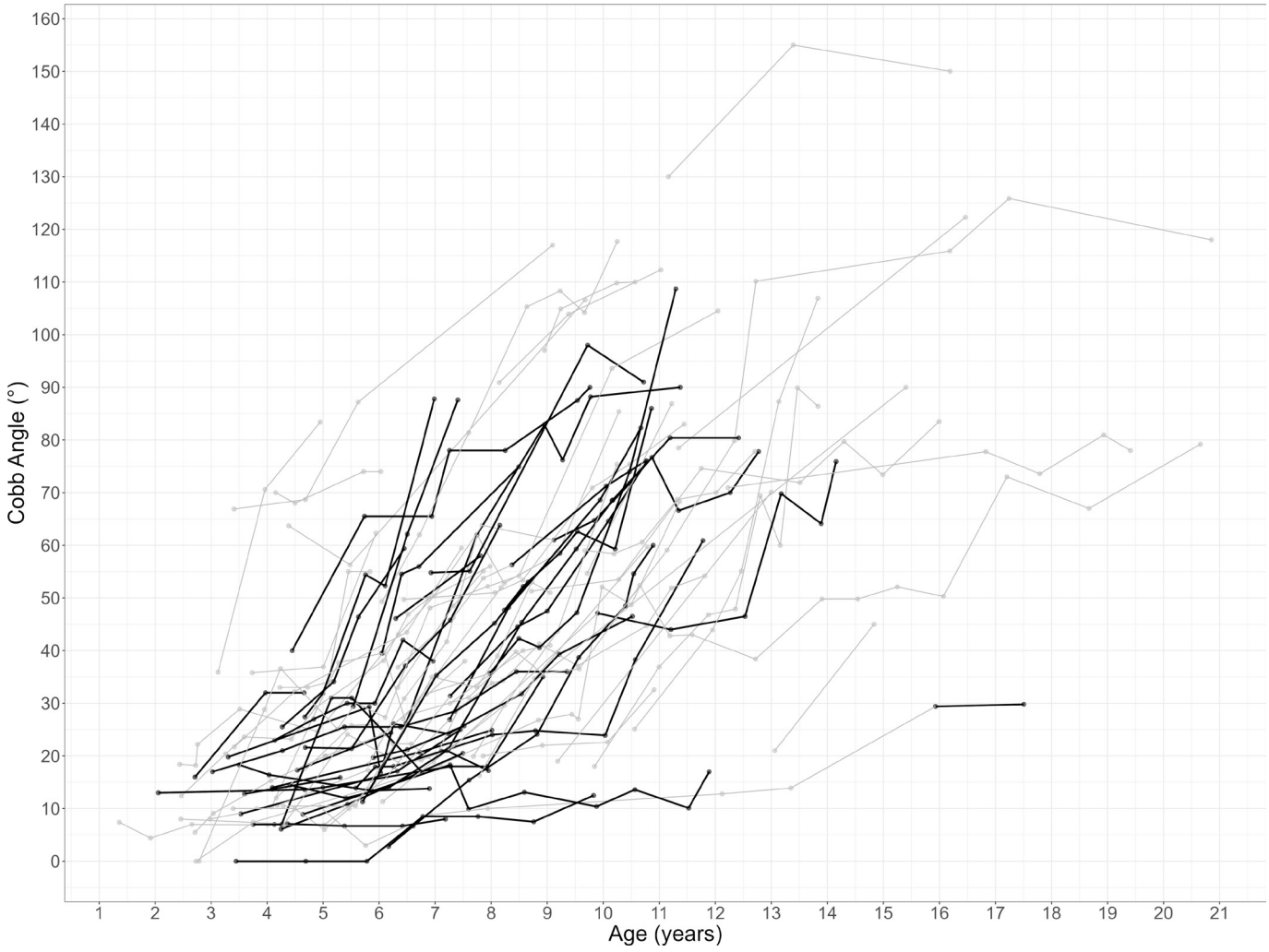

Figure 1 Longitudinal data of the 77 patients selected for the analysis. Key to figure: light grey=untreated patients; black=treated patients.

or unknown), functional status (non sitter, sitter) and HFMSE score at each radiographic examination (<10, 11–22, >22). HFMSE score cut-off points were selected based on the decimal classification, with scores below 10 identifying patients with types 2.0–2.2, scores between 11 and 22 identifying patients with types 2.3–2.4, and scores above 22 identifying children at the best end of the spectrum (2.5 and above).[24] Patients were also stratified according Cobb Angle at baseline, according to the criteria suggested in the recent Standards of Care recommendations: 20° (time to brace initiation) and 50° (time of surgical treatment indication)).[5]

The outcome of interest for the analysis is total Cobb variation over follow-up time, that is, average Cobb variation per year, between patients who have received treatment and those who have not. The cohort was subdivided on the basis of their DMT treatment status at each visit (untreated, treated). In the untreated cohort, patient trajectories were only evaluated up until the point of treatment initiation while for the treated cohort, scoliosis progression was measured only if assessments were performed during the treatment phase. A patient could, therefore, technically be included in both the untreated and treated subgroups if there were enough measurements in each treatment status. This approach guarantees that disease progression is measured distinctly on the basis of treatment status at visit, avoiding possible duplication of data.

To identify the subpopulation for which the effect of the treatment is optimal, a sliding cut-off was applied on the three relevant numerical variables (age, cobb, HFMSE) at first visit by treatment status, and the resulting cohorts were tested for statistical significance via the Mann-Withney U test against the outcome of interest. In case of multiple significative cut-off, the one which led to a higher number of patients was selected. Finally, if a cut-off value was identified in more than one variable, the final subpopulation is selected by joining the different conditions in an inclusive or statement (ie, at least one must be valid). The mean difference outcome value is reported for the two treatment status categories for the final selected subpopulation, along with the statistical significance of the difference expressed as a two-tailed p value. On the selected population (using the sliding cut-off), in addition to the average annual changes of Cobb's angles, a Cox proportional hazards model was also used to assess the effect of treatment (TREATED vs NOT TREATED) on the time to reach a 50° Cobb Angle.

RESULTS

Of the 112 individuals with SMA II who had at least one radiographic examination, 77 had a follow-up >1.5 years, for 428 measurement. At baseline, the mean age and Cobb Angle were 5.67 (SD 2.66) and 29.0 (SD 24.8), respectively. Of the 77 participants, 31 (40.3%) had an HFMSE score below 10, 33

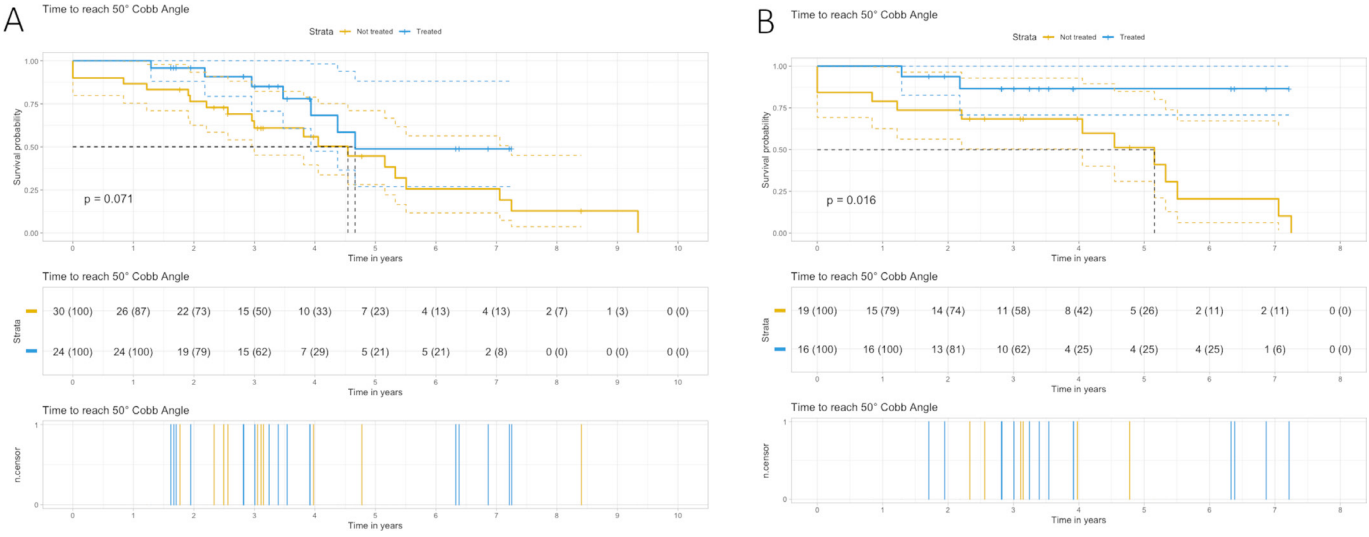

Figure 2 Cox proportional hazards regression analysis. (A) Curves for population selected based on cut-off values (<26° Cobb angle or <4.5 years old); (B) Cohort selected based on <26° Cobb angle only.

(42.29%) had a score between 11 and 22, and 13 (16.9%) had a score above 22. The mean follow-up period was 4.61 (SD 2.87).

Table 1 shows the cohort's characteristics at baseline and at last visit.

Two hundred and one measurements were taken in 38 patients who never received treatment and 150 in 31 patients who were already treated at baseline. The remaining 77 measurements from 8 patients were counted in both groups as they had at least two measurements at 1.5-year interval when untreated and another two after treatment.

Of the 39 patients treated with a DMTs, 9 (23%) were on risdiplam and 30 (77%) on nusinersen. None of the patients switched from one treatment to another.

Table 2 shows the cohorts' characteristics at their first assessments for each treatment subgroup (untreated, treated) and associated p values to test possible differences in the two populations.

Figure 1 shows the longitudinal data from the cohort of treated an untreated patients. The mean value for the total Cobb variation over follow-up was 9.60 (SD 6.03) Cobb degrees/year in the untreated group and 8.40 (SD 7.23) Cobb degrees/year in the treated group (p=0.4).

Analysing the whole cohort subdivided by treatment status and applying a sliding cut-off on Age, Cobb and HFMSE at the first visit, the optimal choice of significant cut-off value is <26° for Cobb value and <4.5 years old for the age. A discernible cut-off value for the HFMSE score that could effectively demarcate significant differences in scoliosis progression between the two cohorts was not identified (online supplemental figure 1).

Online supplemental table 1 shows the characteristics of the population who, at the time of the first visit by treatment status, had a Cobb value <26 or an age <4.5 (untreated n=30, treated n=24, both n=0).

Cobb angle progression per year

On the population selected on the basis of the cut-off values (<26° Cobb angle or <4.5 years old), the mean value for the total Cobb variation over follow-up was 10.05 (SD 6.38) Cobb degrees/year in the untreated group and 5.61 (SD 4.72) Cobb degrees/year in the treated group (p=0.01).

When resampling the cohort based on being <4.5 years old only, the mean value for the total Cobb variation over follow-up was 8.47 (SD 5.37) Cobb degrees/year in the untreated group and 4.16 (SD 4.05) Cobb degrees/year in the treated group (p=0.007) (for baseline characteristics, see online supplemental table 2).

When resampling the cohort on the basis of having <26° Cobb angle only, the mean value for the total Cobb variation over follow-up was 9.61 (SD 6.03) Cobb degrees/year in the untreated group and 5.44 (SD 4.75) Cobb degrees/year in the treated group (p=0.014) (for baseline characteristics, see online supplemental table 3).

Time to reach 50° Cobb angle

On the population selected on the basis of the cut-off values (<26° Cobb angle or <4.5 years old), the univariate Cox proportional hazards regression analysis showed that an HR of 0.46 suggesting that patients who received treatment were 54% less likely to reach a 50° Cobb angle compared with patients who did not receive treatment, but this effect was not statistically significant (figure 2A) (HR 0.46, 95% CI 0.1913 to 1.09, p=0.071). The median age at last follow-up available of those who did not reach 50° Cobb angle was 7.09 (95% CI 5.05 to 14.83) in the untreated (N=10/30; 33%) and 7.49 (95% CI 4.66 to 11.89) in the treated (N=17/24; 71%) cohorts.

When resampling the cohort based on being <4.5 years old only, the univariate Cox proportional hazards regression analysis showed that the effect of treatment on the time to reach a 50° Cobb angle was significant (HR 0.19, 95% CI 0.04235 to 0.8565, p=0.016) (figure 2B). The median age at last follow-up available of those who did not reach 50° Cobb angle was 6.29 (95% CI 5.05 to 7.33) in the untreated (N=6/19; 32%) and 7.47 (95% CI 4.66 to 10.52) in the treated (N=14/16; 87%) cohorts.

When resampling the cohort on the basis of having <26° Cobb angle only, the univariate Cox proportional hazards regression analysis showed that the effect of treatment on the time to reach a 50° Cobb angle was non-significant (HR 0.59, 95% CI 0.221 to 1.547, p=0.27). The median age at last follow-up available of those who did not reach 50° Cobb angle was 7.09 (95% CI 5.05 to 14.83) in the untreated (N=10/24; 42%) and 7.49 (95% CI 4.66 to 11.89) in the treated (N=17/23; 74%) cohorts.

DISCUSSION

We report for the first time a systematic longitudinal assessment of scoliosis in treated type II individuals. The paucity of data on scoliosis compared with other aspects, such as respiratory or motor function, is probably due to the lack of standardised protocols for assessing scoliosis in SMA sitters patients. While there is a long-standing experience of shared protocols for motor and respiratory assessments, generally similar to those used in clinical trials,[25] scoliosis data cannot always be easily shared. Radiographic examinations are not always performed in the tertiary care centres and there is no consensus on a structured protocol to be used in sitters, with some centres performing radiographic examinations in supine and others using different types of sitting and posturing adjustments.[5] This is a major limitation for sharing data in a multicentric setting. One of the advantages of our study is that the radiographic examinations were performed using a similar protocol suggesting the best posture for sitting at the time of the exam.[23] In each centre, the examinations were always reviewed by the same radiologist therefore reducing the bias of interobserver reliability on consecutive assessments.

The results of our study showed that scoliosis is present in treated patients with progression over time. This raises the question whether the progression of scoliosis in treated patients is similar to that observed in untreated patients and, if not, whether possible differences could be related to a number of variables such as age, function or scoliosis severity. As at the time the study was performed over 90% of the type II patients in our centres were treated, it was not too possible to have concomitant untreated patients for comparison. The comparison was, however, possible as we recently assessed progression of scoliosis in all the untreated type II patients examined in the years before they started treatment. While not having a concomitant control group is not ideal, we tried to reduce all the possible biases by having the same radiologist reviewing the radiographic examinations that were performed our routine protocols also used in the treated patients. Despite treated and untreated patients were examined in different time intervals (after 2017 for treated and between 2013 and 2019 for the untreated ones), the overall orthopaedic management of the patients had not significantly changed, with indications to wear a brace when reaching a Cobb's angle of 20° and to perform surgery when reaching 50. While we cannot exclude that the heightened patient motivation to participate in post-treatment physiotherapy and occupational therapy may have potentially exerted subtle impacts on disease progression, this was more often observed in adult patients and the impact is probably more limited in the paediatric cohort included in this study. It is also crucial to emphasise that in the case of untreated patients, despite the implementation of such rigorous interventions, their effectiveness in isolation has been shown to fall short of halting the progression of scoliosis entirely.[4 5 26–28]

The comparative analysis between treated and untreated SMA II patients showed that there were no obvious differences between the two overall cohorts. The subdivision into different subgroups, however, provided a more comprehensive overview of differences in progression. Through the application of a sliding cut-off analysis, we found that Cobb angles and age consistently demonstrate the ability to effectively differentiate disease progression between treated and untreated patients while HFMSE scores do not. More specifically, a Cobb angle <26° or an age <4.5 years old were identified as distinct and meaningful optimal cut-off value for this purpose. These values independently emerge as significant predictors for scoliosis progression in SMA type II patients when comparing the outcomes between treated and untreated groups. The mean Cobb variation was 10.05 (SD 6.38) Cobb degrees/year in the untreated group and 5.61 (SD 4.72) Cobb degrees/year in the treated group (p=0.001), indicating that pharmacological treatment may slow the progression of scoliosis in the resampled SMA type II cohort. We also investigated the proportion of patients reaching a 50° Cobb angle, as this is the value that requires attention for surgery. When we analysed the cohort using age only as cut-off value (below 4.5 years) the univariate Cox proportional hazards regression analysis indicated a significant difference with patients who received treatment being less likely (81%) to reach a 50° Cobb angle. When using both cut-off values (age below 4.5 years or Cobb's angle below 26°) the difference did not reach significance (p=0.07) but with a trend towards a protective effect of treatment on scoliosis progression with patients who received treatment being less likely (54%) to reach a 50° Cobb angle.

These results indicate that while in the overall cohort treatment may not produce a marked response on scoliosis, when initiated in younger infants, especially in those with no sign or minimal scoliosis the progression of scoliosis may be slower. Many of these patients had a rate of progression and reached an angle of 50° at an age and with that was compatible with the possibility to perform the definitive spinal fusion instead of at an earlier age that would have required to perform earlier surgery with growing rods, as often observed in untreated patients.

The findings of this study contribute to a better understanding of scoliosis management in SMA II patients, which is critical for clinicians, patients and caregivers, highlighting the importance of early initiation of treatment to slow the progression of scoliosis. While for other aspects, such as motor function, efficacy can be demonstrated in different age groups,[13 16 17] this appeared to be more limited for scoliosis progression. Additional research in larger cohorts will allow more accurate insights into the impact of individual pharmacological treatment on scoliosis progression in patients with SMA type II (eg, nusinersen and risdiplam), using a level of analysis not feasible in our current study due to the predominance of nusinersen treatment, which constituted nearly 80% of our patient population. Larger studies will also allow to better assess the importance of personalised treatment plans that take into consideration the unique characteristics of each patient, including their Cobb angle and age.

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Acknowledgements Dr Giorgia Coratti is supported by the Italian health ministry grant GR-2021-12374579. Eugenio Mercuri and Maria Carmela Pera received support by the Italian health ministry grants RF-2019-12370334 and GR-2018-12365706.

Contributors GC, JL, MCP, AD'A, CB, CG, NB, MP, LA, MR, AC, GC, CC, RdS, SC, NF and MC were involved in the conception and design of the study, acquisition and analysis of data, and drafting a significant portion of the manuscript or figures. GC, JL, CG, NB, MBD, LL, FM and AL contributed to the acquisition and analysis of data and provided critical input during manuscript preparation. GC, JL and EM provided critical input during the conception and design of the study, data analysis, and manuscript preparation.EM supervised the entire study, including the conception and design, data analysis, and manuscript preparation, and made substantial contributions to all aspects of the research. EM takes full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. All authors reviewed and approved the final manuscript.

Funding The work was partially funded from Biogen and Roche that are supporting the Italian registry and/or studies related to the use of its data.

Disclaimer Funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Competing interests GC, MCP, AD'A, MP, RdS, MC, EB, MP and EM have been a consultant for BIOGEN S.R.L. which owns patent rights to nusinersen of which data from patients in treatment were used in this study. GC, MCP, AD'A, MP, RdS, MC, EB, MP and EM have been a consultant for ROCHE which owns patent rights to risdiplam of which data from patients in treatment were used in this study.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was the study was approved by the Ethical Committees of all participating centres (Fondazione Policlinico Gemelli IRCCS, Catholic University, Rome; IRCCS Istituto Giannina Gaslini, Genoa; Ospedale Bambino Gesù, Rome). The coordinating centre (FPG) IRB approval number is #0030504/18. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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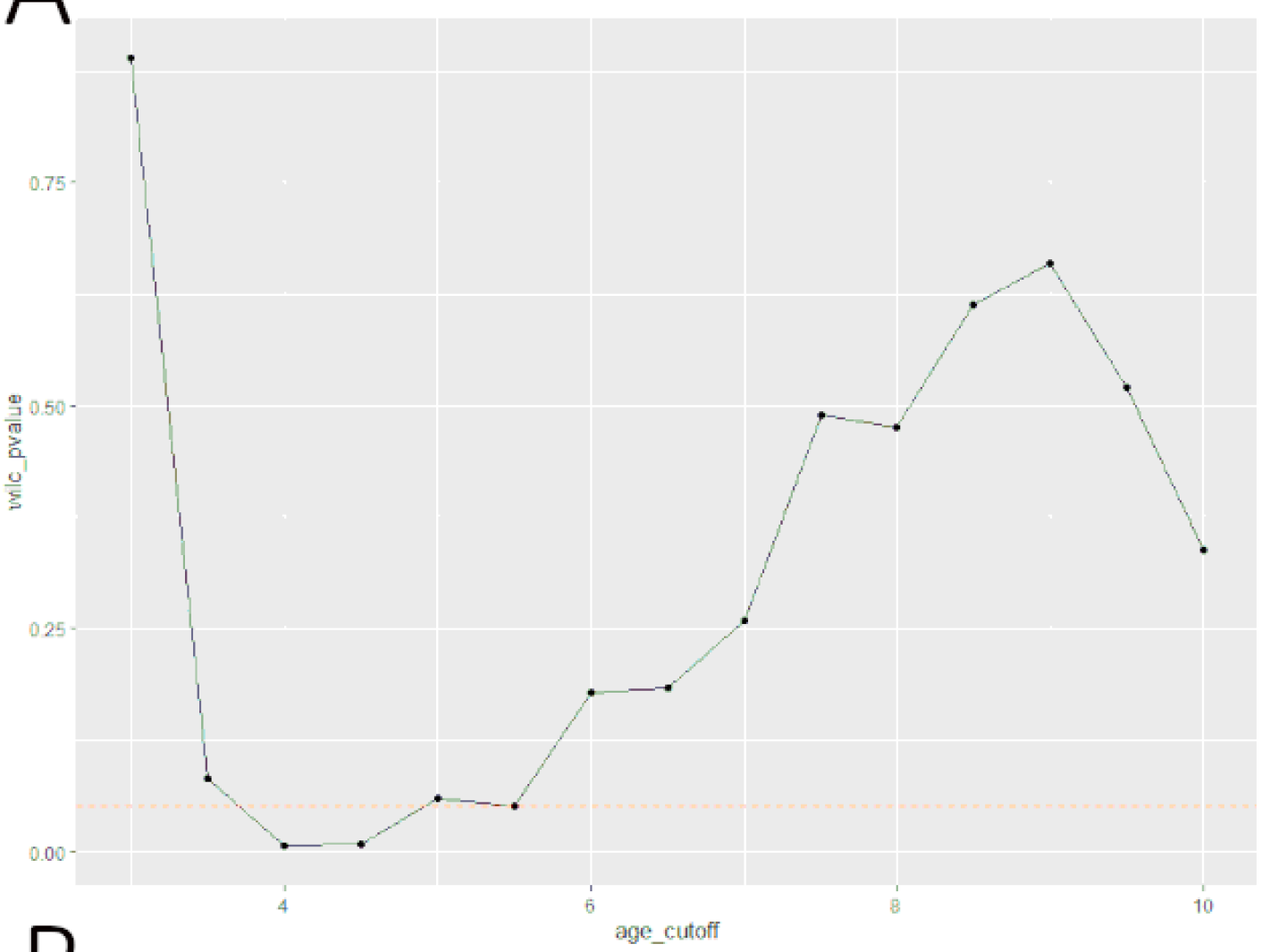
Sfondo

A



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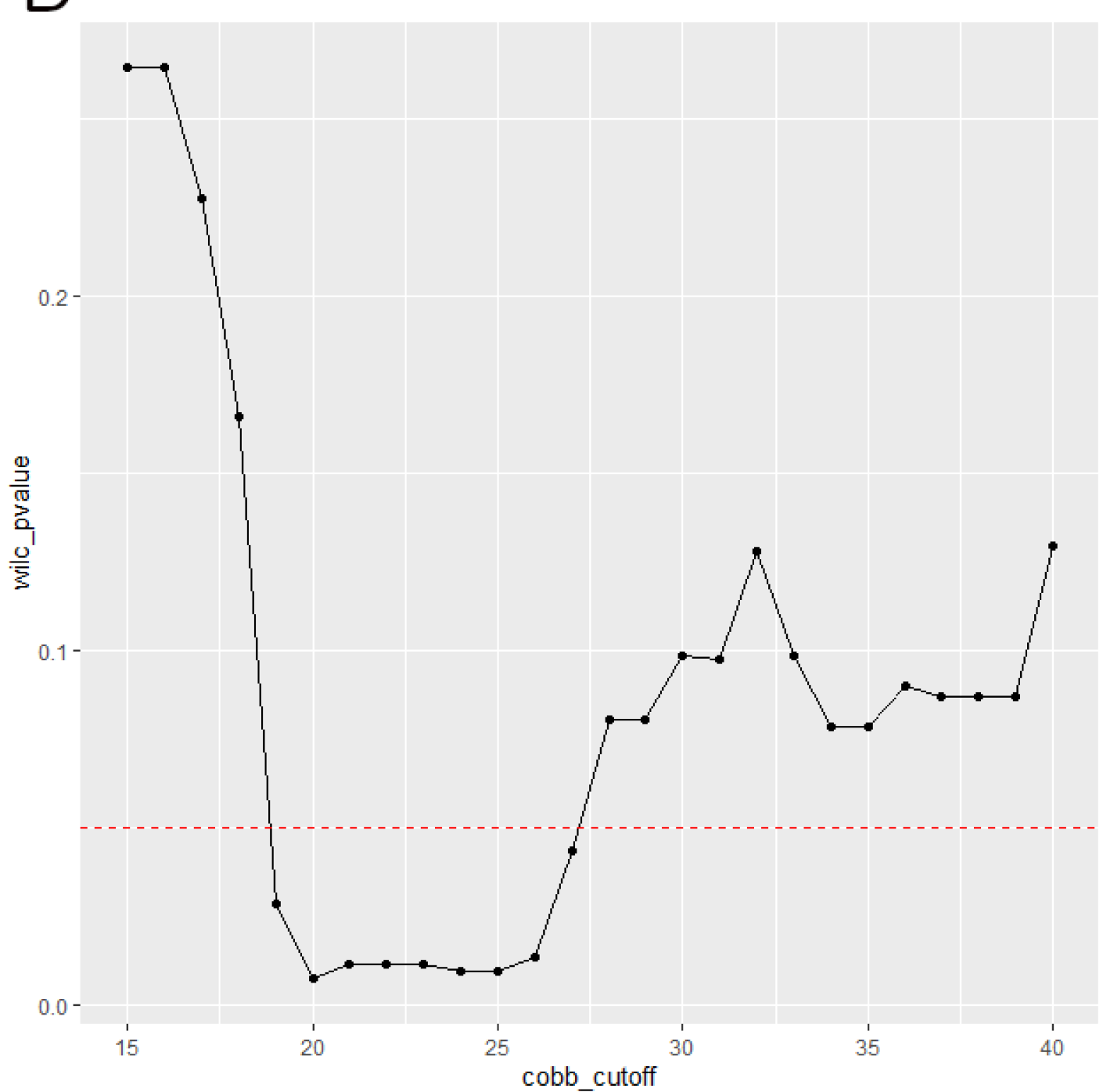

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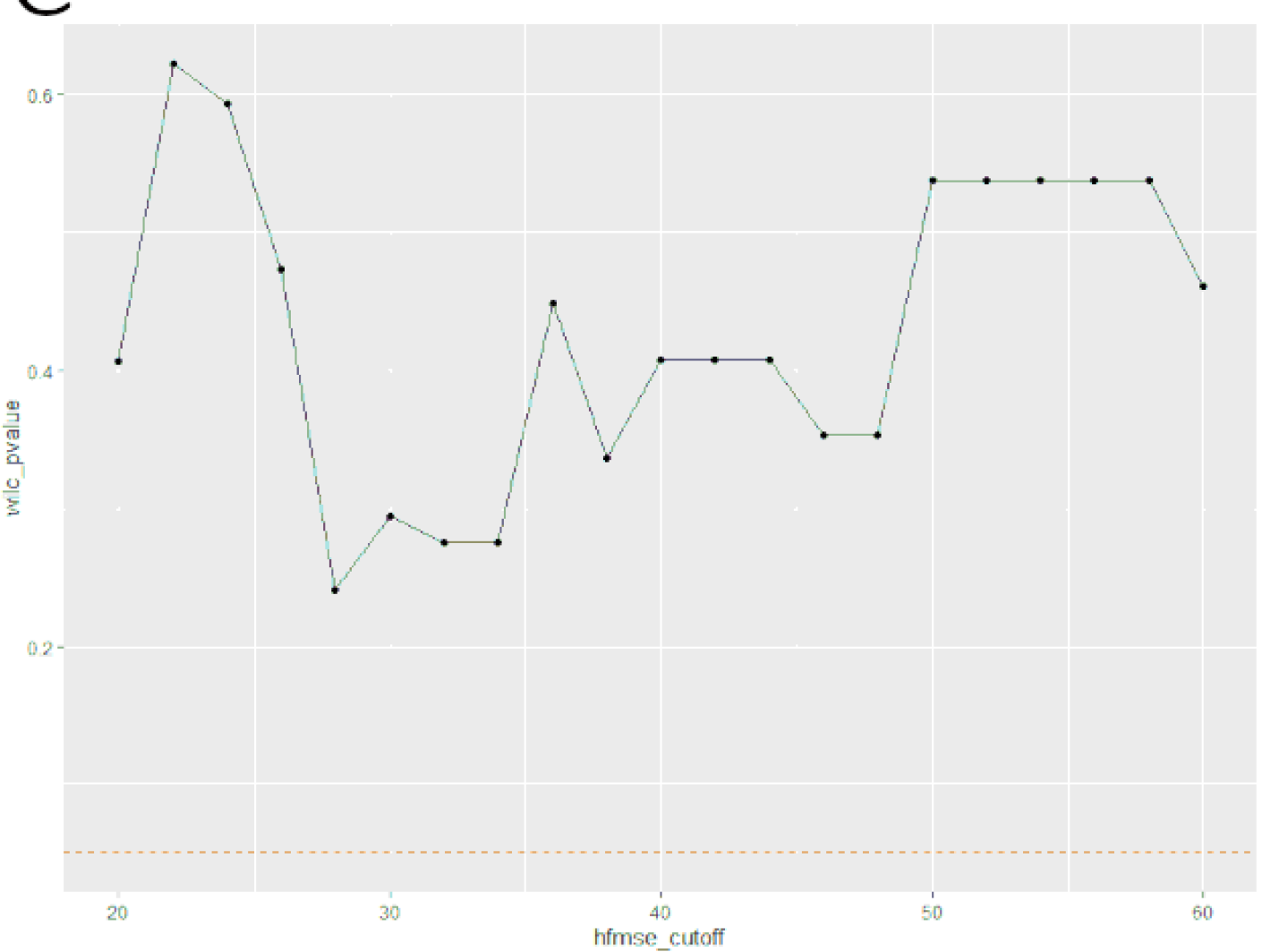

Supplementary Material

Supplementary figure 1. Graphical representation of the sliding cut-off analysis. Panel A: Age; Panel B: Cobb Angle, Panel C: HFMSE cutoff

	Untreated (N=30)	Treated (N=24)	p-value
Age			
Mean (SD)	5.01 (2.82)	4.30 (1.16)	0.217
Median [Min, Max]	4.17 [1.36, 13.06]	4.26 [2.06, 7.12]	
Sex			
Female	14 (46.7 %)	14 (58.3 %)	0.563
Male	16 (53.3%)	10 (41.7 %)	
SMN2 Copy number			
2	5 (16.7 %)	4 (16.7 %)	0.938
3	22 (73.3 %)	17 (70.8 %)	
4+	2 (6.7 %)	1 (4.2 %)	
Missing	1 (3.3 %)	2 (8.3 %)	
SMA function			
Non sitter	1 (3.3 %)	0 (0%)	1.000
Sitter	29 (96.7 %)	24 (100 %)	
HFMSE score			
Mean (SD)	15.90 (9.14)	18.12 (9.14)	0.379
Median [Min, Max]	14.0 [1, 35]	16.0 [6, 44]	
Cobb Angle			
Mean (SD)	20.97 (17.94)	14.97 (8.40)	0.112
Median [Min, Max]	18.2 [0, 70.0]	14.2 [0, 40.0]	

Supplementary Table 1. Characteristics of the cohort selected based on the cut-off values (<26° Cobb Angle or <4.5 years old) and subdivided by treatment status

	Untreated (N=19)	Treated (N=16)	p-value
Age			
Mean (SD)	3.28 (0.83)	3.68 (0.68)	0.127
Median [Min, Max]	3.39 [1.36 - 4.39]	3.67 [2.06 - 4.45]	
Sex			
Female	10 (52.6%)	11 (68.7%)	0.533
Male	9 (47.4%)	5 (31.3%)	
SMN2 Copy number			
2	1 (5.3%)	3 (18.8%)	0.274
3	17 (89.4%)	11 (68.8%)	
4+	1 (5.3%)	0	
Missing	0	2 (12.4%)	
SMA function			
Non sitter	0	0	0.612
Sitter	19	16	
HFMSE score			
Mean (SD)	16.16 (9.50)	16.75 (7.51)	0.839
Median [Min, Max]	11.00 [5.00 - 35.00]	16.00 [6.00 - 36.00]	
Cobb Angle			
Mean (SD)	22.62 (22.38)	15.18 (9.36)	0.199
Median [Min, Max]	12.00 [0.00 - 70.00]	14.10 [0.00 - 40.00]	

Supplementary Table 2. Characteristics of the cohort subdivided by treatment status and selected based on the cut-off values (<4.5 years old).

	Untreated (N=24)	Treated (N=23)	p-value
Age			
Mean (SD)	5.30 (3.08)	4.29 (1.19)	0.146
Median [Min, Max]	4.23 [1.36 - 13.06]	4.25 [2.06 - 7.12]	
Sex			
Female	9 (37.5%)	14 (60.9%)	0.190
Male	15 (62.5%)	9 (39.1%)	
SMN2 Copy number			
2	5 (20.8%)	3 (13.0%)	0.679
3	16 (66.6%)	17 (73.9%)	
4+	2 (8.3%)	1 (4.4%)	
Missing	1 (4.3%)	2 (8.7%)	
SMA function			
Non sitter	1 (4.2%)	0 (0%)	1.000
Sitter	23 (95.8%)	23 (100%)	
HFMSE score			
Mean (SD)	16.50 (9.82)	18.39 (9.25)	0.500
Median [Min, Max]	14.50 [1.00 - 35.00]	16.00 [6.00 - 44.00]	
Cobb Angle			
Mean (SD)	13.49 (6.80)	13.88 (6.63)	0.843
Median [Min, Max]	12.20 [0.00 - 25.10]	13.90 [0.00 - 25.50]	

Supplementary Table 3. Characteristics of the cohort subdivided by treatment status and selected based on the cut-off values (<26° Cobb Angle).