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RESEARCH

Italian validation of the SMA independence scale–upper limb module

Chiara Bravetti[1] · Giorgia Coratti[1,2] · Maria Carmela Pera[1,2,3] · Giulio Gadaleta[4] · Tiziana Mongini[4] · Michela Coccia[5] · Amanda Ferrero[5] · Emanuele Maria Costantini[5] · Antonella Longo[6] · Francesca Cumbo[6] · Michela Catteruccia[6] · Adele D'Amico[6] · Simone Morando[7] · Noemi Brolatti[7] · Claudio Bruno[7] · Lorenzo Verriello[8] · Maria Elena Pessa[8] · Laura Antonaci[1,2] · Claudia Faini[10] · Rocco Liguori[9,10,11] · Veria Vacchiano[9,11] · Lucia Ruggiero[12] · Dario Zoppi[12] · Anna Russo[12] · Francesca Torri[13] · Giulia Ricci[13] · Roberto Chiappini[13] · Gabriele Siciliano[13] · Antonio Trabacca[14] · Caterina Agosto[15] · Francesca Benedetti[15] · Marika Pane[1,2] · Eugenio Mercuri[1,2] · ITASMAC working group

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Abstract

Spinal muscular atrophy (SMA) is a progressive disorder caused by SMN1 mutations. While therapies have changed its course, current motor scales often miss aspects. This study aimed to validate the Italian SMA Independence Scale (SMAIS-ULM) for reliability, applicability, and expansion across diverse SMA phenotypes. Patients with genetically confirmed 5qSMA were recruited from 12 Italian centers. Analyses included Intraclass Correlation Coefficients (ICCs) for test–retest reliability, the Kruskal–Wallis for group comparisons, and the Spearman correlations with functional measures. Ceiling/floor effects were defined as ≥ 85% of a group reaching the maximum or minimum score. The study analyzed 472 completed questionnaires: 263 from caregivers (mean age 26.4 ± 17.6; 29 SMA I, 123 SMA II, 104 SMA III, 7 presymptomatic) and 209 from patients (mean age 33.1 ± 16.4; 3 SMA I, 101 SMA II, 104 SMA III; 1 SMA IV), including 195 matched caregiver-patient pairs. ICC was conducted in 29 caregivers and 31 patients; values ranged from 0.97 to 1.00. SMAIS-ULM scores differed by SMA type, with SMA III/presymptomatic subjects scoring higher than SMA I/II ($p < 0.001$) and walkers scoring higher than sitters/non-sitters ($p < 0.001$). Floor effects were found in 18.9% of non-sitters and 50% of walkers, with comparable patterns in patient responses. Strong correlations with functional measures were found, with no significant differences between caregiver and patient reports. *Conclusion*: The findings confirm the reliability and validity of the SMAIS-ULM as an effective tool for measuring functional independence in individuals with SMA, both from the caregiver and patient perspectives.

What is Known:

- *Disease-modifying therapies have modified natural history of all SMA types.*
- *Patient-reported tools are increasingly used to assess daily task assistance, independence and participation.*

What is New:

- *SMAIS-ULM proved applicable across a wide functional spectrum in SMA, with strong score variation by type and function in Type II/III SMA.*
- *Ambulant individuals often had ceiling effect but ~50% of them showed limited independence, supporting the scale's value in a discriminating among patients who have maintained ambulation.*

Keywords Spinal muscular atrophy · SMA Independence Scale · Activities of daily life · Patient reported outcome measures

Abbreviations

SMA	Spinal muscular atrophy
SMAIS- ULM	SMA Independence Scale
ICCs	Intraclass Correlation Coefficients
SMN	Survival motor neuron
DMTs	Disease-modifying therapies
ICF	International Classification of Functioning

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Chiara Bravetti, Giorgia Coratti, and Maria Carmela Pera are co-first authors.

Extended author information available on the last page of the article

HFMSE	Hammersmith Functional Motor Scale – Expanded
RULM	Revised Upper Limb Module
ITASMAC	Italian Spinal Muscular Atrophy Consortium
SD	Standard deviation
IQR	Interquartile range
6MWT	6-Minutes walk test
FDA	Food and Drug Administration

Introduction

Spinal muscular atrophy (SMA) is a progressive 5q-related neuromuscular disorder caused by mutations in the SMN1 gene, leading to reduced levels of survival motor neuron (SMN) protein [1]. The disease is characterized by motor impairment, muscle weakness, and functional decline [1]. SMA presents across a phenotypic spectrum, ranging from Type I, the most severe and early-onset form, to milder, later-onset forms such as Type II and Type III [2].

Disease-modifying therapies (DMTs) have significantly changed the course of SMA, with a wider range of motor abilities within each SMA type, including new phenotypes and achievements of milestones, such as sitting in type I infants, that were never achieved before DMTs became available [3, 4]. This has made it harder to rely on traditional classifications to assess function. For this reason, individuals with SMA are now classified using a functional classification (non-sitters, sitters, standers, and walkers) that provides a more accurate representation of functional status and disease burden [5]. It has also become obvious that the existing motor function scales available for SMA do not always cover some of the aspects of the new phenotypes or older/weaker individuals and increasing attention is being devoted to new patient/carers reported tools aimed at assessing other functional aspects, including functional independence in daily activities with a few attempts to develop disease-specific measures that may better reflect functional abilities and real-life independence [6–13].

The SMA Independence Scale (SMAIS-ULM) was created to evaluate independence and the level of support needed for individuals with Type II and non-ambulant Type III SMA to complete everyday tasks [14]. This module is designed to be a relevant, reliable, and valid tool for evaluating the upper limbs' role in maintaining independence in daily activities. The concept of assistance is central to the scale, as it is strongly linked to a person's independence in daily life. The SMAIS–ULM was developed following a literature review and the analysis of qualitative data gathered from interviews aimed at ensuring that the chosen activities were meaningful and reflective of real-life functional challenges. The scale offers a broad view of self-care and domestic life also aligning with the World Health Organization's International Classification of Functioning (ICF), which encompasses both activities (task execution) and participation (engagement in life situations) [14]. While the scale was originally developed for Type II and non-ambulant Type III SMA, it was felt that its use could be extended to cover the evolving clinical landscape of SMA, shaped by earlier diagnosis and access to disease-modifying therapies which has resulted in greater functional variability across patients [15]. Such an extension could potentially capture the perspectives of individuals across the full spectrum of motor function and be more responsive to the changing needs of the SMA community.

This study aimed to assess reliability, validity, and applicability of the Italian version of the SMAIS-ULM, across a wide range of SMA phenotypes and functional levels, also including non-sitters and ambulatory patients.

By comparing SMAIS-ULM scores with established motor function assessments such as the Hammersmith Functional Motor Scale – Expanded (HFMSE) and the Revised Upper Limb Module (RULM), and analyzing caregiver- and patient-reported responses, we sought to determine the scale's effectiveness in capturing independence across the different SMA phenotypes.

Methods

Patients with a genetically confirmed diagnosis of SMA were recruited from 12 neuromuscular centers across Italy, all part of the Italian network part of the International Spinal Muscular Atrophy Consortium (ITASMAC) [16, 17]. These included centers in Genoa, Rome, Milan, Messina, Ancona, Pisa, Udine, Padua, Naples, Torino, Brindisi, and Bologna. All participants, or their legal guardians when applicable, provided written informed consent before enrollment. The study received ethical approval from the Ethics Committee at the coordination center, Gemelli Hospital in Rome.

All patients and their caregivers who attended our facilities between 05/02/2023 and 02/12/2024 were invited to complete the questionnaire. The SMAIS-ULM questionnaire was provided in paper format and filled out during the visit. In our clinical practice, the patient is typically accompanied by only one caregiver. If two caregivers were present, the one primarily responsible for the patient's daily care was asked to complete the questionnaire.

Comprehensive demographic and clinical data were collected for all participants at the time of questionnaire completion. These data included age, SMN2 copy number, age at symptom onset, sex assigned at birth, SMA type, and

pharmacological treatment (nusinersen, risdiplam, onasemnogene abeparvovec).

Unlike the original validation, focusing on type II and non-ambulant type III, we included a wider functional range, categorizing our cohort into non-sitters, sitters, standers, or walkers.

Non-sitters were defined as individuals with severe weakness who are unable to maintain a seated posture independently for 3 s. Sitters as individuals maintain an upright seated position unassisted for 3 s but lack the ability to stand or walk. Standers can bear weight for 3 s unassisted, while walkers retain the ability to ambulate independently for at least 10 m.

SMA independence scale–upper limb module (SMAIS–ULM)

The SMAIS-ULM is a validated tool designed to assess functional independence in individuals with SMA [14]. It takes a maximum of 10 min to complete, making it a quick and efficient measure. The SMAIS-ULM serves as a patient-reported outcome measure for individuals aged 12 years and older, allowing them to directly report on their functional abilities, and as a caregiver-reported outcome measure for caregivers of individuals as young as 2 years. The scale was originally developed and validated to address the need for an SMA-specific assessment that captures real-world functional capabilities in type 2 and non-ambulant type 3, therefore mainly focusing on upper limbs. SMAIS-ULM evaluates the ability to perform daily activities and participate in life roles, making it particularly relevant for both clinical settings and research studies aiming to measure meaningful changes in functional independence. Its reliability and validity have been demonstrated in previous studies. Italian translation was already available at the time we started the study. The Italian version of the SMAIS-ULM was obtained from https://eprovide.mapi-trust.org/, using the translation already implemented in various clinical trials [18–24].

Each of the 22 items in the SMAIS-ULM is scored on a 3-point ordinal scale, with higher scores indicating greater independence:

- 2: Individual can perform the activity independently without assistance.
- 1: Individual requires partial assistance to complete the activity.
- 0: Individual is unable to perform the activity without help.

Items deemed non-applicable are assigned a score of zero.

For clarity, the following guidance is provided to participants when completing the questionnaire:

- Does not need help: The individual can perform all aspects of the activity independently.
- Needs some help: The individual can complete part of the activity independently but requires assistance with other parts.
- Cannot do this at all without help: The individual depends entirely on others to complete the activity.
- Not applicable: The activity is not relevant to the individual (e.g., no access to a bath) or the individual is too young to perform the activity independently.

The SMAIS-ULM combines the 22 individual item scores into a total upper-limb summary score, which ranges from 0 to 44.

In this study, as per questionnaire development, the caregiver-reported version was used not only for patients below the age of 12 years but also, for comparison, in those older than 12 years in whom the patient-reported version was also available. Per protocol, the questionnaire was not proposed to individuals with cognitive delays or illiteracy.

HFMSE

The HFMSE is a validated motor function assessment designed to evaluate gross motor abilities in individuals with SMA [25]. It consists of 33 items, covering activities such as rolling, sitting, standing, and walking, with a total score ranging from 0 to 66. Higher scores indicate better motor function, while lower scores reflect greater impairment.

RULM

The RULM is a motor function assessment specifically designed to evaluate upper limb abilities in individuals with SMA [26]. It consists of 20 items, assessing movements ranging from proximal to distal control, with a total score ranging from 0 to 37. Higher scores indicate better upper limb function, while lower scores reflect more severe impairment.

Statistical analysis

Statistical analyses were conducted to evaluate the distribution of total SMAIS-ULM scores across various groups. Descriptive statistics, including mean, median, standard deviation (SD), and range, were computed for each group. Normality of continuous variables was assessed using the Shapiro–Wilk test.

Test–retest reliability of the total SMAIS-ULM score between two visits was assessed using Intraclass Correlation Coefficients (ICCs) and calculated through a two-way random effects model with both single and average ratings.

Internal consistency of the scale was evaluated using both Cronbach's alpha and McDonald's omega coefficients.

Group differences between SMA subtypes and functional status categories (non-sitters, sitters, standers, walkers) were compared using the Kruskal–Wallis test, followed by Dunn's test for pairwise comparisons, with p-values adjusted for multiple comparisons using the Holm method.

Ceiling and floor effects were evaluated, with thresholds defined as reaching the highest or lowest possible score in at least 85% of participants within a specific group [27].

The relationship between total SMAIS-ULM scores and functional motor outcomes was analyzed using Spearman correlation.

The Wilcoxon signed-rank test was employed to examine whether systematic differences were present between caregiver and patient reports within each functional subgroup. To further evaluate the degree of agreement between patient- and caregiver-reported SMAIS-ULM total scores, the Concordance Correlation Coefficient (CCC) was calculated.

No missing data were present in the dataset. All statistical analyses were performed using R and RStudio, with the significance level set at $p < 0.05$.

Results

A total of 472 individuals were invited to complete the questionnaire, and all participated (100% response rate), including 263 caregiver-reported and 209 patient-reported questionnaires. All individuals were treated with one of the two available DMTs (either nusinersen or risdiplam). All patients/caregivers filling the questionnaires were Italians or were able to read and speak Italian fluently.

For the caregiver group, the distribution of SMA types was as follows: 29 patients (11.0%) had SMA type I, 123 patients (46.8%) had SMA type II, and 104 patients (39.5%) had SMA type III. Additionally, 7 patients (2.7%) were presymptomatic. There were no patients with SMA type IV. For the patient group, the distribution was: 3 (1.4%) SMA type I, 101 (48.3%) SMA type II, 104 (49.8%) SMA type III, and 1 (0.5%) SMA type IV.

Table 1 shows the characteristics of all individuals participating in the study.

Reliability

Test–retest reliability was assessed in 31 patients and 29 caregivers. The median time interval between test and retest was 123 days (IQR: 29.5) for patients and 119 days (IQR: 110) for caregivers. For the patient-reported questionnaire, the ICC (2,1) for single ratings was 0.99 (95% CI [0.99, 1.00]), and the ICC (2,k) for average ratings was 1.00 (95% CI [0.99, 1.00]). For the caregiver-reported questionnaire, the ICC (2,1) for single ratings was 0.97 (95% CI [0.94, 0.99]), and the ICC (2,k) for average ratings was 0.99 (95% CI [0.97, 0.99]). All ICCs were statistically significant ($p < 0.001$).

Internal consistency was examined for both the patient-reported and caregiver versions of the questionnaire. Cronbach's alpha was $\alpha = 0.95$, 95% CI [0.92, 0.97] for the patient-reported version and $\alpha = 0.96$, 95% CI [0.93, 0.98] for the caregiver version, indicating a high level of internal consistency. The standardized alpha values were identical (0.95). McDonald's omega (ω) was 1.00 for the patient-reported and 0.99 for the caregiver version.

Caregivers reported SMAIS-ULM

A total of 263 caregivers of patients having an age at assessment between 2.02 and 75.6 years completed the SMAIS-ULM.

Of the 263 caregivers' questionnaire, 60.0 (23%) were completed from caregivers of individual aged 2–12 years, of which 11 non-sitters (7 SMA I, 4 SMA II), 33 sitters (14 SMA I, 19 SMA II), 6 standers (2 SMA I, 2 SMA II, 2 SMA III) and 10 walkers (1 SMA I, 2 SMA III, 7 Presymptomatic patients). The remaining were completed from caregivers of individuals aged > 12 years, of which 63 non-sitters (5 SMA I, 50 SMA II, 8 SMA III), 97 sitters (48 SMA II, 49 SMA III), 13 standers (13 SMA III), and 30 walkers (30 SMA III).

Total score

The SMAIS-ULM scores ranged between 0 and 44 (mean 23.1).

A Kruskal–Wallis test was conducted to evaluate differences in the total SMAIS-ULM score between SMA types and, within each SMA type, based on their functional status (Fig. 1). The analysis revealed significant differences both between SMA types and within SMA types by functional status ($p < 0.001$ for all tests), indicating that the score distributions varied across the groups. Figure 1 shows results of the analysis and post-hoc comparison.

A Spearman's rank-order correlation was conducted to assess the relationship between age and total SMAIS-ULM scores. There was no statistically significant correlation between the two variables, $\rho(263) = 0.01$, $p = 0.880$.

A Mann–Whitney U test was conducted to examine differences in total SMAIS scores based on sex assigned at birth. The difference was not statistically significant, $U = 9003.50$, $p = 0.55$, indicating no evidence of a difference in SMAIS-ULM

Table 1 Characteristics of all individuals participating in the study subdivided by responder and functional status of the participant

		Non-sitters		Sitters		Standers		Walkers		Overall	
		Caregiver (*N* = 74)	Patient (*N* = 61)	Caregiver (*N* = 130)	Patient (*N* = 102)	Caregiver (*N* = 19)	Patient (*N* = 14)	Caregiver (*N* = 40)	Patient (*N* = 32)	Caregiver (*N* = 263)	Patient (*N* = 209)
Age	Mean (SD)	29.2 (17.6)	33.0 (15.8)	25.3 (17.4)	32.6 (16.6)	28.1 (21.5)	40.3 (20.6)	23.8 (16.3)	31.9 (15.0)	26.4 (17.6)	33.1 (16.4)
	Median [Min, Max]	24.8 [2.10, 75.6]	28.4 [12.6, 75.6]	19.3 [4.09, 72.9]	26.6 [12.1, 72.9]	22.8 [2.56, 69.0]	37.8 [14.2, 72.6]	22.4 [2.02, 70.2]	26.7 [12.4, 70.2]	22.2 [2.02, 75.6]	27.8 [12.1, 75.6]
SMN2 copy number	2	15 (20.3%)	6 (9.8%)	23 (17.7%)	10 (9.8%)	3 (15.8%)	1 (7.1%)	6 (15.0%)	3 (9.4%)	47 (17.9%)	20 (9.6%)
	3	50 (67.6%)	48 (78.7%)	78 (60.0%)	66 (64.7%)	11 (57.9%)	8 (57.1%)	12 (30.0%)	8 (25.0%)	151 (57.4%)	130 (62.2%)
	4 +	4 (5.4%)	3 (4.9%)	17 (13.1%)	18 (17.6%)	4 (21.1%)	4 (28.6%)	22 (55.0%)	21 (65.6%)	47 (17.9%)	46 (22.0%)
	Unknown	5 (6.8%)	4 (6.6%)	12 (9.2%)	8 (7.8%)	1 (5.3%)	1 (7.1%)	0 (0%)	0 (0%)	18 (6.8%)	13 (6.2%)
SMA type	I	12 (16.2%)	3 (4.9%)	14 (10.8%)	0 (0%)	2 (10.5%)	0 (0%)	1 (2.5%)	0 (0%)	29 (11.0%)	3 (1.4%)
	II	54 (73.0%)	51 (83.6%)	67 (51.5%)	50 (49.0%)	2 (10.5%)	0 (0%)	0 (0%)	0 (0%)	123 (46.8%)	101 (48.3%)
	III	8 (10.8%)	7 (11.5%)	49 (37.7%)	52 (51.0%)	15 (78.9%)	14 (100%)	32 (80.0%)	31 (96.9%)	104 (39.5%)	104 (49.8%)
	IIIA	4	4	30	31	9	7	7	6	50	48
	Pre-symptomatic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (17.5%)	0 (0%)	7 (2.7%)	0 (0%)
	IV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.1%)	0 (0%)	1 (0.5%)
HFMSE	Mean (SD)	0.667 (1.10)	0.474 (0.868)	10.9 (9.22)	8.47 (6.87)	36.8 (9.60)	34.5 (9.83)	53.7 (9.77)	52.0 (10.3)	17.4 (20.0)	14.8 (19.2)
	Median [Min, Max]	0 [0, 4.00]	0 [0, 3.00]	8.00 [2.00, 43.0]	6.00 [2.00, 37.0]	39.0 [17.0, 54.0]	37.5 [17.0, 54.0]	57.0 [32.0, 65.0]	55.0 [32.0, 65.0]	8.00 [0, 65.0]	5.00 [0, 65.0]
	N	60	57	127	102	19	144	40	32	246	205
RULM (LEFT)	Mean (SD)	7.17 (6.45)	5.19 (5.98)	16.7 (7.45)	15.7 (7.35)	28.6 (6.49)	26.7 (7.31)	35.1 (3.91)	35.6 (3.13)	19.5 (11.4)	19.0 (12.3)
	Median [Min, Max]	5.00 [0, 17.0]	2.50 [0, 16.0]	18.0 [0, 37.0]	17.0 [0, 37.0]	31.0 [15.0, 37.0]	25.0 [15.0, 37.0]	37.0 [22.0, 37.0]	37.0 [25.0, 37.0]	19.0 [0, 37.0]	18.0 [0, 37.0]
	N	30	26	89	64	15	11	31	29	165	130
RULM (RIGHT)	Mean (SD)	5.50 (5.42)	5.19 (5.31)	18.4 (7.30)	18.1 (7.37)	29.3 (6.12)	28.1 (6.85)	35.6 (3.27)	36.1 (2.63)	18.7 (11.5)	18.1 (12.0)
	Median [Min, Max]	5.00 [0, 19.0]	3.00 [0, 17.0]	19.0 [0, 37.0]	18.0 [0, 37.0]	29.5 [20.0, 37.0]	27.0 [19.0, 37.0]	37.0 [25.0, 37.0]	37.0 [26.0, 37.0]	19.0 [0, 37.0]	17.0 [0, 37.0]
	N	54	54	120	97	18	14	33	31	225	196
SMAIS-ULM (SCORE)	Mean (SD)	10.1 (8.06)	11.6 (8.43)	23.5 (9.69)	24.8 (9.12)	32.8 (8.50)	37.4 (5.42)	41.3 (4.86)	42.8 (2.44)	23.1 (13.3)	24.5 (13.2)
	Median [Min, Max]	9.50 [0, 34.0]	11.0 [0, 34.0]	23.0 [2.00, 44.0]	24.0 [3.00, 44.0]	34.0 [14.0, 44.0]	37.5 [25.0, 44.0]	43.5 [21.0, 44.0]	44.0 [33.0, 44.0]	22.0 [0, 44.0]	24.0 [0, 44.0]

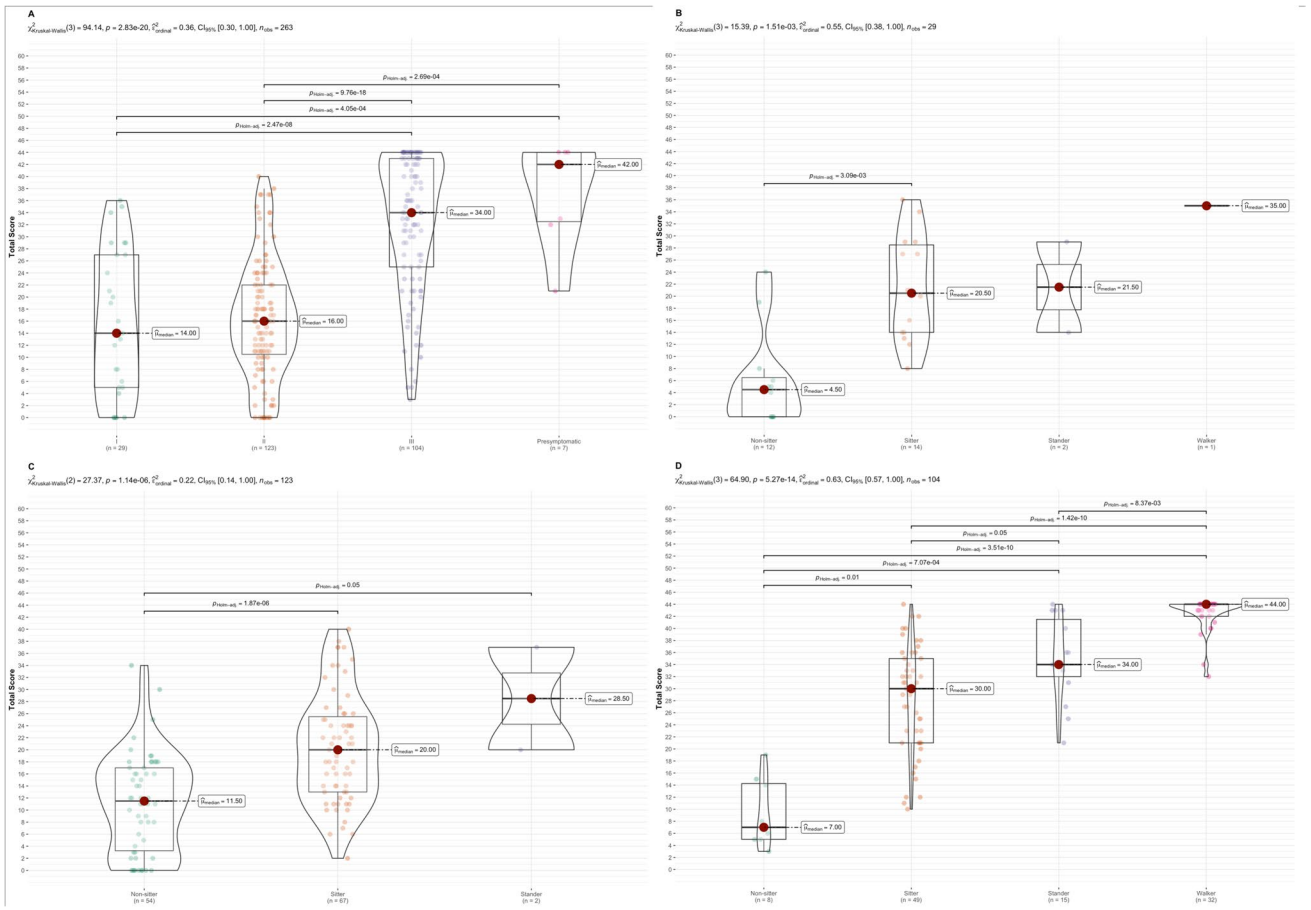

Fig. 1 Kruskal–Wallis test results for total SMAIS-ULM score in the entire cohort. Key to figure: **A** analysis between SMA types; **B** analysis within SMA I by functional status; **C** analysis within SMA II by functional status; **D** analysis within SMA III by functional status

scores between groups. The effect size was small ($r = 0.04$), with a 95% confidence interval for the difference ranging from –0.10 to 0.18.

Ceiling and floor effect

In the entire population, a ceiling effect on the total SMAIS-ULM score was observed in 8.4% of cases, while a floor effect was noted in 5.3%. When analyzed by functional status, the ceiling effect was absent in non-sitters, observed in 0.8% of sitters, 5.3% of standers, and 50% of walkers. Conversely, the floor effect was present in 18.9% of non-sitters and absent in sitters, standers and walkers.

A difference was observed within the walker's population when comparing those who reached the ceiling effect to those who did not. Those who reached the ceiling had higher HFMSE scores (57.4 ± 7.82 vs. 50.0 ± 10.3) and 6MWT distances ((479 ± 152 vs. 274 ± 148), and 80% of them were SMA IIIB (vs. 45%), compared to those unable to achieve the maximum score on the scale (mean SMAIS-ULM 38.7 ± 5.78).

Item by item analysis

Specific items exhibiting floor or ceiling effects across different functional subgroups are detailed in Fig. 2A.

Correlation with outcome measures

The relationship between total SMAIS-ULM and HFMSE scores was assessed using a Spearman correlation, the analysis revealed a significant positive correlation, $\rho = 0.80$, $p < 0.001$, indicating a strong relationship between the two variables (Online Resource 3).

The analysis of the relationship between total SMAIS-ULM and RULM demonstrated a strong, significant positive correlation, the analysis revealed a significant positive correlation, $\rho = 0.83$, $p < 0.001$, indicating a strong relationship between the two variables (Online Resource 3).

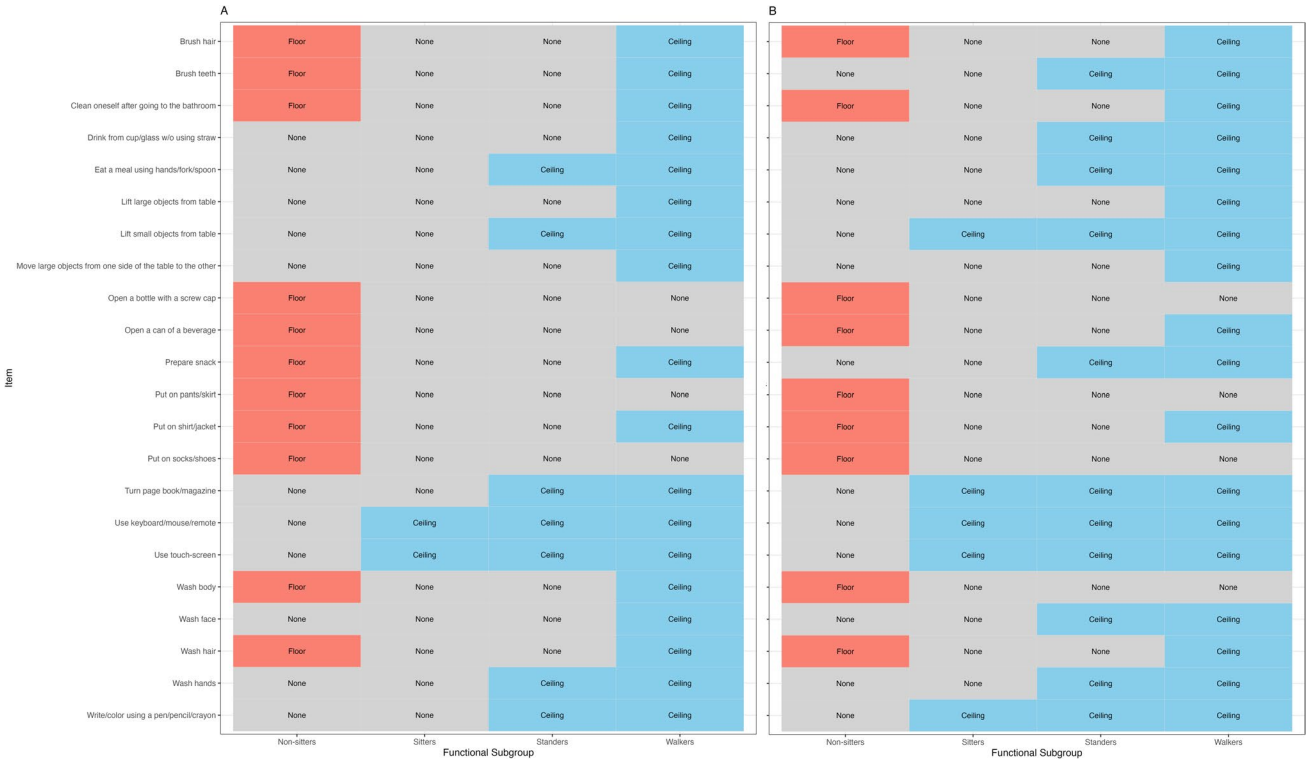

Fig. 2 Items showing floor or ceiling effects across different functional subgroups in the caregiver-reported (**A**) and patient-reported SMAIS-ULM questionnaire (**B**)

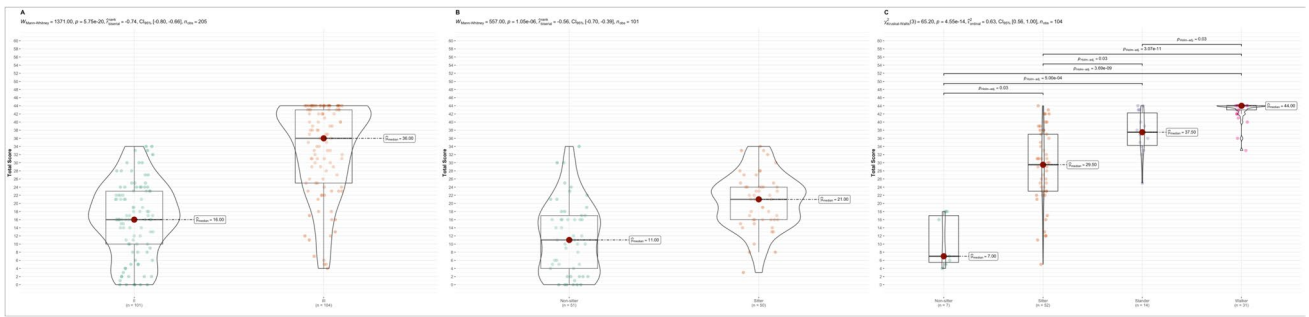

Fig. 3 Kruskal–Wallis test results for total SMAIS-ULM score. Key to figure: **A** analysis between SMA type II and III; **B** analysis within SMA II by functional status; **C** analysis within SMA III by functional status

Patients reported

A total of 209 patients of age above 12 years completed the SMAIS-ULM.

Total score

The SMAIS-ULM scores ranged between 0 and 44 (mean 24.5).

A Mann–Whitney *U* test was conducted to evaluate differences in the total SMAIS-ULM score between SMA types and, within each SMA type, based on their functional status (Fig. 1). The analysis revealed significant differences both between SMA types and within SMA types by functional status ($p < 0.001$ for all tests), indicating that the score distributions varied across the groups. Figure 3 shows the results of the analysis and post hoc comparison. No testing was conducted within SMA I or SMA IV due to the small sample size.

A Spearman's rank-order correlation was conducted to assess the relationship between age and total SMAIS-ULM scores. There was no statistically significant correlation between the two variables, $\rho(209) = 0.03$, $p = 0.691$.

A Mann–Whitney U test was conducted to examine differences in total SMAIS-ULM scores based on sex assigned at birth. The difference was not statistically significant, $U = 5258.00$, $p = 0.65$, indicating no evidence of a difference in SMAIS-ULM scores between groups. The effect size was small ($r = 0.04$), with a 95% confidence interval for the difference ranging from –0.10 to 0.12.

In the entire population, a ceiling effect on the total SMAIS-ULM score was observed in 11% of cases, while a floor effect was noted in 2.9%. When analyzed by functional status, the ceiling effect was absent in non-sitters, observed in 1% of sitters, 14.3% of standers, and 62.5% of walkers. Conversely, the floor effect was present in 9.8% of non-sitters, and absent in sitters, standers, and walkers.

A difference was observed within the walkers population when comparing those who reached the ceiling effect to those who did not. Those who reached the ceiling had higher HFMSE scores (55.9 ± 8.33 vs. 45.6 ± 10.3) and 6MWT distances (465 ± 145 vs. 214 ± 75.1) compared to those unable to complete the scale (mean SMAIS-ULM 40.8 ± 3.16). In particular, 80% of the patients scoring ≥ 50 on the HFMSE and 70% of the patients walking ≥ 400 m on the 6MWT showed a ceiling effect on the SMAIS-ULM.

Item by item analysis

Specific items exhibiting floor or ceiling effects across different functional subgroups are detailed in Fig. 2B.

Correlation with outcome measures

The relationship between total SMAIS-ULM and HFMSE scores was assessed using a Spearman correlation, which revealed a strong, significant positive correlation, the analysis revealed a significant positive correlation, $\rho = 0.86$, $p < 0.001$, indicating a strong relationship between the two variables (Online Resource 3).

Similarly, the analysis of the relationship between total SMAIS-ULM and RULM demonstrated a strong, significant positive correlation, the analysis revealed a significant positive correlation, $\rho = 0.89$, $p < 0.001$, indicating a strong relationship between the two variables (Online Resource 3).

Caregiver vs patient perception

A subgroup of 195 paired questionnaires featured concomitant responses from both caregivers and patients, comprising 3 cases of SMA type I, 93 of type II, and 99 of type III. Mean age for this cohort was 32.6 (16.2), ranging between 12.3 and 75.6 years. Mean total SMAIS-ULM was 23.6 (SD 13.5), ranging between 0 and 44.

Table 2 summarizes the characteristics of the sample.

A Wilcoxon signed-rank test was conducted to compare questionnaire responses between caregivers and patients for non-sitters, sitters, standers and walkers. All three tests revealed no significant difference between caregivers and patients ($p = 0.98$, $p = 0.44$, $p = 0.69$, $p = 0.98$, respectively). No statistical differences were also found when considering responses between caregivers and patients for SMA type II or III and SMAIS-ULM total score results ($p = 0.47$ and $p = 0.74$, respectively).

No statistical differences were found between item-by-item responses in both functional status or SMA type groups ($p > 0.05$).

A concordance correlation coefficient (CCC) was calculated to assess the agreement between patient and caregiver SMAIS-ULM total scores. For non-sitters, the CCC was 0.94, 95% CI [0.90, 0.96], with a scale shift of 0.96 and a location shift of −0.11, indicating strong agreement.

For sitters, the CCC was 0.91, 95% CI [0.87, 0.94], with a scale shift of 1.03 and a location shift of −0.10, also suggesting good concordance.

For walkers, the CCC was 0.96, 95% CI [0.92, 0.98], with a scale shift of 0.98 and a location shift of 0.01, reflecting excellent agreement between respondents.

Discussion

Following the FDA recommendation to use patient-reported outcome measures in addition to observer-rated measures [28–31], a number of tools have been developed or adapted for SMA [10, 12, 32–40]. The SMAIS-ULM, originally validated for type II and non-ambulant type III [14], has been used both in clinical trials [18–24] and clinical real-world settings, showing sensitivity to change in non-ambulant patients [41]. Our study expands the existing literature, providing a comprehensive analysis of the SMAIS-ULM questionnaire in a broader age and function ranging from non-sitters to ambulant. Our findings indicate that SMAIS-ULM can be used in a heterogeneous cohort, with scores that significantly vary across SMA types and functional categories, demonstrating the ability of the scale to discriminate disease severity and functional abilities. The application of the scale to a wider functional group allowed to better establish the possible ceiling and floor effects at the two functional extremes of our heterogenous cohort. The ceiling effect was common but not consistently observed among walkers. A full total score was achieved in approximately 50% of walkers, more specifically in those with better results on the HFSME and 6MWT while those with lower motor function had relatively limited independence that could be identified by the relatively lower scores on the SMAIS. While we confirm that the scale is better suited

Table 2 Characteristics of the sample

		Non-sitters (*N* = 60)	Sitters (*N* = 93)	Standers (*N* = 13)	Walkers (*N* = 29)	Overall (*N* = 195)
Age	Mean (SD)	33.5 (16.6)	32.0 (16.2)	37.9 (19.1)	30.3 (14.0)	32.6 (16.2)
	Median [Min, Max]	28.5 [12.3, 75.6]	26.2 [12.4, 72.9]	33.5 [14.2, 69.0]	25.5 [12.4, 70.2]	27.4 [12.3, 75.6]
SMN2 copy number	2	4 (6.7%)	10 (10.8%)	1 (7.7%)	3 (10.3%)	18 (9.2%)
	3	48 (80.0%)	59 (63.4%)	8 (61.5%)	7 (24.1%)	122 (62.6%)
	4 +	4 (6.7%)	16 (17.2%)	3 (23.1%)	19 (65.5%)	42 (21.5%)
	Unknown	4 (6.7%)	8 (8.6%)	1 (7.7%)	0 (0%)	13 (6.7%)
SMA type	I	3 (5.0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.5%)
	II	49 (81.7%)	44 (47.3%)	0 (0%)	0 (0%)	93 (47.7%)
	III	8 (13.3%)	49 (52.7%)	13 (100%)	29 (100%)	99 (50.8%)
	IIIA	4 (50%)	30 (61.2%)	7 (53.8%)	5 (17.2%)	46 (46.5%)
HFMSE	Mean (SD)	0.564 (1.01)	8.74 (7.03)	35.3 (9.73)	52.9 (10.3)	14.9 (19.3)
	Median [Min, Max]	0 [0, 4.00]	7.00 [2.00, 37.0]	38.0 [17.0, 54.0]	57.0 [32.0, 65.0]	5.00 [0, 65.0]
	N	55	93	13	29	190
RULM (LEFT SIDE)	Mean (SD)	7.04 (6.56)	15.7 (7.61)	27.6 (7.07)	35.7 (3.11)	19.3 (12.1)
	Median [Min, Max]	5.00 [0, 17.0]	17.0 [0, 37.0]	28.0 [15.0, 37.0]	37.0 [25.0, 37.0]	18.0 [0, 37.0]
	N	26	59	10	27	122
RULM (RIGHT SIDE)	Mean (SD)	5.27 (5.18)	18.1 (7.53)	28.8 (6.58)	36.1 (2.71)	18.3 (12.0)
	Median [Min, Max]	5.00 [0, 16.0]	18.0 [0, 37.0]	29.0 [20.0, 37.0]	37.0 [26.0, 37.0]	18.0 [0, 37.0]
	N	49	90	13	29	181
SMAIS-ULM (SCORE)	Mean (SD)	10.7 (8.01)	24.2 (9.46)	36.3 (6.12)	42.8 (2.48)	23.6 (13.5)
	Median [Min, Max]	11.0 [0, 34.0]	24.0 [7.00, 44.0]	36.0 [25.0, 44.0]	44.0 [32.0, 44.0]	22.0 [0, 44.0]

for non-ambulant patients, our results also suggest the SMAIS-ULM can also be applied within the range of ambulant patients, to identify those, who despite being still ambulant, already show signs of the disease that have an impact on independence.

At the other end of the functional spectrum, the floor effect was only observed in a limited number of non-sitters, with values below the commonly considered threshold of 15–20% [27].

The analysis of the individual items allowed to identify the activities that more often had full scores in the walkers and those that were more often found to be challenging for non-sitters' patients, highlighting the potential need for refinement. These findings have prompted the need for further steps to develop a new version of the scale that is being designed to better capture disease-related impairments in ambulant individuals [42].

Even with the reported limitations of a frequent ceiling effect in the more able walker patients there was an overall strong, significant correlations between SMAIS-ULM and HFMSE and RULM in the whole cohort, indicating that SMAIS-ULM aligns well with established motor functional scales.

While in previous studies exploring patients and caregivers' perspectives there was often a discrepancy between the two [33, 43–45], in our study the comparative analysis of paired caregiver- and patient-reported responses using the SMAIS-ULM revealed no statistically significant differences in the whole cohort and also across SMA types or functional groups. This held true both for the total scores and at item level. The high level of agreement supporting the reliability of SMAIS-ULM as a consistent measure of function regardless of the respondent.

This study supports the validity and reliability of SMAIS-ULM as a caregiver- and patient-reported measure of function in SMA. These findings however should be interpreted with caution, while the strong correlations with HFMSE and RULM reinforce the clinical meaningfulness of the observer-rated functional scales, it will be interesting to further analyze in which way the different tools complement each other and whether the SMAIS-ULM provides additional information to the RULM or HFMSE. Future research will explore the role of the SMAIS-ULM in longitudinal studies to establish the responsiveness to change over time and its utility as a longitudinal outcome measure.

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Data availability Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Coordinating Center (Gemelli Hospital, n° 0033773/22-Oct 26 th 2022).

Consent to participate Written informed consent was obtained from all individual participants/their parents or caregiver included in the study.

Competing interests Coratti G, D'Amico A, Bruno C, Trabacca A, Maggi L, Pera MC, Ricci F, Mongini T, Pane M, Mercuri E report personal fees from BIOGEN S.R.L., ROCHE, AVEXIS and NOVARTIS outside the submitted work; Pane M and Mercuri E report personal fees from PTC THERAPEUTICS and SAREPTA outside the submitted work; Coratti G reports personal fees from GENESIS PHARMA and Biologix outside the submitted work; Bruno I reports personal fees from Biogen and Astrazeneca outside the submitted work; Mercuri E reports from personal fees SANTHERA outside the submitted work; Siciliano G and Ricci G received consulting fees from Biogen and Roche. Bravetti C, Gadaleta G, Coccia M, Ferrero A, Costantini E, Longo A, Catteruccia M, Morando S, Brolatti N, Verriello L, Cumbo F, Pessa ME, Antonaci L, Vacchiano V, Faini C, Liguori R, Ruggiero L, Zoppi D, Caterina Agosto, Francesca Benedetti, Russo A, Torri F, have nothing to disclose. Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Chiara Bravetti, Giorgia Coratti and Maria Carmela Pera. The first draft of the manuscript was written by Chiara Bravetti, Giorgia Coratti, Maria Carmela Pera, Eugenio Mercuri and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Authors and Affiliations

Chiara Bravetti[1] · Giorgia Coratti[1,2] · Maria Carmela Pera[1,2,3] · Giulio Gadaleta[4] · Tiziana Mongini[4] · Michela Coccia[5] · Amanda Ferrero[5] · Emanuele Maria Costantini[5] · Antonella Longo[6] · Francesca Cumbo[6] · Michela Catteruccia[6] · Adele D'Amico[6] · Simone Morando[7] · Noemi Brolatti[7] · Claudio Bruno[7] · Lorenzo Verriello[8] · Maria Elena Pessa[8] · Laura Antonaci[1,2] · Claudia Faini[10] · Rocco Liguori[9,10,11] · Veria Vacchiano[9,11] · Lucia Ruggiero[12] · Dario Zoppi[12] · Anna Russo[12] · Francesca Torri[13] · Giulia Ricci[13] · Roberto Chiappini[13] · Gabriele Siciliano[13] · Antonio Trabacca[14] · Caterina Agosto[15] · Francesca Benedetti[15] · Marika Pane[1,2] · Eugenio Mercuri[1,2] · ITASMAC working group

✉ Eugenio Mercuri
eugeniomaria.mercuri@unicatt.it

[1] Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

[2] Pediatric Neurology, Università Cattolica del Sacro Cuore, Rome, Italy

[3] Child Neuropsychiatry Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy

[4] Neuromuscular Unit, Department of Neuroscience "Rita Levi Montalcini", University of Turin, Turin, Italy

[5] NeMO Clinical Center Ancona - Azienda Ospedaliero-Universitaria Delle Marche, Ancona, Italy

[6] Unit of Muscular and Neurodegenerative Diseases, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

[7] Center of Translational and Experimental Myology, Department of Neuroscience, Rehabilitation, Ophthalmology Genetics, Maternal and Child Health, IRCCS Istituto Giannina Gaslini and University of Genoa, Genoa, Italy

[8] Neurology Unit, "Head, Neck and Neurosciences" Department, University Hospital of Udine, 33100 Udine, Italy

[9] UOC Clinica Neurologica, IRCCS Istituto Delle Scienze Neurologiche Di Bologna, 40139 Bologna, Italy

[10] Dipartimento Di Scienze Biomediche E Neuromotorie, Università Di Bologna, 40139 Bologna, Italy

[11] Centro Clinico NeMO, IRCCS Istituto Delle Scienze Neurologiche Di Bologna, 40139 Bologna, Italy

[12] Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, Naples, Italy

[13] Department of Clinical and Experimental Medicine, Neurological Institute, University of Pisa, Pisa, Italy

[14] Scientific Institute IRCCS "E. Medea", Scientific Direction, Via Don L. Monza 20, 23842 Bosisio Parini, LC, Italy

[15] Pediatric Pain and Palliative Care Service, Department of Women's and Children's Health, University Hospital, Padua, Italy