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ORIGINAL ARTICLE

Health-related quality of life in type 1 diabetes mellitus pediatric patients and their caregivers in Spain: an observational cross-sectional study

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ABSTRACT

Objectives: This study assessed the health-related quality of life (HRQOL) of pediatric patients with type 1 diabetes mellitus (T1DM) and their caregivers.

Methods: CHRYSTAL was an observational cross-sectional study conducted in Spain in 2014 on 275 patients under 18 years old diagnosed with T1DM. Patient/caregiver pairs were stratified by patients' HbA1c level (≥7.5% versus <7.5%) and by presence or absence of T1DM complications and/or comorbidities. EQ-5D and PedsQL questionnaires were administered to patients and caregivers.

Results: On the EQ-5D, according to caregivers' perception, 17.7% of children experienced moderate pain or discomfort, 9.7% suffered problems performing usual activities, and 13.2% demonstrated moderate anxiety or depression. Mean EQ-5D index score was 0.95 and mean visual analog scale (VAS) score was 86.1. By HbA1c level (≥7.5% versus <7.5%), mean index scores were 0.94 and 0.95, and mean VAS scores were 82.8 and 89.2, respectively. Mean index scores were 0.91 for children with complications and/or comorbidities and 0.96 for children without. Mean VAS scores were 83.7 and 87.2, respectively. HRQOL per the PedsQL tool ranged from 68.1 (ages 2–4) to 73.1 (ages 13–18). EQ-5D index and VAS scores were significantly correlated (rho = 0.29–0.43) with several age groups of the PedsQL. EQ-5D scales showed significant moderate correlation between EQ-5D-Y and EQ-5D-3L proxy VAS score (rho = 0.45; $p < .001$).

Conclusions: Patients with few complications and controlled HbA1c reported a relatively high HRQOL. The results suggest that parent-proxy EQ-5D ratings are valid for use as part of an overall health outcomes assessment in clinical studies of T1DM in pediatric patients.

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Introduction

The prevalence of type 1 diabetes mellitus (T1DM) in Spain is between 1.1 and 1.4 per 1000 people under 15 years old[1]. Previous research has demonstrated that better glycemic control (lower HbA1c) is associated with higher quality of life[2]; however, structured and current information about health-related quality of life (HRQOL) in the pediatric population with T1DM in Spain is very limited[3].

It is well known that T1DM care is associated with high costs and significant family burden in the pediatric population[4–8]. Little is known, however, about overall HRQOL as perceived by T1DM pediatric patients, particularly those with an early onset of the disease and their caregivers[9].

A growing literature has recently analyzed the HRQOL of adults with diabetes mellitus[10–17]. Evaluating HRQOL in pediatric patients, however, presents several challenges since young children may not have the cognitive ability to complete measurement tasks and thus HRQOL values must be estimated by proxy assessors[18].

At the time of this study, no studies have used the brief and well established EQ-5D to estimate the HRQOL of T1DM patients or their caregivers in Spain. The EQ-5D is a preferences-weighted instrument that incorporates utility values for health outcomes and that can be used in cost–effectiveness analyses to aid resource allocation decisions[19].

The objective of this study was to cover this gap in measuring and analyzing the HRQOL of T1DM pediatric patients and their caregivers. Furthermore, we examined whether the proxy version of the EQ-5D would be feasible and valid for assessment of HRQOL among pediatric patients with T1DM.

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Methods

Research design and subjects

The CHRYSTAL study (Costs and Health Related qualitY of life Study for Type 1 diAbetes meLlitus pediatric patients in Spain) was a multicenter, cross-sectional, observational study of pediatric patients diagnosed with T1DM who received outpatient care in pediatric endocrinology specialized centers within the healthcare system in Spain. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[20]. Patients under 18 years of age who had been diagnosed with T1DM for at least 12 months were eligible for inclusion. Patients diagnosed with any other type of diabetes, patients participating in clinical trials and inpatients were excluded. The patient's primary caregiver was defined as the adult responsible for controlling the patient's diabetes most of the time (usually the mother or father). Caregivers provided their informed consent to participate in the study and to release information, and the study was approved by the hospitals' ethics committees in accordance with national and regional regulations.

Study population

The number of patients to enroll was estimated according to the distribution of pediatric patients with T1DM in Spain[21]. We randomly selected 12 centers across Spain and the researchers randomly selected patients fulfilling the inclusion criteria. More information about the study population selection can be found in López-Bastida and co-authors[22].

Data collection

Data were collected between May and August 2014, at one single time for each patient, by the investigators of each center (pediatric endocrinologists or diabetes specialist nurses). A Case Report Form (CRF) was completed by the investigator using the patient's medical record and one questionnaire was completed by the patient's primary caregiver. The CRF included the patient's demographics (e.g. sex, age, height, weight), clinical indicators for T1DM control (e.g. HbA1c level), and diabetes-related complications and comorbidities (DCC) not including hypoglycemia but including ketosis without acidosis, ketoacidosis, dawn phenomenon, retinopathy, nephropathy, peripheral neuropathy, hypothyroidism and celiac disease.

Caregivers completed three questionnaires: the EQ-5D-3L proxy version, the EQ-5D-5L and the Diabetes Module of the Pediatric Quality of Life Inventory (PedsQL) (2–7 years old). Patients completed two questionnaires: EQ-5D young version (EQ-5D-Y) (8–17 years old) and PedsQL (8–17 years old).

Questionnaire (EQ-5D)

The EQ-5D is a simple generic instrument developed by a multidisciplinary group of researchers[23]. This questionnaire has been validated in many countries in Europe, including Spain, and it is commonly used in economic evaluation and technology assessment[19]. There are five dimensions in the EQ-5D covering the areas of mobility, self-care, daily activities, pain/discomfort and anxiety/depression. Evaluations of these health states have been performed for the general population using the time-trade-off method[24]. Health-state classification systems like the EQ-5D provide an indirect means of obtaining preference scores: patients and caregivers are assigned an EQ-5D classification based on responses to the questionnaire, and the validated preference scores are applied. The second part of the EQ-5D consists of a vertical 20 cm, 0–100 visual analogue scale (VAS), where 0 represents the worst and 100 represents the best imaginable health state. Respondents mark a point on the scale to reflect their overall self-perception of health on the day of the interview.

Caregivers assessed patients' HRQOL as proxy respondents using the EQ-5D-3L proxy version and also assessed their own HRQOL through the EQ-5D-5L instrument, which has been validated in Spain[25]. The EQ-5D-3L proxy version questionnaire included a standard proxy version of the EQ-5D, which asked caregivers how they would rate their child's health. We also assessed patients' HRQOL using the EQ-5D-Y in children aged 8 years old or over. The EQ-5D-Y is a generic measure of health status in children and young people with a design architecture analogous to that of the original three-level version of EQ-5D (EQ-5D-3L) used with adults[26]. The practical feasibility and validity of EQ-5D-Y has been demonstrated in several studies[27–29]; however, there is currently no recommended value set to derive a utility score from the EQ-5D-Y profile.

Other health status measure (PedsQL)

The PedsQL measures diabetes-specific HRQOL in the population under 18 years of age. The PedsQL is a validated HRQOL pediatric instrument for the Spanish speaking population in Spain[30–31]. Its recall period is 7 days, and it is composed of 5 dimensions comprising 28 items: "Diabetes symptoms" (11 items), "Treatment 1" or treatment barriers (4 items), "Treatment 2" or treatment adherence (7 items), "Worry" (3 items) and "Communication" (3 items). All items are graded on a 5 point Likert scale from 0 (Never) to 4 (Almost always). Dimension scores are obtained as the mean of items and the total score is the mean of dimension scores which are converted to a 0 to 100 scale, where higher scores indicate lower problems and higher HRQOL. The PedsQL questionnaire was self-administered to patients aged 8 to 17 and completed by the principal caregiver for children aged 2 to 7, using the appropriate available age versions (ages 2–4, 5–7, 8–12 and 13–18). No instrument is available for patients under 2 years of age and therefore these patients were excluded from analysis of HRQOL.

Statistical analysis

All continuous variables were summarized by mean and standard deviation. Usual tests for normality were applied and we used ordinary least squares to assess the relationship between the HRQOL and HbA1c level or the presence of DCC. In the models, we included sex and age as control variables. Moreover, we estimated the correlations between the PedsQL and the EQ-5D instruments, both the proxy

(EQ-5D-3L) and the self-reported (EQ-5D-Y) versions, using Spearman's rank correlation coefficient (rho). According to Cohen[32], correlation coefficients with values from 0.1 to 0.29 were assumed low, from 0.3 to 0.49 moderate and 0.5 and above were assumed high.

Results

A total of 267 patients and their caregivers were included for analysis (97% of total sample); 8 were excluded because of incomplete information for calculating HRQOL. Only 194 patients could complete the EQ-5D young version due to age restrictions. The main characteristics of patients and their caregivers are shown in Table 1.

As shown in Table 2, the results of the proxy version (EQ-5D-3L) by HRQOL dimension revealed that, according to their caregiver's perception, 17.7% of children ($n = 47$) suffered moderate pain or discomfort, 13.2% ($n = 35$) felt anxiety or mild depression, 9.7% ($n = 26$) had some trouble carrying out daily activities, and only one child (0.4%) had some trouble dressing or washing themselves. The results of EQ-5D-Y, completed by children 8 years old and over, showed that 21.0% of children suffered moderate pain or discomfort ($n = 41$), 19.1% felt moderate anxiety or depression ($n = 37$), 6.7% had problems carrying out daily activities ($n = 13$), and 1.5% had some trouble getting dressed or washing alone ($n = 3$).

Table 3 shows the HRQOL by HbA1c level and by presence of DCC in the past year according to the PedsQL instrument. HRQOL was numerically higher in children with better glycemic control, but no statistical significance was observed. Likewise, better HRQOL was observed in children with no presence of DCC.

The results of the EQ-5D-3L (proxy version) and the EQ-5D-5L (caregivers' self-administered instrument) showed that the mean utility index scores were 0.95 and 0.92, respectively, and the mean VAS scores were 86.1 and 81.8, respectively (Table 1). The VAS scores varied significantly depending on HbA1c level for both pediatric patients and caregivers, with VAS scores significantly higher for HbA1c <7.5%. However, both children (proxy responses) and caregivers reported similar mean utility index scores by HbA1c level. By DCC category (DCC versus no DCC), mean index scores for patients were statistically different (0.91 and 0.96 respectively) as per the proxy questionnaire. In the case of caregivers, the mean VAS score was statistically higher when children had no DCC.

Table 1. Patient and caregiver characteristics and HRQOL.

	HbA1c level		Presence of DCC		All sample
	HbA1c <7.5% ($n = 159$)	HbA1c ≥7.5% ($n = 108$)	No ($n = 209$)	Yes ($n = 58$)	Total ($n = 267$)
Patient characteristics					
Patient age, mean (SD)	**10.5 (3.9)**	**11.7 (3.9)**	**10.8 (4.0)**	**11.9 (3.4)**	11.0 (3.9)
Time since diagnosis (years)	4.8 (3.2)	5.4 (3.3)	4.9 (3.2)	5.3 (3.4)	5.0 (3.2)
Sex (% male)	52.8	53.7	56.0	43.1	53.2
HbA1C last measurement, mean (SD)	**6.8 (0.4)**	**8.3 (0.8)**	**7.3 (0.8)**	**7.7 (1.3)**	7.4 (0.9)
HRQOL of patients					
EQ-5D-3L proxy (VAS)	**88.0 (12.9)**	**83.3 (14.0)**	86.8 (13.1)	83.6 (15.0)	86.1 (13.6)
EQ-5D-3L proxy (index score)	0.95 (0.13)	0.94 (0.11)	**0.96 (0.11)**	**0.91 (0.15)**	0.95 (0.12)
EQ-5D-3L young (VAS)	**89.2 (12.6)**	**82.8 (14.3)**	87.2 (13.0)	83.7 (15.4)	86.4 (13.7)
Caregiver characteristics					
Caregiver age, mean (SD)	42.1 (6.6)	42.9 (6.5)	42.2 (6.6)	43.3 (6.2)	42.4 (6.6)
Sex (% male)	20.1	14.8	19.1	13.8	18.0
HRQOL of caregivers					
EQ-5D-5L (VAS)	**83.5 (15.4)**	**79.4 (15.7)**	**82.8 (15.2)**	**78.3 (16.7)**	81.8 (15.6)
EQ-5D-5L (index score)	0.92 (0.13)	0.91 (0.14)	0.92 (0.14)	0.90 (0.12)	0.92 (0.14)

Abbreviations. DCC, Diabetes-related complications and comorbidities; HRQOL, Health-related quality of life; SD, Standard deviation; VAS, Visual analog scale.
Bold text represents a statistically significant difference ($p < .05$ in the two-sided test of equality for column mean, t-test, or χ^2 z-test) between categories in each group (HbA1c level, presence of DCC).

Table 2. HRQOL by dimension (EQ-5D scales).

EQ-5D dimension	EQ-5D-level	EQ-5D-3L (Proxy) $n = 267$	EQ-5D-Y (Young) $n = 194$
Mobility	No problems in walking about	98.9%	97.4%
	Some problems in walking about	1.1%	2.1%
	Confined to bed	0.0%	0.5%
Self-care	No problems with self-care	98.9%	97.9%
	Some problems washing or dressing himself/herself	0.4%	1.5%
	Unable to wash or dress himself/herself	0.8%	0.5%
Daily activities	No problems with performing usual activities	89.5%	91.8%
	Some problems with performing usual activities	9.7%	6.7%
	Unable to perform usual activities	0.7%	1.5%
Pain/discomfort	No pain or discomfort	82.3%	78.5%
	Moderate pain or discomfort	17.7%	21.0%
	Extreme pain or discomfort	0.0%	0.5%
Anxiety/depression	Not anxious or depressed	85.3%	80.9%
	Moderately anxious or depressed	13.2%	19.1%
	Extremely anxious or depressed	1.5%	0.0%

Abbreviation. HRQOL, Health-related quality of life.

Table 3. Patient HRQOL according to the PedsQL instrument/questionnaire.

	HbA1c level, mean (SD), *n*		Presence of DCC, mean (SD), *n*		Total ($n = 228$)
	HbA1c <7.5%	HbA1c ≥7.5%	No	Yes	
PedsQL (2–4) $n = 18$	70.5 (14.5), 9	65.7 (11.0), 9	67.5 (12.9), 17	77.7[a]	68.1 (12.7)
PedsQL (3–7) $n = 50$	70.6 (14.1), 35	64.9 (12.3), 15	68.7 (13.5), 39	69.6 (15.4), 11	68.9 (13.8)
PedsQL (8–12) $n = 89$	72.2 (11.1), 60	71.5 (15.9), 29	72.9 (12.5), 68	69.0 (13.5), 21	72.0 (12.8)
PedsQL (13–17) $n = 103$	74.6 (12.9), 50	71.8 (12.0), 53	74.4 (12.4), 79	68.8 (11.9), 24	73.1 (12.5)
PedsQL (all ages) $n = 260$	72.5 (12.6), 154	70.2 (13.3), 106	72.2 (12.8), 203	69.2 (13.0), 57	71.6 (12.9)

[a]Only one patient in the 2–4 age group had diabetes-related complications.
Abbreviations. DCC, Diabetes-related complications and/or comorbidities; HRQOL, Health-related quality of life; PedsQL, Diabetes module of the Pediatric Quality of Life Inventory; SD, Standard deviation.

Table 4. Correlations between HRQOL of the children, measured through PedsQL and EQ-5D questionnaires.

Children's HRQOL (PedsQL)	EQ-5D-Y: VAS	EQ-5D proxy version: VAS	EQ-5D proxy version: utility index
Age 2–4 ($n = 18$)	–	0.35 ($p = .16$)	0.21 ($p = .43$)
Age 5–7 ($n = 50$)	–	0.22 ($p = .12$)	**0.34 ($p = .02$)**
Age 8–12 ($n = 89$)	**0.29 ($p = .006$)**	0.11 ($p = .31$)	0.17 ($p = .12$)
Age 13–17 ($n = 103$)	**0.43 ($p < .001$)**	**0.26 ($p = .008$)**	0.17 ($p = .08$)
All ages ($n = 260$)	**0.33 ($p < .001$)**	**0.22 ($p < .001$)**	**0.20 ($p = .002$)**

Abbreviations. HRQOL, Health-related quality of life; PedsQL, Diabetes module of the Pediatric Quality of Life Inventory; VAS, Visual analogue scale.
Bold text indicates statistical significance. Values between 0.1 and 0.29 indicate low correlation, between 0.3 and 0.49 moderate correlation and equal to or above 0.5 high correlation.

Table 5. Correlations between HRQOL of caregivers and HRQOL of children.

Caregivers' HRQOL (EQ-5D-5L)	EQ-5D-Y: VAS	PedsQL (all ages)	EQ-5D-3L proxy version: utility index
VAS	**0.25 ($p = .001$)**	**0.19 ($p = .003$)**	**0.30 ($p < .001$)**
Index score			**0.47 ($p < .001$)**

Abbreviations. HRQOL, Health-related quality of life; PedsQL, Diabetes module of the Pediatric Quality of Life Inventory; VAS, Visual analogue scale.
Bold text indicates statistical significance. HRQOL of the caregivers was measured through the EQ-5D-5L; HRQOL of the children was measured through the PedsQL questionnaire and EQ-5D questionnaires (EQ-5D-Y and EQ-5D-3L proxy).

The results of the regression models confirmed statistically significant differences by HbA1c level in VAS results of the EQ-5D of patients or caregivers after adjusting the differences by age and sex. The presence of DCC was also associated with statistically lower HRQOL.

Correlations between the EQ-5D-3L proxy and PedsQL

The correlation between the different instruments used in the study to estimate the HRQOL (EQ-5D scores and PedsQL scales) was low to moderate (Table 4). Both the EQ-5D index and the VAS scores were significantly correlated with several age groups of the PedsQL. The highest correlation was observed between the values of the VAS and the 13–17 year old PedsQL age group (rho = 0.43; $p < .001$). The strongest relationship between utility levels and PedsQL was observed in children 5–7 years old, using the proxy utility values (rho = 0.34; $p = .016$). Further correlations showed values lower than 0.3, demonstrating a low to moderate correlation between the different tools applied to assess the HRQOL.

Table 5 shows that the HRQOL of caregivers was correlated with the HRQOL of children, with a rho = 0.55 ($p = .02$) between the caregivers' VAS and the PedsQL score of children in the 2–4 year old age group (results by age group not shown in table). Regardless of age, the correlation between the HRQOL of caregivers and the PedsQL score for children was rho = 0.19 ($p = .003$). On the other hand, correlation between caregivers' index scores and children's index scores measured through the EQ-5D-3L proxy version was moderate (rho = 0.47; $p < .001$) (Table 5). Only a moderate correlation was observed between the EQ-5D-Y version VAS score (perception of HRQOL from children 8 and over) and the EQ-5D-3L proxy version VAS score (perception of the HRQOL from caregivers of children 8 and above) with a rho = 0.45 ($p < .001$).

Discussion

This is the first study to assess HRQOL in T1DM pediatric patients and their caregivers in Spain. Our results show that HRQOL is mainly affected by the pain/discomfort and depression/anxiety dimensions in patients and caregivers. Mean utility index scores were 0.95 and 0.92 for children (proxy measurement) and caregivers (self-assessment), respectively. It is important to note that it is unknown whether questionnaires for patients and caregivers were completed independently of each other; a factor which could influence the concordance of the results. Data from the Spanish National Health Survey 2011–2012 indicate that the mean utility index score of the general population in the same age range as

the caregivers in our sample was 0.96. Therefore, caregivers of children diagnosed with T1DM experience a slightly lower HRQOL relative to the general population. However, caregivers have a HRQOL similar to that of the general population after controlling for age[33].

As studies conducted in the United States have found[34], HRQOL of both patients and caregivers is negatively affected by poor glycemic control and by the presence of DCC. The EQ-5D has not been used frequently to assess HRQOL of diabetic children in previous research[9]. The few pediatric studies that have used this instrument have focused on medical conditions including asthma, hemophilia and congenital anorectal malformations[18,35,36]. Use of the EQ-5D instrument has the advantage that it is a generic questionnaire, which allows researchers to elicit utilities which can then be used in cost-effectiveness analyses. While it was developed for an adult population and is meant to be self-reported, some studies have used the EQ-5D in parent-proxy ratings and have shown it to be both feasible and valid[37,38]. Differences in utilities in patients with T1DM by age, self-reported versus proxy reported and elicitation method raise important questions about whose utilities should be used in economic analyses[34].

There is considerable debate in the literature about whether proxies can be used to estimate the HRQOL of children with T1DM and no clear consensus has been found. The use of proxies has been justified due to the lack of verbal capacity of the children being evaluated[39].

The current study builds on this previous research by suggesting that the EQ-5D is also a feasible and valid brief measure of HRQOL among pediatric patients with T1DM. All caregivers in this study were able to rate their children on the five dimensions of the EQ-5D, and scores reflected the moderate level of impairment that would be expected in this population.

Construct validity of the EQ-5D was demonstrated through statistically significant correlations with HRQOL domains as assessed by multi-item scales of the PedsQL and the EQ-5D-Y and VAS score. The use of VAS provides a complementary score to the descriptive system of the self-assessment of the health status of the patients. However, without the descriptive system we do not know which dimension of health is affected.

These findings suggest that the brief, proxy version of the EQ-5D may be used among parents of children and adolescents with T1DM to obtain an estimate of the child's HRQOL when it is not feasible to administer a longer parent-reported HRQOL instrument. Statistically significant correlations were also found between the EQ-5D and the PedsQL, suggesting that PedsQL symptoms and their impact likely contributed to parents' proxy EQ-5D ratings.

There are a number of limitations to note. Firstly, this was a cross-sectional study: one-time assessments in T1DM can be influenced by the inherent variations of assessment conditions on a particular day. Future researchers might conduct longitudinal assessments to monitor changes in patients' and caregivers' utility scores and to test the ability of the measures to predict health service utilization, as worsening utilities are associated with higher resource utilization.

Secondly, there is the possibility of misrepresentation when assigning health status to children. As concluded elsewhere, the values for health states when ascribed to adults are higher than when those same states are ascribed to children[40]. Finally, there may also be questions about the representativeness of the sample, as patients were drawn from selected sites and most had employed caregivers. Although sites were selected randomly, patients or families with social or economic problems which may lead to less compliance with medical appointments may be under-represented.

Conclusions

The findings of this study illustrate opportunities and challenges in measuring HRQOL in T1DM pediatric patients. Caregivers seemed willing and able to complete the EQ-5D questionnaires as proxies. Moreover, the EQ-5D discriminated well among T1DM severity. The results reveal the extensive consequences of T1DM on pediatric patients and could potentially be used in cost–effectiveness analyses of pharmacologic and non-pharmacologic interventions in T1DM. The data suggest that utility scores for caregivers may worsen slightly for patients with Hb1Ac $\geq$7.5% and DCC.

This is the first study to assess HRQOL in T1DM pediatric patients and their caregivers in Spain with different generic and specific validated questionnaires. The results of this study provide baseline information about HRQOL in pediatric T1DM in Spain. Patients with few DCC and well controlled HbA1c reported a relatively high HRQOL. This information will help evaluate the effectiveness of further intervention focused on improving HRQOL in T1D pediatric patients and their caregivers.

Transparency

Declaration of funding

This research was supported by Eli Lilly and Company; however, this participation was limited to sponsoring the project and did not influence the results.

Authors' contributions

J.L.-B., J.P.L.-S., L.A.V., J.R., T.D. and M.P.-N. were involved in the primary study concept, design and execution. J.L.-B., J.O.-M. and I.A.-R. were involved in the specific data analysis. All authors contributed to the interpretation of data and performed a critical revision of content. All authors reviewed and approved the final manuscript.

Declaration of financial/other relationships

J.R., T.D. and M.P.-N. have disclosed that they are employees and stockholders of Eli Lilly and Company. L.A.V. has disclosed that he is a former employee and stockholder of Eli Lilly and Company. No potential conflict of interest was reported by the other authors. *CMRO* peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Ethics approval and consent to participate: The involved human participants provided their informed consent to participate in the study and to release information, and the study was approved by the hospitals' ethics committees in accordance with national and regional regulations.

Consent for publication: The patients' primary caregivers provided their informed consent to participate in the study and for publication of results. The study investigators named above also provided their consent to be mentioned in this publication.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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