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Validation of the Neuro-QoL Measurement System in Children with Epilepsy

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Abstract

OBJECTIVE—Children with epilepsy often face complex psychosocial consequences that are not fully captured by existing patient-reported outcome (PRO) measures. The Neurology Quality of Life Measurement System "Neuro-QoL" was developed to provide a set of common PRO measures that address issues important to people with neurologic disorders. This paper reports

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Conflict of interest
All authors report no conflict of interest to be disclosed.

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Neuro-QoL (Anxiety, Depression, Interaction with peers, Fatigue, Pain, Cognition, Stigma, and Upper and Lower Extremity Function) validation in children with epilepsy.

METHOD—Patients (aged 10–18 years) diagnosed with epilepsy completed Neuro-QoL and legacy measures at time-1 and 6-month follow-up. Internal consistency reliability was also evaluated. Concurrent validity was assessed by comparing Neuro-QoL measures with more established "legacy" measures of the same concepts. Clinical validity was evaluated by comparing mean Neuro-QoL scores of patients grouped by clinical anchors such as disease severity. Responsiveness of the Neuro-QoL from time-1 to 6-month was evaluated using self-reported change as the primary anchor.

RESULTS—61 patients (mean age=13.4 years; 62.3% male, 75.9% white) participated. Most patients (64.2%) had been seizure free in the 3 months prior to participation, and seizure frequency was otherwise described as follows: 17.8% daily, 13.3% weekly, 35.6% monthly and 33.3% yearly. All patients were taking anti-epileptic drugs. Patients reported better function/less symptoms compared to the reference groups. Internal consistency (alpha) coefficients ranged from 0.76 – 0.87. Patients with different seizure frequency differed on Anxiety ($p<.01$) and Cognition ($p<.05$). Compared to patients on polytherapy, those on monotherapy had better Upper Extremity scores ($p<.05$). Compared to those with localized seizures, those experiencing generalized seizures reported worse stigma ($p<.05$). Depression, Anxiety, Lower Extremity, Fatigue, Pain, Interaction with peers, and Stigma also significantly discriminated patients with different levels of quality of life, $p<=.05$. All Neuro-QoL measures were significantly correlated with other measures assessing similar domains. Stigma was related to self-reported change in several areas of functioning, but in sometimes unexpected directions.

SIGNIFICANCE—Neuro-QoL is a valid and reliable assessment tool for children with epilepsy and can be used in research and clinical settings.

Keywords

Epilepsy; Neuro-QoL; Quality of Life; Children; Measurement

1. Introduction

The prevalence of epilepsy among patients seen in pediatric neurology practice may be as high as 70%,[1] and these children often experience a variety of comorbid conditions such as attention problems and cognitive deficits.[2] Children with epilepsy often face complex psychosocial consequences that can derail the course of normal development, often extending to adulthood.[3, 4] They have approximately a threefold increased risk of subnormal mental ability or other learning and behavior problems,[1, 5–7] twice the referral rate for mental health services, and a threefold increase in utilization of special education services.[8, 9] Adolescents with epilepsy are also noted to have a higher frequency of behavioral problems than peers who are healthy or have other chronic health problems.[10] Thus, it is important to monitor their health-related quality of life (HRQL) regularly.

Several factors complicate the assessment of HRQL in children and adolescents with epilepsy, including development-related change in basal functioning; difficulties associated with proxy-assessment; limitations related to learning ability, behavioral disorders and

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motor handicap; and the episodic nature of the disease.[5] Recently, pediatric and adolescent measures have been designed to address the above concerns. Carpay et al.[11] developed a seizure severity (SS) and side effects (SE) scale for children, designed for parent completion. The Quality of Life in Childhood Epilepsy questionnaire (QOLCE) by Sabaz et al[12] is a parent report scale sampling five core functional domains across 16 subscales. Adolescent self-report measures include the Adolescent Psychosocial Seizure Inventory,[13] which does not offer a complete HRQL assessment, and the more comprehensive Quality of Life in Epilepsy for Adolescents inventory (QOLIE-AD-48).[12, 14, 15]

From 2004–2009, the National Institute of Neurologic Disorders and Stroke (NINDS) sponsored a multi-site project to develop a clinically relevant and psychometrically sound HRQL measurement tool for adults and children with neurological disorders.[16–19] This effort, Neuro-QoL, enables clinical researchers to compare the HRQL impact of different interventions within and across various conditions. The pediatric Neuro-QoL consists of ten self-report measures: 8 item banks (anxiety, depression, anger, interaction with peers, fatigue, pain, cognition and stigma) and 2 scales (upper and lower extremity function). These measures are applicable for use with children ages 8 through 17, and available in both English and Spanish. Different from other HRQOL measures used with epilepsy patients, all Neuro-QoL item banks were developed using rigorous qualitative and quantitative approaches, and were calibrated using Item Response Theory (IRT) models.[20–22] An item bank provides the foundation for the development of dynamic computer adaptive testing (CAT), as well as the creation of a variety of static, fixed-length short-forms. The scores produced by any of the instruments created from an item bank are calibrated on the same latent trait and are comparable regardless of the specific questions asked of a given individual or group of respondents. Fixed-length short-forms, in which a subset of bank items can be selected from across the trait spectrum to produce a static instrument, can be used when access to computers is limited. When computers are available, CAT, a dynamic process of test administration in which items are selected on the basis of patients' responses to previously administered items, can provide brief-yet-precise measures.[23–26] The purpose of this paper is to report the validation of Neuro-QoL fixed-length forms in a sample of children with epilepsy.

2. Material and methods

2.1. Pediatric Neuro-QoL Measurement System

Details of pediatric Neuro-QoL development have been previously described in Lai et al. [17] In brief, items were generated by gathering concerns from parents, patients and clinicians. Because generic item sets (pools) could be answered by a person without a medical condition, generic domains were field tested on samples from the US pediatric general population. Targeted item pools, typically symptoms or side effects of a disease process (i.e., fatigue, cognitive function, stigma and pain in this study), were field tested on children with either epilepsy or muscular dystrophy. Samples were recruited via internet panel companies: Toluna (www.toluna.com) and YouGovPolimetrix (www.polimetrix.com) for the US general population and clinical samples, respectively. Companies sent e-mail invitations to parents of potential participants from their database to participate in the field

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testing. After parents provided online consent on behalf of their children, parents completed a series of sociodemographic and clinical questions (for disease samples only) and children completed appropriate Neuro-QoL items. Different testing forms (containing different sets of items) were used to lessen respondent burden and sample sizes differed, ranging between n=500 and 600, depending on the form administered. Because of difficulty recruiting children with epilepsy or muscular dystrophy via panel, we also recruited patients from Ann and Robert H. Lurie Children's Hospital of Chicago (formerly Children's Memorial Hospital, Chicago, Illinois), NorthShore University HealthSystem (Evanston, Illinois), the University of California at Davis Medical Center, and Dartmouth-Hitchcock Medical Center. In-clinic testing procedures were similar to those used by the online panel companies, except that paper versions of the informed consent and assent forms were used. Sample characteristics of each domain were described in details in Lai et al.[17] as well as on the Neuro-QoL official website (http://www.neuroqol.org). Cognitive function and fatigue measures were initially calibrated using Neuro-QoL clinical sample as described above. Given the evidences that cognition and fatigue are prevalent among general population,[27, 28] we updated these two measures using data from 507 children with ages 8–18 drawn from the US pediatric population via Toluna (www.toluna.com). The same recruitment procedures and analytic approaches as described above were used.

In order to reduce patient response burden, and enabled by the flexible scoring properties of item bank subsets, short-forms (no more than 10 items in each domain), rather than full-length generic item banks, were used. For targeted domains (pain, stigma, cognitive function and fatigue), the full-length scales (numbers of items range from 10–14) were used. Each short-form was constructed using the approach described in Cella et al.[16] by selecting items with strong psychometric characteristics (IRT model fit; highly informative; most frequently selected by CAT) and high appeal to clinical and measurement experts.

All Neuro-QoL scores were converted to T-Scores prior to analyses; with a T = 50 indicating average functioning compared to the reference population and with a standard deviation of 10. Of nine domains included in this testing, all but two domains were referenced to the US pediatric general population. The two domains referenced to the clinical sample (i.e., epilepsy and muscular dystrophy) were stigma and pain. Neuro-QoL T-scores referenced to the general population sample are indicated by GPT (General Population T-Score) while those referenced to a clinical sample are indicated by CT (Clinical T-Score).

2.2. Subjects

All procedures were approved by the Institutional Review Boards (IRBs) of all participating sites and informed consent was obtained from each participant prior to data collection.

Patients were recruited from the Ann and Robert H. Lurie Children's Hospital of Chicago, NorthShore University HealthSystem, and Dartmouth-Hitchcock Medical Center. The inclusion criteria were: 1) a diagnosis of epilepsy, ranging from severe (e.g., several events daily) to mild (no events within the past year); 2) ages 10–18 years; and 3) sufficiently proficient in English to provide assent/consent and complete questionnaires. After informed consents/assents were obtained, participants completed the following measures at time-1 and

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6-month follow-up when they visited clinics: Neuro-QoL measures,[17] neuropsychological tests (oral digit symbol modalities;[29] symbol search;[30] digit symbol coding[30]), EuroQOL five dimensions questionnaire (EQ-5D),[31] PROMIS Global Health Scale,[32] Pediatric Quality of Life Inventory (PedsQL™V4.0),[33] Multidimensional Fatigue Scale (PedsQL™-MFS),[34] a global HRQL Question "I am content with the quality of my life right now", Karnofsky performance rating (100= Normal no complaints; 0=dead), and a single 0–10 pain severity rating. Subjects also completed Neuro-QoL measures 7 days later via telephone interview to evaluate test-retest reliability. At 6-month follow-up, participants also completed global ratings of change which asked them to rate how much their physical, emotional, cognitive, social/family and symptomatic well-being and their overall quality of life had changed over the past 6 months according to the following scale: +3 = "Very much better" to −3 = "Very much worse".

2.3. Analysis

We evaluated internal consistency using Cronbach's alpha coefficients; test-retest reliability using intraclass correlation coefficients (ICC) between time-1 and 7-day assessments; and concurrent validity using Spearman rho correlations between Neuro-QoL and other measures administered at time-1. Clinical validity was evaluated at time-1 by comparing mean Neuro-QoL scores of patients grouped by clinical anchors such as disease severity. Analysis of variance (ANOVA) was used to test for differences between groups. Effect sizes (mean difference / pooled standard deviation) were calculated to aid in interpretation of group differences.

We examined the self-reported Global Rating of Change (GRC) as a patient-based anchor of meaningful change. The GRC has 7 levels: +3= very much better; +2=moderately better; +1=a little better; 0 = about the same; −1=a little worse; −2=moderate worse; −3 = very much worse. To achieve adequate power for analysis, we collapsed the three "better" categories (i.e., +3, +2 & +1) into one, and the three "worse" categories (i.e., −1, −2 & −3) into one, leaving three categories ("better;" "about the same;" "worse"). These three categories were compared using ANOVA followed by least significant difference testing of adjacent groups when the overall F statistic was significant. For each analysis, we required that at least 5 patients be represented in each of these three categories. If fewer than five patients were represented in a category, it was collapsed with the adjacent category and the two remaining groups were compared using a t-test. Six GRC questions were used to assess change: Physical well-being, Cognitive function, Emotional well-being, Social/Family well-being, Disease-related symptoms, and Overall quality of life. Less than 5 participants reported worse functioning at follow-up for each GRC measure except Emotional Well-being. As such, "worse" and "about the same" were grouped together and compared to "better" for these GRC measures, using t-tests to assess responsiveness. Responsiveness to changes in Emotional Well-being was assessed using ANOVA, as previously planned. We compared the mean change scores of groups based on their responses to the relevant (i.e., relevant to that particular Neuro-QoL measure) GRC questions. Planned comparisons included: 1) Physical well-being GRC versus Upper Extremity, Lower Extremity, Fatigue, and Pain; 2) Cognitive well-being GRC versus Cognitive Function; 3) Emotional well-being GRC versus Depression, Anxiety, and Stigma; 4) Social well-being GRC versus Social

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Relation-Interaction with peers and Stigma; and 5) Symptoms GRC versus Fatigue, Depression, Anxiety, and Pain. We also evaluated the score changes on each Neuro-QoL measure in relation to reported change on the overall quality of life GRC.

3. Results

3.1. Subjects

Participants (N=61) were primarily male (62.3%), white (75.9%), and non-Hispanic (79.3%) with average age=13.4 years (SD=2.6; range = 10 to 18). At time-1, 91.8% were a full-time student (1.6% part-time student and 6.6% did not attend school). Average time since diagnosis was 5 years (SD=4.1, range from 0.2 to 14.8). Medical records revealed that most patients (64.2%) had not experienced a seizure in the past 3 months; 17.8% reported having a seizure daily, 13.3% weekly, 35.6% monthly and 33.3% yearly. In terms of seizure location, 50% had primary generalized epilepsy and 50% location related epilepsy (56% frontal, 32% temporal, 8% occipital and 4% parietal). Typical seizure duration varied, with 17.6% reporting 0–1 minutes, 37.3% reporting 1 minute, and 25.5% reporting 1 to 5 minutes. All patients were taking anti-epilepsy drugs (AEDs) at the time of testing, with 69.6% receiving monotherapy and 30.4% receiving polytherapy. Similar seizure characteristics were reported at 6-month follow-up (shown in Table 1).

3.2. Analysis

Mean T-scores and standard deviations for the short-forms are shown in Table 2. In all domains, pediatric epilepsy patient QOL ratings fell within ½ SD (i.e., within 5 T-score units) of the reference group. Similarly to Neuro-QoL, patients reported a normal range of function and well-being on almost all of the pedsQL subscales (data were presented here) lending credence that this was a relatively high-functioning group. Internal consistency and one week test-retest reliability of the short forms are presented in Table 2, with Cronbach's alphas ranging from .76 to .87 and ICCs from .44 to .94. Spearman rho correlations between the Neuro-QoL measures and other measures are shown in Table 3. All Neuro-QoL measures were significantly correlated with other measures assessing similar domains, except for physical functioning. "Lower Extremity" and "Upper Extremity" were significantly correlated with Karnofsky performance ratings, PROMIS Physical Function and EQ-5D index but not with PedsQL Physical Functioning.

Patients with different seizure frequency (daily, weekly, monthly, yearly) differed significantly on ratings of Anxiety ($F=3.36$, $p=0.025$) and Cognitive Function ($F=3.05$, $p=0.0358$). Patients on AED monotherapy (n=39) had better Upper Extremity ratings than those on polytherapy (n=17), $t=-2.12$, $p=0.04$. Patients with generalized seizure onset (n=28) reported worse stigma than those with localization-related onset (n=25), $t=-2.07$, $p=0.04$. Although the overall F statistic for years since diagnosis was not significant ($F=2.86$, $p=0.07$), patients who were diagnosed within one year (n=9) reported significantly ($p<.05$) worse stigma than those diagnosed five or more years previously (n=22). The Neuro-QoL Depression, Anxiety, Lower Extremity, Fatigue, Pain, Social Relations, and Stigma measures significantly discriminated patients with different levels of quality of life,

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as assessed by the item “I am content with the quality of my life right now”, p<.05 (p=0.05 for Stigma).

Mean change scores from time 1 to 6-month follow-up were minimal (around 1 T-score unit) as shown in Table 2, except for anxiety, in which patients reported less anxiety (T=2.69) at 6-month follow-up than at time 1. The percentages of patients who responded “better”, "the same” or “worse” on each GRC item is shown in Table 1; most patients reported stable or better function at the 6-month follow-up. Of 23 planned comparisons using GRC, only one was statistically significant. Stigma was significantly correlated with Emotional Well-being, F=3.24, p<0.05. Post hoc comparisons showed that patients who reported either worse or better Emotional Well-being at 6-month follow-up also reported higher stigma than patients who reported the same Emotional Well-being, effect size=0.53 and 0.78, respectively. Stigma was also significantly related to change on both the Physical GRC, t=−2.73, p<0.01, and the Cognition GRC, t=−2.11 p<.05. In both instances, however, the relationship was in an unexpected direction. Patients who reported better Cognition at 6-months reported more stigma than those who reported stable Cognition (no patient reported worse cognition), with an effect size of 0.75. Similarly, those who reported worse Physical Function at 6 months reported an overall decline in stigma from time-1, whereas those who reported improved physical function showed a slight increase in stigma, with an effect size of .59.

4. Discussion

Childhood epilepsy may impact several key aspects of patients’ well-being such as cognition and physical, emotional, and social functioning. A valid and reliable measure can facilitate understanding of the impact of childhood epilepsy upon QOL and also enable prompt interventions. The Neuro-QoL measurement system is clinically-relevant and psychometrically-sound, providing a core set of questions sampling domains that are relevant to patients with many chronic neurological diseases. This paper provides psychometric information about the use of Neuro-QoL with children who have epilepsy, and sets the stage for the inclusion of this important clinical population in future comparative effectiveness studies using Neuro-QoL. Particularly, results of this study showed that Neuro-QoL fixed-length short forms (and thus Neuro-QoL CAT platform) and its general-population based scoring systems can be used in children with epilepsy in a psychometric sound manner. Since items included in short-forms and CAT are from the same IRT-calibrated item banks, scores from both modes of administration are comparable and can be referenced to the same norm. With CAT, only the most informative items are presented, based on the respondent’s responses to previously presented items.[35] Using this approach, a precise estimate of Neuro-QoL domains can be obtained with the presentation of only a few items (typically 4–7 items); such brevity is well-suited for busy clinical practice.

Acceptable psychometric properties are indicated by good internal consistency (Cronbach’s alpha), test-retest reliability, and concurrent validity (correlations between the Neuro-QoL and concurrent measures). Non-significant correlations between Neuro-QoL physical function domains (Upper Extremity and Lower Extremity) and PedsQL Physical Functioning were not a complete surprise. The Neuro-QoL Upper Extremity and Lower

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Extremity scales were developed to capture a full spectrum of physical function ranging from basic gross motor movements to the more sophisticated motor functions such as anticipatory movements (i.e., functional performance), in order to monitor patients' improvement from acute care settings to community living. In contrast, PedsQL items focus on moderate to high functional levels. Because the current study sample was a high functioning group, one would not observe a high correlation between PedsQL and Neuro-QoL Physical Functioning.

Some, but not all, measures included in the Neuro-QoL were able to differentiate patients with different seizure frequency (i.e., Anxiety & Cognition), mono- vs poly-therapy (i.e., Upper Extremity), seizure localization (i.e., Stigma), and global rating of quality of life (i.e., Depression, Anxiety, Lower Extremity, Fatigue, Pain, Social Relations, and Stigma). All were of the expected strength and direction. Although years since diagnosis was not significantly correlated with any Neuro-QoL measures, we found that patients within one year post-diagnosis perceived more stigma than those who were 5 or more years post diagnosis, which may be related to how well their seizures were controlled and patients' adjustment to their condition. However, in the current study, only 16% (n=9) were one-year post-diagnosis. Future studies should be conducted to evaluate the impact of years since diagnosis by recruiting more recently diagnosed patients. Contrary to expectations, when using GRC questions as anchors, Neuro-QoL measures did not appear to be sensitive to differences over time (only one planned analysis showed a significant difference). However, when we evaluated the responsiveness of PedsQL using the same GRC anchor items (total scores, physical functioning, emotional functioning, school functioning, social functioning, and psychosocial functioning) we found a similar result; no statistical significance was detected (results were not reported here). This may be due to the low number of patients who reported meaningful change, even with collapsing of categories, or to the small association between the GRC and the Neuro-QoL change scores. Revicki et al[36] recommend 0.30 – 0.35 as a correlation threshold to define an acceptable association between an anchor and a PRO change score. In this study, correlations (results were not reported here) between Neuro-QoL change scores and GRC were all <0.3, except for stigma and Cognitive GRC (rho=0.42). We note that the current sample was not recruited for the purpose of evaluating change. As shown in Table 1, participants were generally high functioning and only a few patients reported deterioration at 6-month follow-up.

The primary limitation of the current study is the fact that we enrolled a convenient clinical sample with no clear expectation for change (i.e., a naturalistic observational longitudinal design). Also, the sample size was modest. Most participants' epilepsy was well controlled, with only a few patients reporting deterioration at six-month follow-up. Although psychometric properties of the Neuro-QoL were supported in children with epilepsy using cross-sectional data, future studies should be conducted to validate this measure by recruiting patients with a wider range of presentations who can be stratified into different severity levels and studied over time. In particular, it will be important to include patients who have intractable epilepsy, such as candidates for epilepsy surgery. A sample with such diversity will help to estimate clinically minimal important difference for each Neuro-QoL measure.

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5. Conclusion

In conclusion, pediatric Neuro-QoL is a valid and reliable measure of quality of life for children with epilepsy. Yet the validity of the pediatric Neuro-QoL needs to be evaluated further by recruiting a more diverse sample across the severity spectrum. Since the adult version of the Neuro-QoL was validated on patients with epilepsy,[19] the same measurement system can be used to monitor these children throughout the lifespan in a consistent manner.

The pediatric Neuro-QoL can be used in research and is available at http://www.neuroqol.org. A computerized adaptive testing platform for the Neuro-QoL is also available.

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Highlights

- Neuro-QoL is a valid and reliable assessment tool for children with epilepsy.
- Neuro-QoL is a comprehensive measurement system measuring 10 domains.
- Neuro-QoL was developed using Item Response Theory models and a computerized adaptive testing platform is available.

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Table 1

Clinical information at time-1 and follow-up (6 months)

		Time-1 (n=61), %	Follow-up (n=55), %
Seizure frequency	daily	17.78	17.50
	weekly	13.33	5.00
	monthly	35.56	40.00
	yearly	33.33	37.50
Number of seizure in the past 3 months	0	60.34	64.15
	1–3	15.52	16.98
	3+	24.14	18.87
Average duration of seizure (in minutes)	0	7.02	7.84
	between 0–1	21.05	17.65
	1	35.09	37.25
	between 1 – 5	26.32	25.49
	5+	10.53	11.76
Type of medication	Monotherapy	69.64	
	Polytherapy	30.36	
Seizure type	Generalized	50.00	
	Focal	39.29	
	Both Generalized and focal	10.71	
Seizure location	Primary Generalized Disorder	50.00	
	Location Related Disorder	50.00	
GRC-Physical well-being	Better		62.96
	Same		33.33
	Worse		3.70
GRC-Emotional well-being	Better		48.15
	Same		40.74
	Worse		11.11
GRC-Social/Family well-being	Better		59.26
	Same		33.33
	Worse		7.41
GRC-Cognitive well-being	Better		49.06
	Same		50.94
	Worse		0
GRC-Symptomatic well-being	Better		48.15
	Same		48.15
	Worse		3.7

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		Time-1 (n=61), %	Follow-up (n=55), %
GRC-Overall quality of life	Better		62.96
	Same		29.63
	Worse		7.41

[a] GRC: Global rating of change

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Table 2

Descriptive and reliability statistics for Neuro-QoL short-form T-scores

Neuro-QoL Short-form	N_{items}	$N_{persons}$	M_{GPT}	M_{CT}	*SD*	α	T-R[b] ICCs	Mean change[d] (min; max)
Social Relations – Interactions with Peers[a]	8	59	52.70		9.77	.86	.62	−0.83 (−39.5; 18.4)
Cognitive Function[a]	14	61	48.99		7.25	.86	.68	0.87 (−11.1; 15.2)
Depression	8	59	45.16		7.13	.85	.74	−0.86 (−11.9; 16.2)
Anxiety	8	58	49.02		7.58	.76	.70	−2.69 (−16.4; 17.8)
Stigma	8	61		45.39	5.73	.79	.44	−0.75 (−12.0; 19.3)
Fatigue	11	61	49.10		7.26	.80	.64	0.08 (−13.3; 13.1)
Pain	10	59		46.88	6.87	.87	.64	−0.63 (−13.7; 12.8)
Lower Extremity Function –Mobility[a]	20	56	95.65[c]		9.06	.77	.78	0.1 (−27.6; 36.5)
Upper Extremity Function -Fine Motor, ADL[a]	20	59	96.72[c]		8.34	.86	.94	−1.1 (−36.3; 15.0)

[a] For these banks, a high score indicates better function; for all other banks a high score indicates worse function

[b] Time 1 vs. Time 2 (7 days)

[c] These two scales were not calibrated using IRT due to skewed distributions. Possible scores range from 0 (unable to do) −100 (without difficulty).

[d] Time 3 (6 month) – Time 1

M_{GPT} – Mean General Population T-Score; M_{CT}- Mean Clinical T-Score

α - Cronbach's alpha

T-R - Test-Retest

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Table 3

Correlations for Neuro-QoL measures T-scores with other measures at time 1 (only significant correlations are shown in the table)

Neuro-QoL Short-form	Depression	Anxiety	Stigma	Cognition	Lower Extremity (Mobility)	Upper Extremity (Fine Motor, ADL)	Fatigue	Pain	Social Relations – Interactions with Peers
PedsQL Core	−.70***	−.60***	−.50***	.51***	.46***	.41**	−.39**	−.48***	.49***
PedsQL Emotional Functioning	−.66***	−.51***	−.41**	.40**	.44***		−.38**	−.48***	.38**
PedsQL Physical Functioning	−.36**								
PedsQL Psychosocial Health	−.68***	−.55***	−.57***	.51***	.45***	.38**	−.44***	−.46***	.43***
PedsQL School Functioning	−.51***	−.46***	−.42**	.49***	.28*	.30*	−.40**	−.33*	
PedsQL Social Functioning	−.49***	−.37**	−.61***	.34**	.53***	.46***	−0.29*	−.28*	.56***
Multidimensional Fatigue Scale (MFS)	−.63***	−.47***	−.34**	.51***	.40**	.35**	−.49***	−.48***	.39**
MFS Cognitive Fatigue	−.59***	−.44***	−.40**	.61***	.38**	.39**	−.55***	−.43***	.26*
MFS General Fatigue	−.64***	−.49***	−.36**	.49***	.45***	.31*	−.52***	−.36**	.50***
MFS Sleep/Rest Fatigue	−.47***	−.39**						−.45***	.27*
Karnofsky Performance Rating (0–100)					.27*	.30*			.28*
Symbol Digit Modalities # Correct									
Symbol Search Raw Score				.33*		.45***	−0.27*		
Digit Symbol Coding # Correct									
PROMIS Physical Function T- Score	−.57***	−.57***	−.28*	.47***	.36**	.38**	−.41**	−.44***	.45***
PROMIS Mental Health T-Score	−.71***	−.60***	−.34**	.54***	.32*	.30*	−.40**	−.35**	.34**
Pain Scale (0−10)					−.37**	−.38**	.30*	.57***	−.30*
EQ-5D Index Score	−.32*	−.33*	−.37**	.47***	.42**	.55***	−.57***	−.36**	.27*
Global HRQL (0–4)	−.43***	−.40**		.27*			−.35**	−.40**	.30*

* p < .05;

** p < .01;

*** p < .001