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The impact of disease duration on quality of life in children with nephrotic syndrome: a Midwest Pediatric Nephrology Consortium study

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Abstract

Background—The Patient Reported Outcomes Measurement Information System (PROMIS) II is a prospective study that evaluates patient reported outcomes in pediatric chronic diseases as a

measure of health-related quality of life (HRQOL). We have evaluated the influence of disease duration on HRQOL and, for the first time, compared the findings of the PROMIS measures to those of the PedsQL™ 4.0 Generic Scales (PedsQL) from the PROMIS II nephrotic syndrome (NS) longitudinal cohort.

Methods—This was a prospective study in which 127 children (age range 8–17 years) with active NS from 14 centers were enrolled. Children with active NS defined as the presence of nephrotic range proteinuria (>2+ urinalysis and edema or urine protein/creatinine ratio >2 g/g) were eligible. Comparisons were made between children with prevalent (*N*=67) and incident (*N*=60) disease at the study enrollment visit.

Results—The PROMIS scores were worse in prevalent patients in the domains of peer relationship (p=0.01) and pain interference ($p < 0.01$). The PedsQL showed worse scores in prevalent patients for social functioning ($p < 0.01$) and school functioning ($p = 0.03$). Multivariable analyses showed that prevalent patients had worse scores in PROMIS pain interference (p=0.02) and PedsQL social functioning (p<0.01).

Conclusion—The PROMIS measures detected a significant impact of disease duration on HRQOL in children, such that peer relationships were worse and pain interfered with daily life to a greater degree among those with longer disease duration. These findings were in agreement with those for similar domains in the PedsQL legacy instrument.

Keywords

Patient-reported outcomes; Quality of life; Nephrotic syndrome; Pediatrics; Children

Introduction

Nephrotic syndrome (NS) is a challenging relapsing and remitting disease typified by a spectrum of disease trajectories, ranging from a single episode, infrequently relapsing, frequently relapsing, to persistent progressive disease [1]. In the worst cases, the disease course in children can result in multiple complications, frequent hospitalizations, and end-stage kidney disease. Frequently, the disease process spans a significant portion of the formative years of a child's life and can extend into adulthood. As a result, the comprehensive care of children with NS may benefit by the formal assessments of the impact of disease on the physical and psychosocial aspects of health-related quality of life (HRQOL). A better understanding of the HRQOL in children with NS can assist in understanding how children feel and function to better guide clinical care.

Disease characteristics inherent to NS including edema, repeated corticosteroid exposures, and the relapsing nature of the disease pose challenges to patients' HRQOL [2, 3]. Recent studies in children on the impact of NS on HRQOL have shown impairments in physical, social, and emotional functioning [2–4]. Gipson et al. recently reported the initial validation of the Patient Reported Outcomes Measurement Information System® (PROMIS®) pediatric measures (grant U01AR052181) in children with NS. The PROMIS measures were responsive to disease status, with worse HRQOL in the domains of anxiety, fatigue, pain interference, and mobility in children with active NS [3]. To date these studies have

investigated elements inherent to the disease that influence HRQOL, but have not investigated the influence of disease duration on HRQOL.

For those seeking to evaluate HRQOL in children with chronic diseases, the PROMIS and PedsQL™ 4.0 Generic Core Scales (PedsQL) represent two tools available to both the researcher and the clinician. The PROMIS measures were created through a National Institutes of Health initiative to improve the assessment of HRQOL [5]. In the first phase of PROMIS, nine “item banks” were developed for the measurement of self-reported outcomes in children aged 8–17 years: depression, anxiety, anger, social-peer relationships, pain interference, fatigue, mobility, upper extremity functioning, and asthma impact [6–11]. An item bank is a library of items that have gone through extensive qualitative and quantitative evaluation to ensure reliable and valid representations of the HRQOL domain they are measuring (e.g., fatigue). The measurement properties of each item in the PROMIS item banks were calibrated with item response theory (IRT) models to determine an item’s discrimination ability and the level (or severity) of the HRQOL construct the item is measuring. Thus, PROMIS is very different from patient-reported outcome (PRO) measures such as the PedsQL or the Short Form (36) Health Survey (SF-36) in that it allows investigators to tailor PRO measures to an individual or group by selecting items in the item bank which are relevant for their population [5]. With PROMIS, investigators have a great deal of control and can select the HRQOL domains they want to measure, determine if the system will administer individually tailored questionnaires (i.e., computerized adaptive testing) or fixed item short forms, and select the length of the questionnaire. The PROMIS measures have been validated in a number of childhood chronic illnesses, including cancer, asthma, obesity, chronic kidney disease, and NS, in cross-sectional studies [3, 12–14]. In comparison, the PedsQL is a well-used legacy instrument that was developed utilizing classical test theory and which assesses physical, emotional, social, and school functioning [15–18]. To date, the information provided by the PROMIS and PedsQL instruments has not been compared in the setting of pediatric NS.

PROMIS II was designed as a follow-up study to the initial validation of the pediatric PROMIS instrument that seeks to evaluate change in HRQOL longitudinally in children with a number of chronic diseases, including those with NS (prevalent or incident). The current study focuses on the baseline HRQOL data from the PROMIS II NS cohort at the initial assessment. The goal of our analysis was to compare the differences in HRQOL in children with prevalent versus incident NS to investigate the impact of disease duration on HRQOL as measured by the PROMIS measures. A secondary aim of this study was to compare the consistency of the findings of the PROMIS and the PedsQL instruments. We hypothesized that children with longer disease duration would have increased symptom burden and worse HRQOL. Furthermore, we hypothesized that the PROMIS and PedsQL instruments would provide complementary information on the impact of NS disease on the children’s HRQOL.

Methods

The children enrolled in the PROMIS II NS longitudinal cohort study had active NS and were being treated at one of the 14 participating centers (12 from the Midwest Pediatric

Nephrology Consortium and 2 other centers in the USA). Each participating center obtained Institutional Review Board approval. Parents and children gave informed consent and assent, respectively.

Consistent with the target age for the PROMIS pediatric measures, the PROMIS II NS cohort included children aged 8–17 years. Children with active NS, defined as the presence of nephrotic range proteinuria [>2+ urinalysis and edema or urine protein/creatinine (UPC) ratio >2 g/g] were eligible for entry. Exclusion criteria included co-existing medical, psychiatric, or cognitive impairments that would prevent the patient from answering the computer-administered questionnaire, the inability to speak and read English, or kidney failure defined as dependence on dialysis or kidney transplant.

The longitudinal study included three assessments. In the current study, we evaluated data from the assessments at the enrollment visit. The child completed the PROMIS and the PedsQL™ 4.0 Generic Core Scale measures (parent proxy measures were not measured in this study). The parent completed the Family and Medical Information form, which included information on his/her relationship to the child, guardian education level, socioeconomic data, and disease-specific questions. Demographic data and data on disease characteristics were collected for each child (Table 1). Children were asked to describe their symptoms in the previous 7 days (Table 2). Children at their initial presentation and with <14 days of therapy before enrollment were defined as having “incident” disease; the remaining patients were classified as having “prevalent” disease. For the sub-class analysis, the prevalent patients were then classified as into those with infrequently relapsing steroid-responsive disease, frequently relapsing steroid-responsive disease, steroid-dependent disease, and steroid-resistant disease [1]. Children that were never edematous were classified as never relapsed. The glomerular filtration rate (GFR) was estimated by the new Chronic Kidney Disease in Children (CKiD) equation [19].

The PROMIS pediatric measures include the domains of depression, anxiety, social-peer relationships, pain interference, fatigue, and mobility. We used the PROMIS Assessment Center web-based interface (www.assessmentcenter.net) to administer the questionnaires. Each PROMIS question used the context statement “In the past 7 days.” Responses included five options ranging from “never” to “almost always” in the majority of domains, and from “with no trouble” to “not able to do” for the physical functioning measures (Electronic Supplementary Material 1). Each PROMIS pediatric measure generates a *t* score relative to a mean of 50 and a standard deviation (SD) of 10 in the original PROMIS-I calibration population that included both children with disease and healthy children [6]. Higher scores indicate higher levels of the domain consistent with the measure’s name, thus signifying worse symptoms of depression, anxiety, fatigue, and pain interference and better functioning for mobility and peer relationships. The PROMIS instrument is designed for children to be able to answer five questions per minute. The PROMIS pediatric measures have not been validated in healthy children, but such a study is currently underway.

The PedsQL is a legacy instrument designed to measure HRQOL in children. The instrument measures physical, emotional, social, school, and overall functioning. This instrument has been evaluated in healthy children and in multiple pediatric chronic

conditions including chronic kidney disease [17]. The PedsQL asks subjects to review statements and rate the degree that the subject has experienced that symptom in the past week. The domain scores result from the summation of problem frequency within each domain. Higher scores indicate better function, with a range of 0–100 and a SD of 15. The PedsQL instrument is designed for children to be able to complete the instrument in 10 min.

Statistical considerations

Descriptive statistics on key variables of interest were provided via proportions and means for the full cohort and by eligibility type. Medians were provided for non-normally distributed continuous variables. PedsQL scores were compared to a normative sample using independent sample *t* tests [18]. This was done separately for the full sample and for patients with incident and prevalent disease, respectively. The main outcome variables of interest were the 11 HRQOL measures. We began with a series of bivariate linear regression models for each outcome using the following covariates: sex, age, race, Hispanic ethnicity, obesity (body mass index>95th percentile), edema, number of symptoms, estimated (e)GFR [19], UPC ratio, serum albumin, hospitalization in the past 6 months, emergency room visit in the past 6 months, number of medications, and disease duration coded as incident versus prevalent. For each outcome, any factor that was a significant predictor at α=0.25 was included for multivariable backward selection steps. Variables were eliminated from the models in order of descending *p* value until all remaining variables were significant at α=0.05. Finally, we conducted two simultaneous multivariable linear regressions for PROMIS and PedsQL separately, where each covariate was simultaneously regressed on the six PROMIS domains and the four primary PedsQL domains. The same set of covariates was used in the backwards selection in Table 4 to achieve simpler models for better interpretation. Joint tests of significance for a covariate on all domains were performed using Wilks' Lambda statistic, which mitigates the inherent problem of multiple comparisons in the analysis of several separate outcomes. In a separate sensitivity analysis, we estimated the effect that steroid response pattern (infrequently relapsing steroid responsive, frequently relapsing steroid responsive, steroid dependent, steroid resistant, vs. never relapsed) had on PRO measures among prevalent patients.

We also explored the degree to which the PROMIS and PedsQL domains correlate with one another using Pearson correlation coefficients, with the expectation that similar domains across instruments (e.g., PROMIS: Mobility; PedsQL: Physical Functioning) would show a reasonable amount of correlation.

Results

Child demographic and disease characteristics are presented in Table 1. There were 127 children enrolled and included in the analysis. The study population included 60 and 67 patients with incident and prevalent NS, respectively. The median duration of disease for incident patients was 4 [interquartile range (IQR) 0, 11] days with a maximum of 31 days. Children with prevalent disease had a median disease duration of 73 (IQR 35, 126) months prior to enrollment. All prevalent patients had disease duration of >2 months, and 75 % had disease duration of >2 years. The disease characteristics of patients with prevalent NS

included: infrequently relapsing steroid-responsive disease (*N*=9), frequently relapsing steroid-responsive disease (*N*=17), steroid-dependent disease (*N*=24), steroid-resistant disease (*N*=9), never relapsed (*N*= 1), and unknown (*N*=7). Table 2 describes the patient-reported symptoms experienced by children. There were no significant differences in the types of symptoms reported between incident and prevalent patients, but patients with prevalent disease had more symptoms (p=0.04). There was no difference in the number of symptoms between sub-populations within the prevalent patient population (p>0.05).
Feasibility

Six children (5 %) had missing scores for at least one of the PROMIS domains and two (2 %) children had missing scores in the PedsQL. Sixteen children (13 %) skipped one or more PROMIS questions, and ten children (8 %) skipped one or more PedsQL questions. A missing value analysis showed that there was no pattern to the domains/questions missed by disease duration, age, sex, or race. Overall, the frequencies across the two instruments looked similar and missing scores were infrequent (the highest level of missingness was 3 for 3 items in PedsQL and 2 items in PROMIS).

PROMIS

Table 3 shows the unadjusted mean scores for the PROMIS and PedsQL measures in children with incident and prevalent NS at the enrollment visit. The PROMIS scores were significantly worse in prevalent patients compared to incident patients in the domains of pain interference ($p < 0.01$) and peer relationships (p=0.01). On multivariable analysis (Table 4) children with prevalent NS had on average a PROMIS pain interference score which was 5 points worse [standard error (SE) 2.0] than that of the incident patients (p= 0.02).

PedsQL

The PedsQL unadjusted scores were worse in children with prevalent versus incident NS for the social functioning (<0.01) and school functioning (p=0.03) measures. On multivariable modeling, the score for social functioning was about 10 points worse (SE 3.2) for children with prevalent NS versus those with incident NS.

Table 5 shows the scores for the PedsQL domains compared to the previously published normative data [18]. The entire patient population and patients with prevalent NS had significantly lower scores in all domains on the PedsQL when compared to the normative population. Incident patients had significantly lower scores in physical functioning, school functioning, and overall HRQOL than the normative patient population.

Disease characteristics impacting HRQOL

Multivariable modeling described several disease characteristics that adversely impact HRQOL (Table 4). The number of symptoms predicted worse scores for the PROMIS fatigue domain and the PedsQL school functioning measure. The number of medications predicted worse scores in the PROMIS peer relationships domain, the PedsQL overall HRQOL measure, and the PedsQL school functioning measure. Furthermore, higher levels of proteinuria predicted worse scores in the PROMIS mobility domain and PedsQL physical

functioning measure. Sensitivity analyses on patients with prevalent disease showed no difference in HRQOL by steroid response pattern in the univariate and multivariate analysis.

Simultaneous regression analysis showed that disease duration, edema, number of medications, UPC ratio and, to a lesser extent, sex and race were important predictors of overall PedsQL scores. An analogous analysis on the PROMIS domains revealed that number of medications, eGFR, and UPC ratios were strong predictors of HRQOL.

Comparison of PROMIS and PedsQL

Table 6 shows the results of the analysis of correlation among the PROMIS domains and the PedsQL measures. In evaluating similar domains there were strong correlations (correlation coefficient>0.5) between PROMIS mobility and PedsQL physical functioning, between PROMIS pain interference and PedsQL physical functioning, between PROMIS fatigue and PedsQL physical functioning, between PROMIS depression and PedsQL emotional functioning, and between PROMIS anxiety and PedsQL emotional functioning. There were moderate correlations (0.5≥ correlation coefficient>0.3) between PROMIS peer relationships and PedsQL social functioning and between PROMIS peer relationships and PedsQL school functioning.

Discussion

This report represents the largest and most comprehensive study to date evaluating HRQOL in school age children with active NS. We demonstrate that the PROMIS measures were able to detect a negative impact of disease duration on the HRQOL in children with active NS, showing that children with prevalent disease have a significantly worse HRQOL than those with incident disease. These findings were confirmed by the PedsQL measures. We also show that the HRQOL in this sample, as measured by the PedsQL, was impaired when compared to general pediatric (normative) populations. Furthermore, we demonstrate that the PedsQL and PROMIS instruments perform similarly, but with important differences.

In children with chronic illnesses, the focus of research and clinical assessment is frequently the impact of disease activity. The burden on HRQOL may be reflective not only of the current state of disease activity and treatment, but also of the cumulative psychosocial impact of the disease course, duration, and cumulative medication exposure. This may be particularly true with a disease process like NS that is unpredictable—showing a relapsing and remitting nature or manifesting as persistent and progressive disease requiring ongoing management, including medications, dietary restrictions, and laboratory assessments. In the adult literature, a recent study has demonstrated the negative impact of disease duration in NS on HRQOL [20]. By comparing children with incident NS to those with prevalent NS, we focused on evaluating the contribution of disease duration to HRQOL in pediatric NS. Our study is the first to demonstrate that disease duration negatively impacts HRQOL in children with active NS. Specifically, the bivariate analysis showed that PROMIS peer relationships and pain interference scores were worse in children with prevalent NS than in those with incident diseases. On multivariable analysis, prevalent disease continued to predict a worse score in the PROMIS pain interference domain. These findings show the

impact of disease duration on HRQOL and the ability of the PROMIS measures to detect this in children with active NS.

The impact of disease duration on HRQOL in children with active NS was confirmed by the concurrent findings of the legacy instrument (PedsQL). Specifically, on bivariate analysis, the PedsQL social and school functioning scores for the children with active NS were worse in those with prevalent NS than in those with incident NS. In multivariable analysis, prevalent disease continued to predict worse scores in PedsQL social functioning. One might postulate that the poorer HRQOL in the school and social functioning domains reported by patients with prevalent NS may in part reflect cumulative school absences. Unfortunately, this study did not capture school absences. The findings of poor HRQOL on the pain interference and psychosocial domains in the PROMIS and PedsQL may provide opportunities to measure and address the impact of disease and disease duration during clinical encounters.

The impact of NS on HRQOL in children has been reported in a number of studies [2–4]. An important limitation of the PROMIS measures are that there is currently no reference data on scores in a healthy pediatric patient population, but research evaluating this is currently ongoing. As a result, the PedsQL was utilized to compare the HRQOL in children with active NS to healthy general pediatric patients. The HRQOL within this sample was impaired when compared to general healthy pediatric (normative) populations as measured by the PedsQL (Table 5) [18]. This impairment was present in all domains in the entire study cohort, further demonstrating the pervasive impairments in HRQOL in the broadest pediatric NS patient population reported to date. Furthermore, the patterns of impairment were more impressive when the prevalent patient population was compared separately to the control population, with prevalent patients having significant burdens in all domains. Interestingly, children with incident NS did not demonstrate a significantly different HRQOL in the domains of emotional and social functioning when compared to healthy children, indicating that children with new onset disease continue to maintain pre-disease emotional and social functioning.

In evaluating the current study, it is of value to compare the current population to the previously published PROMIS I NS cohort [3]. An interesting finding in comparing the domain scores between the PROMIS I cohort and the current PROMIS II cohort, is that there were worse scores in four of the six domains in the present study. This likely reflects fundamental differences between the studies and the patient populations. In the present study, eligibility was dependent on the presence of active NS with proteinuria at the time of the initial assessment. In addition, the patient cohort of the present study had a higher rate of obesity and hospitalization in the 6 months prior to initial assessment than the PROMIS I sample. We have previously shown each of these factors to strongly impact HRQOL [3, 12]. Another potential and simpler explanation is that disease duration at enrollment was not measured in the PROMIS I cohort and that the differences seen may reflect this contribution of this factor. In PROMIS I we showed the impact of active edema on HRQOL in children with NS. Children with active edema demonstrated worse anxiety, pain interference, fatigue, and mobility scores compared to those without edema. Interestingly, in our current study, which includes only patients with significant proteinuria as an objective measure of disease

activity, edema does not parlay the same increased burden on HRQOL. The most obvious explanation for this would be that every participant in this PROMIS II study was required to have active NS (high-grade protein-uria, with or without edema). In aggregate, we postulate that the impact of NS on HRQOL is more complicated than simply the impairments associated with edema, rather they also reflect the impact of additional characteristics, such as disease duration, medication burden, number of relapses, among others.

PROMIS and PedsQL provide complementary HRQOL information on children's HRQOL. The addition of PROMIS to the HRQOL assessment armamentarium provides the clinician and researcher with a tool that is potentially more expansive, flexible, and precise. As part of the validation of PROMIS, it is important to compare PROMIS with the PedsQL measure in the same patient population. While the instruments were developed utilizing different methodologies, we hypothesized that they would show similar, but not identical findings for domains in common on the measures. To date, there has not been a study simultaneously describing the findings of the PedsQL and PROMIS measures in children with NS. We show that there is a correlation between the scores in similar domains in these measures (Table 6). The majority of domains we tested showed a strong correlation, with the strongest ones existing between the PedsQL emotional functioning domain and the PROMIS domains of depression and anxiety, as expected. The weakest correlation was found between the social function and school functioning domains of the PedsQL instrument and the peer relationships domain of the PROMIS instrument. We have shown that children demonstrated an increased burden of symptoms in similar domains for the PedsQL and the PROMIS instrument, but there remain important differences in the measures of the instruments that likely reflect their different methods of development.

The current study is limited by its cross-sectional nature. The longitudinal follow-up of this cohort is ongoing. The PROMIS pediatric measures are limited to children of ages 8–17 years, which likely explains the age distribution of the study participants. At the time of this study, only an English version and a school age self-report version of the PROMIS pediatric instrument were available. Consequently, the results of this study will be most applicable to English-speaking, school age children. Another limitation of the current study is that there were seven patients with unknown or incomplete steroid-response/disease status. Finally, this study does not address the potential distinct contributions of disease status and medication effects on pediatric HRQOL. Future studies will provide opportunities to address these important issues.

Conclusions

This study demonstrates that the duration of NS directly impacts several aspects of HRQOL. Children with prevalent disease reported poorer HRQOL in the domains of PROMIS peer relationships, PROMIS pain interference, PedsQL social functioning, and PedsQL school functioning scores when compared to children with incident disease. Furthermore, this study shows that the PROMIS and the PedsQL measures provide complementary results but that there remain important differences in the measures of the instruments that likely reflect their different content coverage.

The next steps in this investigation will be to evaluate the longitudinal responsiveness of the PROMIS measures to the change in disease status in children with NS and to develop and test interventions to specifically address the negative HRQOL impact of NS on children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics of the pediatric patients enrolled in the study

Demographic variables	All patients (*N*=127)	Patients with incident NS[a] (*N*=60)	Patients with prevalent NS[a] (*N*=67)	*p*
Age (years)				
8–12	67 (53)	23 (38)	44 (66)	<0.01
13–17	60 (47)	37 (62)	23 (34)	
Male	83 (65)	36 (60)	47 (70)	0.23
Race (*N* = 126)				
White	65 (52)	26 (44)	39 (59)	0.02
Black	36 (29)	18 (30)	18 (27)	
Asian	16 (13)	13 (22)	3 (5)	
Other	9 (7)	3 (5)	6 (9)	
Obese (*N* = 126)	44 (35)	18 (30)	26 (39)	0.30
Edema present	96 (76)	53 (88)	43 (64)	<0.01
Hypertension (*N* = 126)	53 (42)	25 (42)	28 (42)	0.93
Steroid treatment (*N* = 123)	73 (59)	19 (32)	54 (84)	<0.01
Number of symptoms	3 (2,6)	3 (1,5)	4 (2,6)	0.04
Emergency department visits (≥1 visit) (*N* = 124)	49 (40)	27 (46)	22 (34)	0.18
Hospitalizations within the last 6 months (*N* = 125)	57 (46)	34 (57)	23 (35)	0.02
Estimated GFR (mL/min/1.73 m^2) (*N* = 126)	111.3 (81.5, 133.7)	105.5 (76.9, 128.9)	115.0 (92.8, 142.9)	0.09
Urine protein:creatinine ratio (*N* = 110)	5.4 (2.3, 8.7)	6.6 (4.5, 9.6)	3.5 (1.7, 6.8)	<0.01
Albumin (*N* = 126)	2.3 (1.6,3.1)	1.9 (1.6, 2.7)	2.7 (1.7, 3.5)	<0.01
Months of steroid exposure[b]	23 (1, 51)	0 (0, 0.5)	25 (11, 58)	<0.01
Number of medications	2 (1, 4)	2 (1, 3)	3 (1, 6)	0.01

NS, Nephrotic syndrome; GFR, glomerular filtration rate

Data are reported as the number with the percentage (%) in parenthesis, or as the median with the interquartile range (IQR) in parenthesis (continuous variables), as appropriate

[a] Incident patients: children at their initial presentation and with <14 days of therapy before enrollment; prevalent patients: all other patients who were not incident patients

[b] Calculated from the 73 patients receiving steroid therapy at the visit (19 incident and 54 prevalent patients)

Table 2

Symptom burden during the previous 7 days

Symptoms	All patients	Patients with incident NS	Patients with prevalent NS	*p*
Acne	17 (13)	9 (15)	8 (12)	0.61
Behavioral changes	14 (11)	5 (8)	9 (13)	0.36
Mood	27 (21)	8 (13)	19 (28)	0.04
Cough	33 (26)	13 (22)	20 (30)	0.29
Swelling	47 (37)	19 (32)	28 (42)	0.24
Hunger	24 (19)	9 (15)	15 (22)	0.29
Insomnia	19 (15)	9 (15)	10 (15)	0.99
Stomach pain	43 (34)	17 (28)	26 (39)	0.21
Shortness of breath	13 (10)	9 (15)	4 (6)	0.09
Diarrhea	27 (21)	10 (17)	17 (25)	0.23
Nausea/vomiting	25 (20)	10 (17)	15 (22)	0.42
Weight gain	54 (43)	27 (45)	27 (40)	0.59
Total number of symptoms per patient	3 (2, 6)	3 (1, 5)	4 (2, 6)	0.04

Data for individual symptoms are reported as the number with the percentage (%) in parenthesis; data on total number of symptoms are presented as the median with the IQR in parenthesis

Table 3

Comparison of health-related quality of life in children with incident and prevalent nephrotic syndrome

Instrument domains	All	Patients with incident NS	Patients with prevalent NS	*p*
PROMIS				
Mobility	46.3±9.2	46.5±10.3	46.1±8.3	0.85
Depression	49.7±9.3	48.4±9.1	50.8±9.5	0.15
Anxiety	49.4±10.6	48.9±10.9	49.9±10.4	0.63
Fatigue	49.6±12.6	49.0±13.1	50.2±12.2	0.59
Peer relationships	48.6±10.6	51.2±10.2	46.4±10.6	0.01
Pain interference	49.7±11.1	46.6±11.3	52.3±10.3	<0.01
PedsQL				
Physical functioning	69.3±22.7	68.8±25.7	69.8±19.9	0.81
Emotional functioning	72.3±22.1	75.6±21.5	69.2±22.3	0.10
Social functioning	80.6±18.0	86.4±14.4	75.2±19.3	<0.01
School functioning	62.5±21.7	66.9±20.3	58.5±22.3	0.03
Overall HRQOL	71.0±17.0	73.7±17.8	68.6±16.0	0.09

PROMIS, Patient Reported Outcomes Measurement Information System®; PedsQL; PedsQL™ 4.0 Generic Core Scales Data presented as the mean±standard deviation (SD)

Table 4

Linear regression model

HRQOL assessment tools and domains/ variables	β (SE)	|d|	*p*
Patient reported outcomes measurement information system (PROMIS)			
Mobility			
Prevalent patients	−1.6 (1.8)	0.17	0.39
UPC ratio	−0.3 (0.1)		0.01
Depression			
Prevalent patients	2.4 (1.7)	0.26	0.16
Anxiety			
Prevalent patients	0.9 (1.9)	0.10	0.63
Fatigue			
Prevalent patients	0.6 (2.3)	0.02	0.80
Symptom number	0.9 (0.4)		0.05
Peer relationships			
Prevalent patients	−2.7 (2.0)	0.25	0.18
Age	0.8 (0.3)		0.02
Number of medications	−0.8 (0.4)		0.04
Pain interference			
Prevalent patients	4.7 (2.0)	0.42	0.02
Number of medications	0.7 (0.4)		0.07
PedsQL™ 4.0 Generic Core Scales (PedsQL)			
Physical functioning			
Prevalent patients	−1.0 (4.4)	0.04	0.83
Urine protein: creatinine	−0.8 (0.3)		0.01
Emotional functioning			
Prevalent patients	−5.9 (4.1)	0.27	0.15
Number of medications	−0.4 (0.8)		0.61
Social functioning			
Prevalent patients	−9.7 (3.2)	0.54	<0.01
Number of medications	−1.1 (0.6)		0.07
School functioning			
Prevalent patients	−4.2 (3.7)	0.19	0.26
Symptom number	−2.4 (0.7)		<0.01
Number of medications	−1.9 (0.7)		<0.01
Overall HRQOL			
Prevalent patients	−3.5 (3.1)	0.21	0.25
Number of medications	−1.2 (0.6)		0.05

SE, Standard error; HRQOL, health-related quality of life; BMI, body mass index; |d|, effect size

The following variables were considered in each model: sex, age, race, Hispanic ethnicity, obesity (BMI>95th percentile), hypertension, edema, number of symptoms, estimated (e)GFR, UPC ratio, serum albumin, hospitalization in the past 6 months, emergency room visit in the past 6 months, number of medications, steroid exposure, and disease duration coded as incident vs. prevalent

The following variables had no effect on HRQOL: gender, race, ethnicity, weight status, edema, hypertension, steroid treatment, hospital or emergency room visits in the past 6 months, height percentile, eGFR, albumin, and hemoglobin

Table 5

Comparison of PeDsQL scores between children with active nephrotic syndrome and normative children

Measures	All		Patients with incident NS		Patients with prevalent NS		Normative
	Mean (SD)	|d|	Mean (SD)	|d|	Mean (SD)	|d|	Mean (SD)
Physical functioning	69.3±22.7**	1.27	68.8±25.7**	1.30	69.8±19.9**	1.23	86.9±13.9
Emotional functioning	72.3±22.1**	0.32	75.6±21.5	0.14	69.2±22.3**	0.48	78.2±18.6
Social functioning	80.6±18.0*	0.20	86.4±14.4	0.14	75.2±19.3**	0.51	84.0±17.4
School functioning	62.5±21.7**	1.03	66.9±20.3**	0.77	58.5±22.3**	1.27	79.9±16.9
Overall HRQOL	71.0±17.0**	0.90	73.7±17.8**	0.69	68.6±16.0**	1.09	82.9±13.2

Data presented as the mean±standard deviation (SD)

* $p<0.05$ compared to normative population;

** $p<0.01$ compared to normative population

Table 6

Correlations between PROMIS and PedsQL measures

PROMIS domains	PedsQL™ 4.0 Generic Core Scales domains				
	Physical functioning	Emotional functioning	Social functioning	School functioning	Overall HRQOL
Mobility	0.57	0.29	0.35	0.41	0.52
Depression	−0.48	−0.69	−0.43	−0.49	−0.65
Anxiety	−0.49	−0.76	−0.36	−0.35	−0.62
Fatigue	−0.68	−0.62	−0.43	−0.58	−0.75
Peer relationships	0.20	0.27	0.41	0.31	0.34
Pain interference	−0.67	−0.64	−0.41	−0.62	−0.75

Patient reported outcomes measurement information system