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ORIGINAL ARTICLE

The longitudinal relationship between patient-reported outcomes and clinical characteristics among patients with focal segmental glomerulosclerosis in the Nephrotic Syndrome Study Network

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ABSTRACT

Background. Understanding the relationship between clinical and patient-reported outcomes (PROs) will help support clinical care and future clinical trial design of novel therapies for focal segmental glomerulosclerosis (FSGS).

Methods. FSGS patients ≥8 years of age enrolled in the Nephrotic Syndrome Study Network completed Patient-Reported Outcomes Measurement Information System PRO measures of health-related quality of life (HRQoL) (children: global health, mobility, fatigue, pain interference, depression, anxiety, stress and peer relationships; adults: physical functioning, fatigue, pain interference, sleep impairment, mental health, depression, anxiety and social satisfaction) at baseline and during longitudinal follow-up for a maximum of 5 years. Linear mixed-effects models were used to determine which demographic, clinical and laboratory features were associated with PROs for each of the eight children and eight adults studied.

Results. There were 45 children and 114 adult FSGS patients enrolled that had at least one PRO assessment and 519 patient visits. Multivariable analyses among children found that edema was associated with global health (−7.6 points, $P = 0.02$) and mobility (−4.2, $P = 0.02$), the number of reported symptoms was associated with worse depression (−2.7 per symptom, $P = 0.009$) and anxiety (−2.3, $P = 0.02$) and the number of emergency room (ER) visits in the prior 6 months was associated with worse mobility (−2.8 per visit, $P < 0.001$) and fatigue (−2.4, $P = 0.03$). Multivariable analyses among adults found the number of reported symptoms was associated with worse function in all eight PROMIS measures and the number of ER visits was associated with worse fatigue, pain interference, sleep impairment, depression, anxiety and social satisfaction. Laboratory markers of disease severity (i.e. proteinuria, estimated glomerular filtration rate and serum

albumin) did not predict PRO in multivariable analyses, with the single exception of complete remission and better pain interference scores among children (+9.3, P = 0.03).

Conclusions. PROs provide important information about HRQoL for persons with FSGS that is not captured solely by the examination of laboratory-based markers of disease. However, it is critical that instruments capture the patient experience and FSGS clinical trials may benefit from a disease-specific instrument more sensitive to within-patient changes.

Keywords: focal segmental glomerulosclerosis, nephrotic syndrome, patient-reported outcomes, PROMIS, prospective cohort study, proteinuria, remission

BACKGROUND

Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome, frequently chronic and progressive in nature, and accounts for ∼12% of children and 3% of adults with incident end-stage kidney disease in the USA [1]. Currently the most common initial therapy is high-dose glucocorticoids [2, 3]. Unfortunately, >70% of FSGS patients do not respond to glucocorticoid therapy and the prognosis is poor in these patients [4, 5]. Alternative immunosuppressive therapies for FSGS may improve disease control in 20–50% of the remaining patients, but ultimately the disease course is chronic. Furthermore, immunosuppressive therapies are frequently associated with adverse effects that compound disease-specific complications [6–8]. As with the management of any chronic disease, in order to provide the optimal care for each individual patient, it is critical to understand and characterize the impact of disease on the physical and psychosocial aspects of health-related quality of life (HRQoL). In order to begin to achieve this goal, a critical first step is to understand how HRQoL correlates with and diverges from biochemical markers of disease activity.

Reduction and control of proteinuria are widely regarded to be a major therapeutic goal in FSGS. Patients reaching either complete or partial remission of proteinuria within the first 4–8 months after kidney biopsy are significantly less likely to progress to kidney failure [9]. Early work utilizing patient-reported outcome (PRO) measures to evaluate HRQoL in children with nephrotic syndrome has suggested that the disease experience in nephrotic syndrome does not correlate entirely with the traditional markers of disease activity [10–12]. One interpretation of this finding is that the patient disease experience, such as physical limitations, missed school or work or psychological aspects of chronic disease are not captured by clinical laboratory values. A full understanding of this relationship is critical, as PRO measures represent an invaluable tool to optimize clinical care and enrich viable outcomes for clinical trials [11]. In the context of clinical trial design, it is important to understand the magnitude of change in HRQoL (as determined by PROs) in response to changes in disease activity and whether changes in HRQoL are distinct from changes in laboratory-based markers. To date, no study has systematically evaluated prospective clinical and laboratory features associated with HRQoL in children and adults with FSGS, which represents a critical step in the deployment of PROs into patient care and clinical research [11].

The goal of this project was to assess HRQoL in children and adults with FSGS and to identify key demographic, clinical and laboratory predictors of these important outcomes in children and adults. These associations are important because of the increased attention that is being given to changes in HRQoL in drug approval for rare diseases like FSGS with a large unmet clinical need.

MATERIALS AND METHODS

Study design and participants

The Nephrotic Syndrome Study Network (NEPTUNE) is an ongoing prospective observational cohort study of primary proteinuric kidney diseases launched in 2010. Patients were enrolled at the time of their first clinically indicated kidney biopsy [13]. For patients enrolled prior to 2014, inclusion criteria included a urine protein:creatinine ratio (UPCR) >0.5 g/g or 24-h urine total protein >0.5 g/day; from 2014 onward, the inclusion criteria were altered to a UPCR >1.5 g/g or 24-h urine total protein >1.5 g/day. All NEPTUNE subjects with FSGS who completed qualifying study visits by 23 May 2018 were included in these analyses.

As part of this study, NEPTUNE subjects undergo detailed clinical and laboratory phenotyping, including serial assessments of HRQoL using PROs. Data capture includes demographic information, clinical information of symptoms, diagnoses, physical examination, medications, laboratory values, collection of urine and blood biosamples, biopsy tissue, PROs, hospitalizations, emergency department visits and procedures. The study visit schedule includes a baseline assessment within 30 days of the kidney biopsy and follow-up visits every 4 months for the first year and every 6 months thereafter for a maximum of 5 years of follow-up [13]. Institutional review board approval for this study was obtained at all participating sites with appropriate consent and assent forms.

PROs

The Patient-Reported Outcomes Measurement Information System (PROMIS) was developed through a National Institutes of Health project that had the goal of improving the assessment of HRQoL across diseases [14]. In the first round of measure development, nine measures were developed. NEPTUNE used the following PROMIS measures for children 8–17 years of age: global health, fatigue, mobility, pain interference, anxiety, depression, stress and peer relationships. NEPTUNE used the following PROMIS measures for adults (≥18 years): physical functioning, fatigue, pain interference, sleep impairment, mental health, anxiety, depression and social relationships. While NEPTUNE enrolls FSGS patients of all ages, these analyses focused on patients with self-reported PROMIS assessments and thus are limited to patients ≥8 years of age during study participation.

PROMIS item banks were developed using an item response theory approach used to determine each item's discrimination and the level of PRO severity each item is measuring. 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 measures and from 'with no trouble' to 'not able to do' for the mobility measure. PROMIS

item bank scores range from 0 to 100. To aid interpretability in these analyses, we transformed PROMIS scores so that higher scores reflect better PROs for all measures.

Assessment of disease activity and severity

Proteinuria assessments in NEPTUNE are made from centrally collected and assayed urine samples. UPCR values at 24 h were used when available. If 24-h urine was not available, then spot urine was used instead. In all analyses, proteinuria remission is defined as complete remission (UPCR <0.3 g/g); partial remission (≥40% reduction in UPCR from baseline and UPCR between 0.3 and 1.5 g/g) and no response (did not meet either of the other criteria) [9]. This modified definition of partial remission was derived and validated in a recent study to define the optimal proteinuria thresholds in predicting long-term outcomes, where this novel definition performed slightly better than the conventional partial remission definition of ≥50% reduction in UPCR from baseline and baseline UPCR [15]. However, sensitivity analyses will consider the conventional partial remission definition as well.

Demographic characteristics examined as potential predictors of HRQoL included age, sex, race, ethnicity and socioeconomic status as assessed by education level. Education status was dichotomized as less than a college education versus college education and above. For all adult participants over the age of 24 years, the participant's education level was used; the highest parental education level was used for all participants under 24 years of age.

Clinical characteristics included edema (qualitative assessment by a clinician for any of the following: lower extremity, sacral or anasarca), number of symptoms reported (symptom questionnaire, including shortness of breath, swelling, fever, chest pain, foamy urine, diarrhea, nausea/vomiting and a free response for any additional symptoms), weight [categorized using body mass index (BMI) for adults and BMI percentile for children], short stature (based on height) and health care utilization in the past 6 months [collected number of emergency room (ER) visits, wellness visits, illness/injury visits and hospitalizations]. Body weight was categorized as follows: underweight = BMI <18.5 kg/m^2 in adults and BMI percentile <5th in children; overweight = BMI between 25 and 30 kg/m^2 in adults and BMI percentile between 90th and 95th in children; obese = BMI >30 kg/m^2 in adults and BMI percentile >95th in children. Short stature in children was defined as a height percentile <2.5% based on age and sex; among adults, short stature was a height <152 cm in females and <164 cm in males [16]. Medication burden was captured as the total number of medications the patient is currently taking and as exposure to immunosuppressive medication. Laboratory values included proteinuria (categorized as described above), serum albumin and estimated glomerular filtration rate (eGFR) calculated using the creatinine-based modified CKiD formula in children and Chronic Kidney Disease Epidemiology Collaboration equation in adults [17, 18].

Statistical analyses

Because there were different PRO instruments for children and adult participants, all analyses were stratified by child versus adult (8–17 versus ≥18 years). A linear mixed-effects model approach was used to evaluate the relationship between each PROMIS score and each predictor of interest in a series of unadjusted models. Random intercepts were fitted to account for the repeated measures within individuals. All variables with an unadjusted P-value <0.20 were tested in a backward multivariable model selection. Nonsignificant variables were removed in reverse order of P-value until all remaining variables in the model were significant at $P < 0.05$. All analyses were conducted in SAS version 9.4 (SAS, Cary, NC, USA).

RESULTS

Data availability and description

A total of 176 NEPTUNE FSGS subjects were included in this study (Figure 1). Five of these subjects were <8 years old and thus were not eligible to complete the PROMIS self-report. Of the remaining 171 subjects, 148 (87%) completed at least one PROMIS instrument and 23 (13%) did not. The baseline characteristics of the 148 with and 23 without PROMIS data were similar by age, race, ethnicity, baseline eGFR and UPCR, disease duration and immunosuppressive therapy exposure (Supplementary data, Table S1). Subjects who completed the PROMIS assessment had longer follow-up (median follow-up 43 versus 0 months; $P < 0.001$), were less likely to be female (39% versus 65%; $P = 0.002$) and were more likely to have edema (41% versus 22%; $P < 0.001$).

The baseline characteristics of the included 148 subjects are shown in Table 1 separated by children and adults. Subjects who reach the age of 18 years during follow-up may contribute to both the child and adult analyses, as they completed the child instrument until the age of 18 years and the adult instrument afterward. There were a total 45 children and 114 adults (112 child and 407 adult observations, respectively), which includes 11 subjects contributing to both the child and adult analyses. Children were more likely to be treated with immunosuppression at baseline (58% versus 23%; $P < 0.001$), more likely to be female (53% versus 31%; $P = 0.008$) and had better-preserved kidney function at baseline (median eGFR 100 versus 58 mL/min/1.73 m^2; $P < 0.001$). Participants completed a median of 4 assessments [interquartile range (IQR) =2 to 4].

The distributions of all scores across all visits are shown in Figure 2. The majority of measures had mean values close to 50 and standard deviations near 10. In general, 10–20% of observations were <40 (i.e. >1 SD less than the mean) and 10–20% were >60 (domain-specific details in Supplementary data, Table S2).

PROMIS scores across all visits by proteinuria remission status are shown in Table 2 for children and adults. Among child visits, 25 were for children in complete remission, 16 in partial remission and 71 in no remission. There were significant unadjusted differences by remission status in pain interference (median complete remission 60.6 versus partial remission 43.8 versus no remission 48.2; $P = 0.014$) and anxiety (median complete remission 61.8 versus partial remission 66.5 versus no remission 58.0; $P = 0.001$), but subject-visit sample sizes were small in the pediatric cohort. Adult analyses included 89 visits for adults that were in complete remission, 57 in partial remission and 261 in no remission. In the adult unadjusted analyses, complete remission was associated with better fatigue, mental health, anxiety and social satisfaction. Partial remission was associated with higher mental health scores compared with no remission (median 50.5 versus 45.7) but was associated with similar fatigue (median 49.8 versus 49.3), anxiety (48.1 versus 48.8) and social satisfaction (51.6 versus 50.9) despite complete remission being associated with higher scores for these measures.

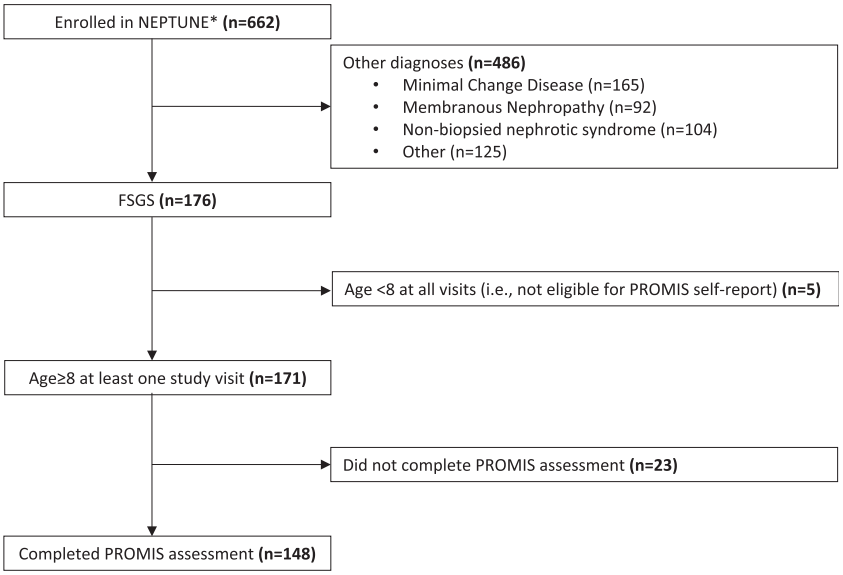

FIGURE 1: Flow diagram of included patients.

Table 1. Characteristics of NEPTUNE FSGS subjects who completed at least one PROMIS assessment

Characteristics	All subjects ($n = 148$)[a]	Children ($n = 45$)	Adults ($n = 114$)	P-value
Age (years), median (IQR)	33 (16–52)	13 (11–15)	43 (28–55)	<0.001
Age at disease onset (years), median (IQR)	29 (14–47)	12 (6–14)	38 (26–52)	<0.001
Female, *n* (%)	57 (38.5)	24 (53.3)	35 (30.7)	0.008
Race, *n* (%)				0.07
White or Caucasian	78 (52.7)	18 (40.0)	63 (55.3)	–
Black or African American	48 (32.4)	21 (46.7)	35 (30.7)	–
Other	17 (11.5)	3 (6.7)	14 (12.3)	–
Unknown	5 (3.4)	3 (6.7)	2 (1.8)	–
Hispanic ethnicity, *n* (%)	29 (19.6)	11 (24.4)	19 (16.7)	0.40
eGFR (mL/min/1.73 m^2), median (IQR)	71 (48–100)	100 (71–115)	58 (42–91)	<0.001
<30	14 (9.5)	0 (0%)	14 (12.3)	–
30–59	48 (32.4)	5 (11.1)	45 (39.5)	–
60–90	35 (23.6)	15 (33.3)	24 (21.1)	–
>90	50 (33.8)	24 (53.3)	31 (27.2)	–
Unknown	1 (0.7)	1 (2.2)	0 (0%)	–
UPCR (g/g), median (IQR)	2.3 (1.0–4.7)	3.4 (1.2–7.7)	2.3 (1.0–3.6)	0.03
Edema, *n* (%)	60 (40.5)	20 (44.4)	44 (38.6)	0.50
Weight, *n* (%)				0.98
Underweight	3 (2.0)	1 (2.2)	2 (1.8)	–
Normal weight	35 (23.6)	12 (26.7)	28 (24.6)	–
Overweight	40 (27.0)	12 (26.7)	29 (25.4)	–
Obese	70 (47.3)	20 (44.4)	55 (48.2)	–
Follow-up (months), median (IQR)	43 (19–56)	44 (24–57)	44 (20–56)	0.50
Disease duration (months), median (IQR), months	4 (1–30)	2 (1–18)	4 (1–29)	0.44
On IST at baseline, *n* (%)	46 (31.1)	26 (57.8)	26 (22.8)	<0.001

[a]Due to the longitudinal data collection with separate child and adult instruments, it is possible for patients to contribute to both the child and adult strata. There are 11 patients with both child and adult data.

IQR: interquartile range; IST: immunosuppressive therapy; underweight: BMI <18.5 in adults and BMI percentile <5th in children; overweight: BMI between 25 and 50 in adults and BMI percentile between 90th and 95th in children; obese: BMI >30 in adults and BMI percentile >95th in children.

Regression analyses

Unadjusted linear mixed effects models were completed for all 16 PROMIS PRO measures and all 19 predictors of interest. All unadjusted results are shown in Supplementary data, Tables S4–S19, and are summarized in Supplementary data, Figure S1. Cells highlighted in red indicate variables that were statistically significant unadjusted predictors of PRO scores ($P < 0.05$); cells in orange are predictors that were not significant in unadjusted models but were tested in multivariable model selection ($P \geq 0.05$–<0.20). The number of symptoms was a significant unadjusted predictor of all adult measures and four of eight child measures (and was included in model building for two

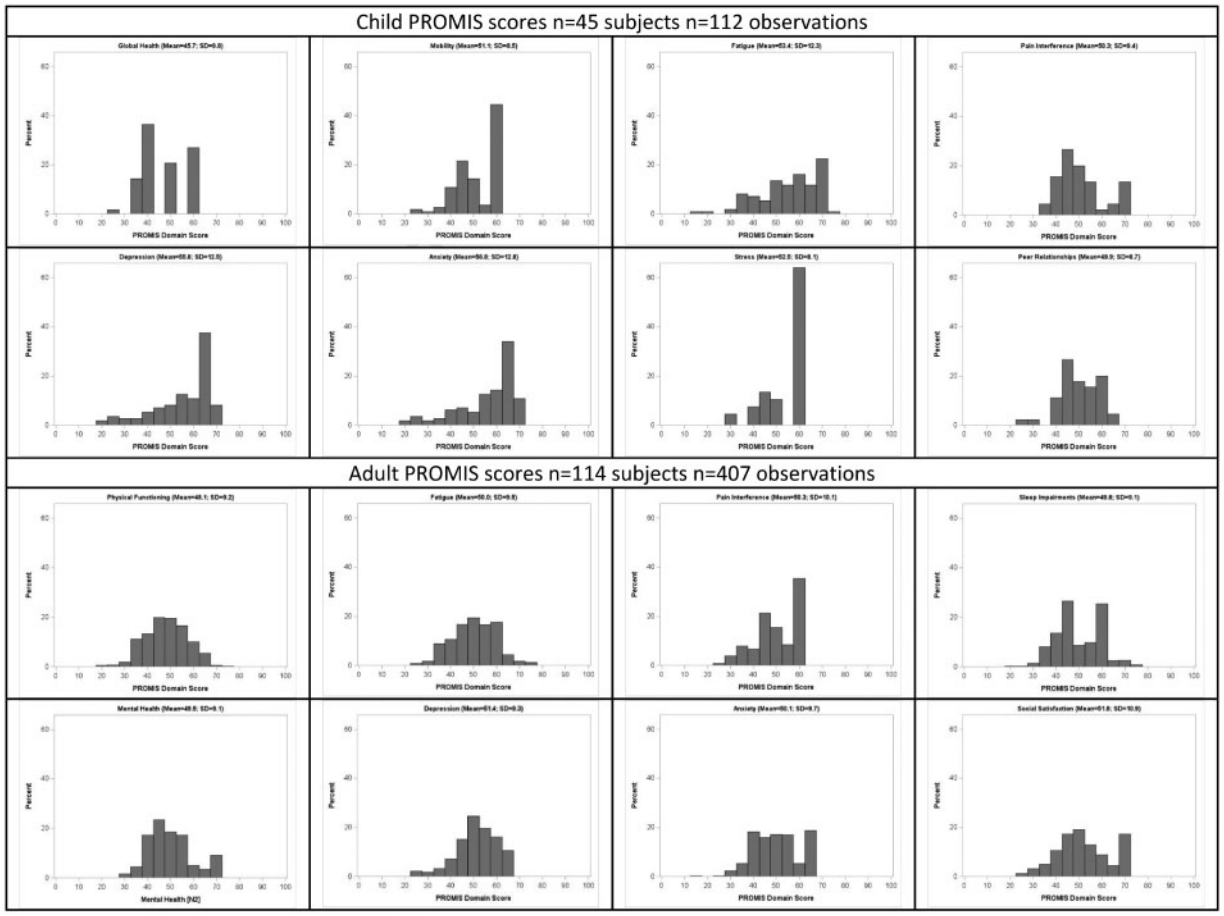

FIGURE 2: Distributions of PROMIS domain scores across all visits. Scores are transformed so that higher scores equal a better PRO.

Table 2. PROMIS domain scores by proteinuria remission status

Child PROMIS scores ($n = 45$ subjects, $n = 112$ observations)				
PROMIS measure	Complete remission ($n = 25$)	Partial remission ($n = 16$)[a]	No remission ($n = 71$)	P-value*
Global health	48.6 (40.0–59.3)	32.5 (32.5–48.6)	40.0 (40.0–59.3)	0.25
Mobility	58.5 (48.5–58.5)	58.0 (44.6–58.5)	50.0 (43.5–58.5)	0.18
Fatigue	60.4 (49.9–64.9)	59.7 (50.2–69.7)	54.4 (44.0–66.5)	0.46
Pain interference	60.6 (51.5–67.8)	43.8 (41.7–46.2)	48.2 (44.7–54.1)	0.01
Depression	64.8 (55.9–64.8)	64.8 (57.3–64.8)	55.9 (46.5–64.8)	0.06
Anxiety	61.8 (55.8–66.5)	66.5 (65.8–67.6)	58.0 (46.0–66.5)	0.001
Stress	58.0 (49.2–58.0)	58.0 (43.3–58.0)	58.0 (43.3–58.0)	0.90
Peer relationships	48.7 (40.9–58.1)	51.6 (46.4–54.2)	50.3 (44.2–57.9)	0.99
Adult PROMIS scores ($n = 114$ subjects, $n = 407$ observations)				
PROMIS measure	Complete remission ($n = 89$)	Partial remission ($n = 57$)[a]	No remission ($n = 261$)	P-value*
Physical functioning	49.8 (43.2–55.2)	49.8 (40.6–56.0)	47.4 (40.6–54.6)	0.13
Fatigue	53.4 (46.9–59.3)	49.8 (41.6–58.6)	49.3 (42.5–55.0)	<0.001
Pain interference	48.0 (42.7–61.4)	49.9 (44.0–61.4)	49.9 (44.0–61.4)	0.99
Sleep-related impairment	49.8 (47.1–57.7)	48.7 (45.7–57.7)	47.1 (41.9–57.7)	0.07
Mental health	50.7 (43.9–56.8)	50.5 (43.6–60.0)	45.7 (42.0–53.1)	0.04
Depression	54.4 (48.7–56.7)	56.4 (49.0–58.3)	51.3 (45.0–57.4)	0.10
Anxiety	54.6 (46.5–63.7)	49.1 (42.0–63.7)	48.8 (41.5–55.7)	<0.001
Social satisfaction	54.2 (50.0–67.8)	51.6 (44.7–67.8)	50.9 (43.4–58.8)	0.03

Scores are transformed so that higher scores equal a better PRO. Scores are presented as medians and interquartile ranges

[a]UPCR <1.5 g/g and 40% reduction in UPCR from baseline.

*Kruskall–Wallis test.

Table 3. Final adjusted mixed effects model for clinical and laboratory predictors of HRQoL domains among children

Characteristics	β (95% CI)	P-value
Global health		
Edema	−7.6 (−13.8 to −1.5)	0.02
Mobility		
Edema	−4.2 (−7.7 to −0.8)	0.02
Number of ER visits in past 6 months	−2.8 (−4.2 to −1.4)	0.0002
Fatigue		
Age (per year)	−1.0 (−1.9 to −0.1)	0.04
Number of ER visits in past 6 months	−2.4 (−4.6 to −0.3)	0.03
Number of medications	−1.1 (−1.8 to −0.3)	0.006
Pain interference		
Proteinuria	–	0.02
Partial remission	−6.0 (−14.1–2.1)	0.13
Complete remission	9.3 (1.2–17.4)	0.03
No remission	Ref	Ref
Depression		
Number of symptoms	−2.7 (−4.7 to −0.7)	0.009
Anxiety		
Number of symptoms	−2.3 (−4.2 to −0.3)	0.02
Stress		
On RAAS blockade	−4.4 (−8.6 to −0.2)	0.04
Peer relationships		
No predictors	–	–

Scores are transformed so that higher scores equal a better PRO.
β: linear regression coefficient (i.e. difference in group means); CI: confidence interval; REF: reference; underweight: BMI <18.5 in adults and BMI percentile <5th in children; overweight: BMI between 25 and 50 in adults and BMI percentile between 90th and 95th in children; obese: BMI >30 in adults and BMI percentile >95th in children.

additional measures). The number of ER visits entered model selection for 13 measures. Other consistent predictors of PROs included edema (which entered 11), number of medications (entered 10), serum albumin (entered 10) and number of hospitalizations (entered 9).

The results of final multivariable models are shown in Tables 3 and 4 for children and adults, respectively. Some indicators of more severe FSGS disease activity, namely edema, symptom number and number of ER visits, were associated with lower PRO scores. Among children (Table 3), edema was associated with worse global health (β = −7.6, P = 0.02) and mobility (β = −2.8, P = 0.0002). The number of symptoms was associated with worse depression (β = −2.7 per symptom, P = 0.009) and anxiety (β = −2.3 per symptom, P = 0.02) and the number of ER visits in the past 6 months was associated with worse mobility (β = −2.8 per visit, P = 0.0002) and fatigue (β = −2.4 per visit, P = 0.03). Complete, but not partial, remission was associated with better pain interference scores (β = 9.3, P = 0.03). Finally, an increased number of medications (β = −1.1 per medication, P = 0.006) and older age (β = −1.0 per year, P = 0.04) was associated with worse fatigue and renin–angiotensin–aldosterone system blockade therapy with worse stress (β = −4.4, P = 0.04).

As shown in Table 4, the number of symptoms was retained as a significant predictor in each of the eight adult final models, with effect size estimates ranging from −0.9 to −1.5 per symptom. The number of ER visits was associated with worse fatigue, pain interference, sleep impairment, depression, anxiety and social satisfaction (effect size estimates per symptom ranging from −1.3 to −1.6). Higher education level was consistently associated with better scores for physical functioning, fatigue, pain interference, mental health and social satisfaction (effect size estimates ranging from 3.1 to 5.0). The number of medications was associated with worse anxiety (β = −0.3 per medication, P = 0.009) and social satisfaction (β = −0.3 per medication, P = 0.02); weight status, particularly being severely obese, was associated with worse physical functioning (β = −4.9, P = 0.001) and depression scores (β = −3.2, P = 0.004) and diuretics with worse mental health (β = −3.3, P = 0.03).

Complete remission was associated with better pain interference scores among children but was not retained in any of the final adult models. Sensitivity analyses tested for differences when using the conventional partial remission definition of ≥50% reduction in UPCR from baseline and UPCR between 0.3 and 3.5 g/g. PROMIS scores by visit are shown in Supplementary data, Table S3. Unadjusted differences for child, anxiety, adult, fatigue, mental health, anxiety and social satisfaction were retained. Conventional and novel remission status were 94% concordant. In this sensitivity analysis, remission status was the sole predictor of child pain interference after multivariable adjustment: complete remission was associated with a 10.0 improvement in score versus no remission (95% confidence interval 1.59–18.3); there was no difference between partial and no remission, as was found using the modified proteinuria remission definition.

DISCUSSION

This study examined the longitudinal relationship between a number of demographic and clinical characteristics of disease activity and HRQoL in 148 patients with FSGS. In general, the strongest and most consistent predictors of HRQoL were symptom burden (measured by the total number of symptoms or presence of edema) and health care utilization (measured by the number of ER visits). Although proteinuria reduction is used as the primary endpoint in most clinical trials of FSGS, proteinuria remission was only significantly associated with pain in children and was not associated with any aspect of self-reported HRQoL in adults. These findings suggest that laboratory-based values, such as proteinuria and eGFR, are not strongly associated with the day-to-day patient disease experience. As such, the inclusion of PROs that evaluate HRQoL offers an opportunity to understand unique aspects of the disease experience that may help optimize clinical care and clinical trials for patients with FSGS.

These findings are consistent with the previous assessment examining the association between changes in self-reported HRQoL and changes in disease status among a cohort of children with nephrotic syndrome (though not necessarily FSGS) [19]. In a cross-sectional analysis of 151 children with nephrotic syndrome (66 specifically with FSGS), children with active edema had significantly worse mobility, fatigue, pain interference and anxiety when compared with children with no edema [20]. A higher degree of pain interference was also observed among patients with a longer duration of active disease [21]. In a longitudinal analysis of PROMIS in 127 children with nephrotic syndrome (16 specifically with FSGS), remission of proteinuria was not associated with changes in PROMIS mobility, fatigue, pain interference, depression or anxiety [11]. Previous cross-sectional analyses among children have shown cross-sectional relationships with both proteinuria and PROMIS measures and edema and PROMIS measures, with a stronger relationship found for edema [12, 22]. Edema and the number of symptoms were also the strongest cross-sectional predictors of HRQoL in a

Table 4. Final adjusted mixed effects model for clinical and laboratory predictors of HRQoL domains among adults

	β (95% CI)	P-value
Physical functioning		
College education	3.2 (0.4–6.0)	0.03
Number of symptoms	−1.0 (−1.5 to −0.5)	0.0002
Weight		0.001
Underweight	−6.3 (−11.4 to −1.2)	
Overweight	−2.8 (−5.3 to −0.2)	
Obese	−4.9 (−7.7 to −2.1)	
Severe obesity	−6.4 (−10.1 to −2.7)	
Normal weight	Ref	Ref
Number of illness/injury visits in past 6 months	−0.1 (−0.2 to −0.1)	0.01
Fatigue		
Female versus male	−4.6 (−7.8 to −1.3)	0.006
College education	3.1 (0.1–6.2)	0.04
Number of symptoms	−1.2 (−1.8 to −0.6)	<0.0001
Number of ER visits in past 6 months	−1.3 (−2.2 to −0.5)	0.002
Pain interference		
Age (per year)	−0.2 (−0.3 to −0.1)	0.01
College education	4.3 (0.2–8.3)	0.04
Number of symptoms	−1.2 (−2.1 to −0.4)	0.005
Number of ER visits in past 6 months	−1.6 (−2.8 to −0.3)	0.01
Sleep impairments		
Number of symptoms	−0.9 (−1.6 to −0.3)	0.005
Number of ER visits in past 6 months	−1.5 (−2.5 to −0.6)	0.001
Mental health		
College education	4.0 (0.3–7.7)	0.04
Number of symptoms	−1.5 (−2.7 to −0.4)	0.01
On diuretics	−3.3 (−6.2 to −0.4)	0.03
Depression		
Number of symptoms	−1.4 (−2.3 to −0.5)	0.002
Weight		0.004
Underweight	0.8 (−8.8–10.3)	
Overweight	−3.5 (−7.2–0.2)	
Obese	−3.2 (−7.4–0.9)	
Severe obesity	−11.6 (−17.4 to −5.8)	
Normal weight	Ref	Ref
Number of ER visits in past 6 months	−1.4 (−2.7 to −0.1)	0.04
Anxiety		
Number of symptoms	−1.4 (−2.1 to −0.6)	0.0003
Number of ER visits in past 6 months	−1.3 (−2.3 to −0.2)	0.02
Number of medications	−0.3 (−0.5 to −0.1)	0.009
Social satisfaction		
College education	5.0 (1.0–8.9)	0.01
Edema	−2.7 (−5.1 to −0.3)	0.02
Number of symptoms	−1.4 (−2.3 to −0.6)	0.001
Number of ER visits in past 6 months	−2.2 (−3.5 to −0.9)	0.0008
Number of medications	−0.3 (−0.6 to −0.1)	0.02

Scores are transformed so that higher scores equal a better PRO.
β: linear regression coefficient (i.e. difference in group means); CI: confidence interval; Ref: reference; underweight: BMI <18.5 in adults and BMI percentile <5th in children; overweight: BMI between 25 and 50 in adults and BMI percentile between 90th and 95th in children; obese: BMI >30 in adults and BMI percentile >95th in children.

large sample of children and adults with glomerular disease [22, 23].

One possible interpretation of these results is that changes in HRQoL simply are not as closely related to changes in laboratory markers such as proteinuria and that perhaps even an FSGS-specific PRO instrument would only correlate modestly with remission status or edema. It may be that improvements in laboratory markers, such as UPCR and eGFR, by themselves are not associated with drastic improvements in HRQoL if they are not accompanied by improvements in symptom management or adverse side effects of medications. Instead, changes in HRQoL are more accurately predicted by changes in symptom burden and health care utilization. If this interpretation is true, then this would still stress the importance of measuring PRO as a distinct outcome in clinical trials of novel therapies rather than assuming that improvements in proteinuria or eGFR are associated with better HRQoL. Clinical trials that focus on proteinuria reduction as the primary endpoint may not reflect what affects patients' HRQoL. As such, trials focusing on improving HRQoL as the primary outcome (or perhaps as a co-primary outcome) rather than proteinuria remission alone may be justified.

An alternative interpretation is that the PROMIS HRQoL measures do not adequately track FSGS- or nephrotic syndrome–related aspects of HRQoL. Developing a disease-specific instrument may be necessary to better detect within-patient changes associated with changes in proteinuria and immunosuppressive therapy use. PROMIS was developed to measure HRQoL concepts that were broadly applicable to persons with chronic health conditions. But the absence of a relationship with immunosuppressive therapy may suggest that these PROMIS measures do not ask the most relevant questions of patients with FSGS. Thus, while these instruments are able to distinguish between patients with a worse phenotype [12, 22], these instruments do not appear sensitive enough to detect more subtle within-patient changes in disease status, at least among patients with nephrotic syndrome [11]. However, as others have postulated, it could be possible that the null relationship with immunosuppressive therapy use could be due to counterbalancing negative and positive impacts on HRQoL, namely, negative impact from the well-known side effect profiles, positive impact from disease control and positive impact from optimism associated with a perceived treatment benefit [22].

While the PROMIS instrument may lack sufficient precision to serve as an outcome for a Phase 2 FSGS clinical trial, certain domains or uses may be more helpful as a clinical tool to track within-patient changes. Physical domains, such as fatigue, tend to have higher correlations with disease activity than mental health or social domains and may be more relevant to patients. The extreme ends of the PROMIS distributions might also be more informative. Distributions of scores in this study found subsets of patients with particularly high or low values. Clinical applications might simply indicate if a score is high or low if it is >1 standard deviation from the mean, instead of over-interpreting small continuous differences, and would identify patients with the strongest HRQoL impairments. Additionally, approaches that combine scores from multiple domains may be helpful. For example, among children and adults with nephrotic syndrome, latent profile analysis, a mixture modeling approach used to create categorical latent variables from observed continuous variables, has been used to stratify patients into distinct categories of good versus average versus poor HRQoL [24]. The same approach has been used in children with cancer [25]. This

type of latent variable approach would likely be not suitable for a clinical trial, but could be helpful in comprehensive patient management.

This study is not without limitations. The pediatric measures are limited to those 8–17 years of age and, at the time of data collection, only an English-language assessment was available and validated. Additionally, NEPTUNE FSGS enrollees entered at the time of the first kidney biopsy, and results might not generalize to patients with a long history of prevalent disease. Another limitation is the lack of a quantified assessment of edema severity [22]. Additionally, many patients presented with subnephrotic-range proteinuria, but findings may be different in a sample with more extreme proteinuria. Despite these limitations, this study adds value to the growing literature of PRO in patients with nephrotic syndrome and is the first longitudinal study of PRO in pediatric and adult FSGS patients.

Importantly, this study found that HRQoL is most strongly predicted by symptoms and health care utilization and not by laboratory-based markers of disease activity. At the very least, changes in proteinuria do not necessarily correspond to changes in HRQoL. Many patients see an improvement in proteinuria without an analogous improvement in HRQoL and vice versa. This study emphasizes the importance of studying clinical outcomes separately from patient-reported HRQoL. While proteinuria may serve as an early marker of progression to kidney disease [9], its relationship with PROMIS-based estimates of HRQoL is weak. Given the known side-effect burden of current immunosuppressive therapies used to treat FSGS, we recommend that disease-specific PROs be developed to incorporate patient-identified concepts. In addition, we recommend that clinical trials of novel therapies incorporate PROs as trial endpoints alongside proteinuria and kidney survival–based endpoints.

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AUTHORS' CONTRIBUTIONS

J.P.T. and D.S.G. conceived the overall research questions and approach for this subanalysis of the NEPTUNE study. J.P.T. and A.W. conducted the statistical analyses. N.E.C., S.M., F.M., H.T., P.H.N., K.J.R. and D.T.S. provided detailed advice on content and subject matter expertise during the analyses. S.M., F.M., H.T., P.H.N., K.J.R., D.T.S., E.G.H., T.S., K.V.L., G.A., J.S., K.M.D., L.A.G., C.-S.W., S.G.A., M.A.A., F.C.F., M.C.H., J.C.L., A.F., M.K., F.J.K., J.B.K., C.B.S., P.S., L.B.H., R.A.L., A.M.A., C.A.G., D.C.C., M.A.H., H.N.R., K.S., E.B., V.K.D., K.L.G.,

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Supplementary data are available at ckj online.

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