Kidney Medicine

Patient-Reported Outcomes Measures, Polycystic Kidney Disease Burden, and Outcomes in Autosomal Dominant Polycystic Kidney Disease

Dorothee Oberdhan, Aaron Yarlas, Jakob B. Bjorner, and Holly Krasa

Rationale & Objective: Using OVERTURE (NCT01430494) study data on patient-perceived health, health care utilization, and productivity in autosomal dominant polycystic kidney disease (ADPKD), this research was conducted to characterize the burden of illness in patients with ADPKD and assess whether patient-reported outcome (PRO) assessment scores predict clinical and health-economic outcomes.

Study Design: Data were analyzed from a prospective, observational study.

Setting & Participants: The study cohort comprised 3,409 individuals with ADPKD in 20 countries who were aged 12-78 years and were in chronic kidney disease (CKD) stages G1-G5 and Mayo risk subclasses 1A-1E.

Predictors: Scores on PRO instruments, including disease-specific assessments [ADPKD-Impact Scale (ADPKD-IS), and ADPKD-Urinary Impact Scale (ADPKD-UIS)] and generic measures were assessed.

Outcomes: Clinical variables [eg, height-adjusted total kidney volume (htTKV), estimated glomerular filtration rate (eGFR), and abdominal girth] and health-economic outcomes were assessed.

Analytical Approach: Associations among variables were evaluated using Spearman correlations, logistic regression, and generalized linear mixed effects repeated measures models.

Results: Baseline CKD stage and Mayo risk classification showed little correlation with baseline PRO scores; however, scores on disease-specific instruments and measures of physical functioning were worse at more severe CKD stages. PRO scores predicted hospitalizations and sick days at 6-18 months, with strongest associations noted for the ADPKD-IS. PRO scores were not associated with htTKV and eGFR, but worse PRO scores were associated with greater abdominal girth. Poor baseline ADPKD-IS scores were positively associated with occurrence of ADPKD-related symptoms up to 18 months, including kidney pain (OR, 5.30; 95% CI, 2.75-10.24), hematuria (OR, 4.58; 95% CI, 1.99-10.53), and urinary tract infection (OR, 4.41; 95% CI, 1.93-10.11; $P < 0.001$ for all).

Limitations: A limitation of the study was the maximum 18 months of follow-up available to assess outcomes.

Conclusions: PRO scores predicted clinical and health-economic outcomes, such as hospitalization and absence from work, underscoring the importance of quality of life assessment of individuals with ADPKD.

Complete author and article information provided before references.

Correspondence to D. Oberdhan (dorothee.oberdhan@otsuka-us.com)

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In autosomal dominant polycystic kidney disease (ADPKD), the formation and growth of fluid-filled cysts causes increased kidney volume and gradual loss of kidney function. Disease progression is associated with burdensome and anxiety-inducing symptoms, such as kidney pain, gross hematuria, and urinary tract infection, as well as systemic complications, such as hypertension.[1] In advanced disease, patients experience severe chronic kidney disease (CKD) and, ultimately, kidney failure.[2,3] The age of symptom onset differs among individuals given that ADPKD has a highly variable rate of progression.[4] Although most patients do not experience symptoms until the third or fourth decade of life, a small proportion (2%-5%) already present overt disease during childhood.[5,6] Individuals with ADPKD thus face a multidimensional and often lifelong disease impact. Symptoms related to kidney enlargement can be severe and may lead to limitations in physical activity, work productivity, and social interaction.[2,7,8] The knowledge of having a progressive yet unpredictable disease, including feelings of guilt or worry about the potential to pass on a hereditary condition, can exert psychological effects, including anxiety and depression.[7] Potential financial impacts include a decreased ability to work, the negative effects of a diagnosis on insurability, and the costs of medical care.[7,8]

Although the impacts of ADPKD increase as the disease progresses, the burden in patients with earlier stage disease can be substantial and is often underestimated and undertreated. This is in part because many patients do not report symptoms early in the disease.[9] Recognition of the importance of patient-centric outcomes in ADPKD has increased, and research has been conducted to better understand the patient's burden. Guidance from the Standardized Outcomes in Nephrology-Polycystic Kidney Disease (SONG-PKD) initiative includes patient-centric parameters as core outcomes for clinical research, particularly ADPKD-related pain.[9] Quality of life has been evaluated using generic measures in an observational study and early interventional trials, such as HALT-PKD and TEMPO 3:4.[10-12] More recently, disease-specific assessment

PLAIN-LANGUAGE SUMMARY

Patient-reported outcomes (PROs) are increasingly recognized as important parameters for assessing the clinical and humanistic burden of autosomal dominant polycystic kidney disease (ADPKD). We analyzed data from the observational OVERTURE study to better characterize disease impact on quality of life and determine whether patient-perceived burden might predict outcomes. Scores on PRO assessment instruments predicted hospitalizations and sick days at 6-18 months, with associations strongest for the disease-specific ADPKD-Impact Scale. Compared to patients who rated their health-related quality of life as good, those with poor baseline scores were significantly more likely to report ADPKD-related signs and symptoms up to 18 months of follow-up. These findings support using disease-specific PRO assessment instruments to assess and predict the impact of ADPKD.

instruments for patient-reported outcomes (PROs) in ADPKD have been developed and validated, including the ADPKD-Impact Scale (ADPKD-IS) for health-related quality of life (HRQoL) and overall disease burden and the ADPKD-Urinary Impact Scale (ADPKD-UIS) to evaluate urinary symptom burden specifically.[7,13] These instruments have been used in observational and interventional clinical trials.[7,14]

The observational OVERTURE study (NCT01430494) demonstrated the impact of total kidney volume (TKV) on multiple measures of patient physical and emotional burden, health care utilization, and productivity in a large prospective cohort. Greater TKV was indicative of worse patient-centric outcomes.[8] The primary objective of the current research, in which we conducted further analyses of PRO data from OVERTURE, was to better characterize the patient burden of ADPKD across the spectrum of disease. Another objective was to assess whether patient-perceived burden might predict the risk of adverse clinical outcomes.

METHODS

Design

This research consisted of analyses of data from a multicenter, longitudinal, observational study of participants with ADPKD (OVERTURE). The OVERTURE study included a worldwide population enrolled to assess rates and determinants of ADPKD progression and was conducted in 20 countries from June 2011 to October 2014. Study visits occurred at baseline; months 6, 12, and 18; and every 6 months thereafter up to 36 months. Participation declined over time, resulting in small sample sizes at later visits; therefore, only results through month 18 are reported here.

As part of the preplanned study assessments, participants were evaluated for PROs, as measured on multiple generic and disease-specific instruments, clinical ADPKD-related outcomes [eg, height-adjusted TKV (htTKV), estimated glomerular filtration rate (eGFR), and hypertension], and medical resource utilization. Data on associations of baseline TKV with clinical endpoints, medical resource utilization, employment status, and some PRO scores were reported previously.[8] In the secondary analyses presented here, PRO data were characterized in more detail and analyzed for associations with ADPKD-related outcomes. Specifically, PRO scores were evaluated for potential relationships with measures of disease progression (CKD stage) and progression risk (Mayo classification) at baseline as well as with longitudinal health-economic outcomes (health care utilization and work productivity) and ADPKD-related clinical variables (eg, htTKV, eGFR, abdominal girth). Patients with good versus poor HRQoL were compared for baseline clinical variables and ADPKD-related symptoms and conditions during follow-up.

Analysis Population

All OVERTURE participants for whom data were available were evaluated in the main analyses, which included analyses by subgroups defined according to CKD stage or risk of rapid progression (ie, Mayo risk subclasses 1A-1E).[15]

To determine whether PRO scores in early disease might predict clinical outcomes, subgroup analyses were conducted that compared patients in CKD stages G1 or G2 with either good or poor HRQoL at baseline. Good HRQoL was defined as a score ≤3 on all 3 subscales of the ADPKD-IS, and poor HRQoL defined as a score >3 on at least 2 of the 3 subscales of the ADPKD-IS.

Predictors and Outcomes

Instruments assessing disease-specific or generic HRQoL evaluated PROs. The ADPKD-IS comprises 18 questions and measures ADPKD-related symptom burden over the past 2 weeks in 3 domains (physical, emotional, and fatigue).[7] The ADPKD-UIS has 11 questions and evaluates ADPKD-related daytime urinary burden (urinary frequency and urinary urgency domains) and nighttime urinary burden (nocturia domain) over a 1-week recall period.[13] For the ADPKD-IS and ADPKD-UIS, each domain is scored from 1 to 5, with 1 indicating "not difficult at all" or "not bothered at all" and 5 indicating "extremely difficult" or "extremely bothered."

The Short Form 12-item Health Survey version 2 (SF-12v2) has 12 items and assesses generic HRQoL in the past month, yielding 2 summary scores, including the Physical Component Summary (PCS) and Mental Component Summary (MCS). PCS and MCS are presented as T scores, with 50 as the mean value for the US population based on the normative scoring algorithm and a standard deviation of 10 points; here, higher scores indicate better health.[16] The Brief Pain Inventory-Short Form (BPI-SF) has 9 questions assessing pain severity and the impact of pain on

daily functioning and well-being (ie, pain interference).[17] Assessment of pain severity includes pain at its worst, at its least, on average over the past 24 hours, and currently. Pain interference over the past 24 hours includes interference with general activity, mood, walking ability, normal work, relationships, sleep, and enjoyment of life. Each item is evaluated on an 11-point numeric rating scale ranging from 0 (no pain or does not interfere) to 10 (as bad as you can imagine or completely interferes), and the pain severity and pain interference subscales are scored as the average of constituent items. The EQ-5D-3L is a generic instrument that assesses 5 health dimensions: mobility, self-care, usual activities (work, study, housework, family, or leisure), pain or discomfort, and anxiety or depression.[18] The health states assessed using the EQ-5D can be expressed as a single summary number (index value) anchored by the values 0 (equivalent to death) and 1 (full health). Other values are based on utility weights for a specific country or region. Utility weights for the United States were used for this analysis.

The clinical variables assessed at baseline and/or during follow-up (months 6-18) included htTKV, eGFR, and abdominal girth. Health-economic variables of interest were measured over 6-18 months of follow-up and consisted of hospitalizations (0 vs ≥1), absenteeism (0 vs ≥1 sick days), and effectiveness at work (measured as the percentage of time participants reported that they were able to work effectively on days they worked with ADPKD symptoms). At each visit, a checklist captured the presence of numerous ADPKD-related symptoms, including kidney pain, hematuria, albuminuria, kidney stones, and urinary tract infection.

Statistical Analyses

Scores on PRO instruments were summarized descriptively for patients in different CKD stages and Mayo risk subclasses at baseline.[15] Associations at baseline between PRO scores and progression risk (defined by Mayo risk subclass; 1A and 1B are slow progressors; 1C, 1D, and 1E are rapid progressors) were assessed using Spearman correlation coefficients with 95% confidence intervals (CIs). PRO scores were compared between slower and rapid progressors at baseline using independent samples t tests to determine differences. Associations between PRO scores and binary health care utilization and employment outcomes were analyzed using logistic regression models with PRO measure, age, sex (female, male), and race included as predictors. Odds ratios (ORs) were calculated for each PRO measure. Associations between PRO data and key clinical variables (eg, htTKV, eGFR, abdominal girth) were evaluated using generalized linear mixed effects repeated measures models.

Values of clinical markers were compared between subgroups of early stage patients with good vs poor HRQoL at baseline using independent samples t tests and Cohen's effect sizes to characterize magnitudes of differences, and the presence of ADPKD-related symptoms and conditions between these subgroups was compared using ORs. No imputation of missing data was performed in the study analyses.

Ethical Conduct

This research was conducted according to principles originating in the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Consolidated Guideline, and the applicable local laws and regulatory requirements of each country. The study protocol was reviewed and approved by the governing institutional review board or independent ethics committee for each investigational site or country. Written informed consent was obtained from all participants (or their guardian or legal representative, as applicable according to local laws). Participants below the legal age of consent provided informed assent.

RESULTS

Analysis Population Characteristics and Baseline PRO Scores

The population in OVERTURE comprised 3,409 patients aged 12-78 years with a baseline CKD stage distribution as follows: G1, 990 patients (29%); G2, 956 patients (28%); G3, 899 patients (26%); G4, 351 patients (10%); and G5, 101 patients (3%). Approximately 3% of enrollees (n = 112) were missing CKD stage information at baseline or were not classified as G1-G5 (ie, dialysis or posttransplant). Participants in Mayo risk subclasses 1A-1E were enrolled: 203 participants (6%) in 1A; 834 participants (25%) in 1B; 1,180 participants (35%) in 1C; 680 participants (20%) in 1D; and 369 participants (11%) in 1E [for 143 participants (approximately 4%), Mayo risk classification was Type 2 or was not calculable].[8] Baseline clinical characteristics and PRO scores are shown in Table 1.

Baseline PRO scores exhibited a worsening trend in patients at later CKD stages on the ADPKD-IS, the SF-12v2 PCS, and the EQ-5D index; however, no such trend was observed for the ADPKD-UIS, the SF-12v2 MCS, or BPI-SF Pain Severity and Pain Interference (Fig 1). Correlations of PROs with progression risk did not exceed 0.3, indicating that progression risk is not an explanatory factor for quality of life or functional impact (Table 2). Mayo risk subclass at baseline exhibited no consistent relationship with PRO scores (Table 3). Rapid progressors (Mayo subclasses 1D-1E) had significantly worse indicators of mental health (ADPKD-IS Emotional and SF-12v2 Mental Health and MCS scores) and general health (SF-12v2 General Health score) compared to slow progressors (Mayo subclasses 1A-1B), whereas slow progressors had significantly worse pain scores (SF-12v2 Bodily Pain and BPI-SF Pain Severity scores) compared to rapid progressors. Plotting ADPKD-IS and BPI-SF scores

Table 1. Baseline Clinical Characteristics and PRO Scores of the Analysis Population

Characteristic or PRO Score	N	Mean (SD)	PRO Score	N	Mean (SD)
Female, n (%)	1,891 (55.5)		ADPKD-IS poor HRQoL subgroup[c]		
Age (y)	3,409	45 (13)	Physical	41	3.6 (0.7)
Abdominal girth (cm)	3,164	93 (15)	Emotional	41	3.6 (0.8)
Systolic BP (mm Hg)	3,387	130 (16)	Fatigue	41	4.0 (0.7)
Diastolic BP (mm Hg)	3,387	82 (11)	ADPKD-UIS		
BMI (kg/m^2)	3,372	26.6 (5.9)	Frequency	1,108	1.4 (0.7)
eGFR (mL/min/1.73 m^2)	3,319	69 (33)	Urgency	1,108	1.4 (0.7)
htTKV (mL/m)	3,305	995 (770)	Nocturia	1,108	1.9 (1.0)
SUN-to-creatinine ratio	3,332	0.1 (0.3)	BPI-SF		
Serum creatinine level (mg/dL)	3,319	1.45 (1.23)	Composite Pain Severity	2,480	1.0 (1.5)
Urine creatinine (mg/dL)	3,333	92.1 (59.9)	Pain Interference	2,480	0.9 (1.8)
Urine albumin concentration (mg/dL)	3,340	7.6 (22.6)	SF-12v2		
Urine albumin-to-creatinine ratio	3,333	26.4 (11.9-70.3)[a]	PCS	1,931	49.9 (9.7)
Urine osmolality (mOsm/kg)	3,326	458.7 (200.9)	MCS	1,931	50.2 (9.6)
			Physical Functioning	1,931	50.5 (9.6)
ADPKD-IS			Role Physical	1,931	49.8 (9.7)
Physical	1,108	1.6 (0.9)	Bodily Pain	1,931	50.9 (9.9)
Emotional	1,108	1.8 (0.9)	General Health	1,931	47.7 (9.9)
Fatigue	1,108	1.9 (1.1)	Vitality	1,931	51.5 (9.9)
ADPKD-IS Good HRQoL Subgroup[b]			Social Functioning	1,931	50.4 (9.1)
Physical	484	1.2 (0.4)	Role Emotional	1,931	48.6 (10.3)
Emotional	484	1.4 (0.5)	Mental Health	1,931	50.9 (9.5)
Fatigue	484	1.4 (0.6)	EQ-5D-3L Index US[d]	1,889	0.9 (0.1)

Note: N is the number of patients with data available for the characteristic.
Abbreviations: ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease-Impact Scale; ADPKD-UIS, Autosomal Dominant Polycystic Kidney Disease-Urinary Impact Scale; BMI, body mass index; BP, blood pressure; BPI-SF, Brief Pain Inventory-Short Form; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HRQoL, health-related quality of life; htTKV, height-adjusted total kidney volume; MCS, Mental Component Summary; PCS, Physical Component Summary; PRO; patient-reported outcome; SD, standard deviation; SF-12v2, Short Form 12-item Health Survey version 2; SUN, serum urea nitrogen.
[a]Urine albumin-to-creatinine ratio is reported as median (25th, 75th percentile).
[b]Defined as participants with a score ≤3 on all 3 ADPKD-IS subscales and in early stage CKD (G1 or G2).
[c]Defined as participants with a score >3 on at least 2 of the 3 ADPKD-IS subscales and in early stage CKD (G1 or G2).
[d]Scored using reference norms for the US population.

based on age and Mayo risk subclass (Fig S1) indicated that although most patients were not reporting high levels of HRQoL impact or pain, older age was associated with worse ADPKD-IS and BPI-SF scores in Mayo risk subclasses 1B-1E. No longitudinal worsening of PRO measures from baseline to month 18 was discernible for subgroups defined by CKD stage (Fig 1).

PRO Assessment Scores as Predictors of ADPKD Impacts

Patterns of association were observed in which PRO assessment scores representing poorer health predicted higher odds for experiencing a hospitalization (Fig 2). Associations were strongest for the ADPKD-IS, with the greatest association seen for the ADPKD-IS physical subscale. Pain and urinary symptoms were also associated with hospitalization. Subanalyses by sex indicated that the associations of the ADPKD-IS emotional subscale, ADPKD-UIS urgency subscale, and pain scores (BPI-SF severity and interference domains) with subsequent hospitalization were statistically significant for women but not for men (Table S1). Associations of PRO scores with subsequent sick days were present across PRO measures, and the strongest associations were noted for the ADPKD-IS physical subscale and the ADPKD-UIS urgency subscale (Fig 3). No sex differences in the associations were observed (Table S2).

Associations of PRO Assessment Scores With Key Clinical Variables

Analyses of relationships between PRO scores and htTKV, eGFR decline, and abdominal girth were conducted for participants within each baseline CKD stage. No consistent patterns were seen for relationships between PRO assessments and htTKV (whether as a baseline value or rate of growth during follow-up) or eGFR decline. Scores on most PRO instruments, however, had strong associations with baseline abdominal girth for patients in CKD stages G1 through G3B, with greater abdominal girth associated with worse HRQoL. In stage G4, the associations weakened, and the associations disappeared in stage G5 (Table S3). No consistent associations of PRO scores with rate of growth in abdominal girth were observed.

Stratified analyses of patients who did or did not experience ≥5% increase in htTKV during follow-up found that greater abdominal girth was associated with worse scores on the ADPKD-IS, ADPKD-UIS, BPI-SF, SF-12v2 PCS and MCS, and EQ-5D index in both

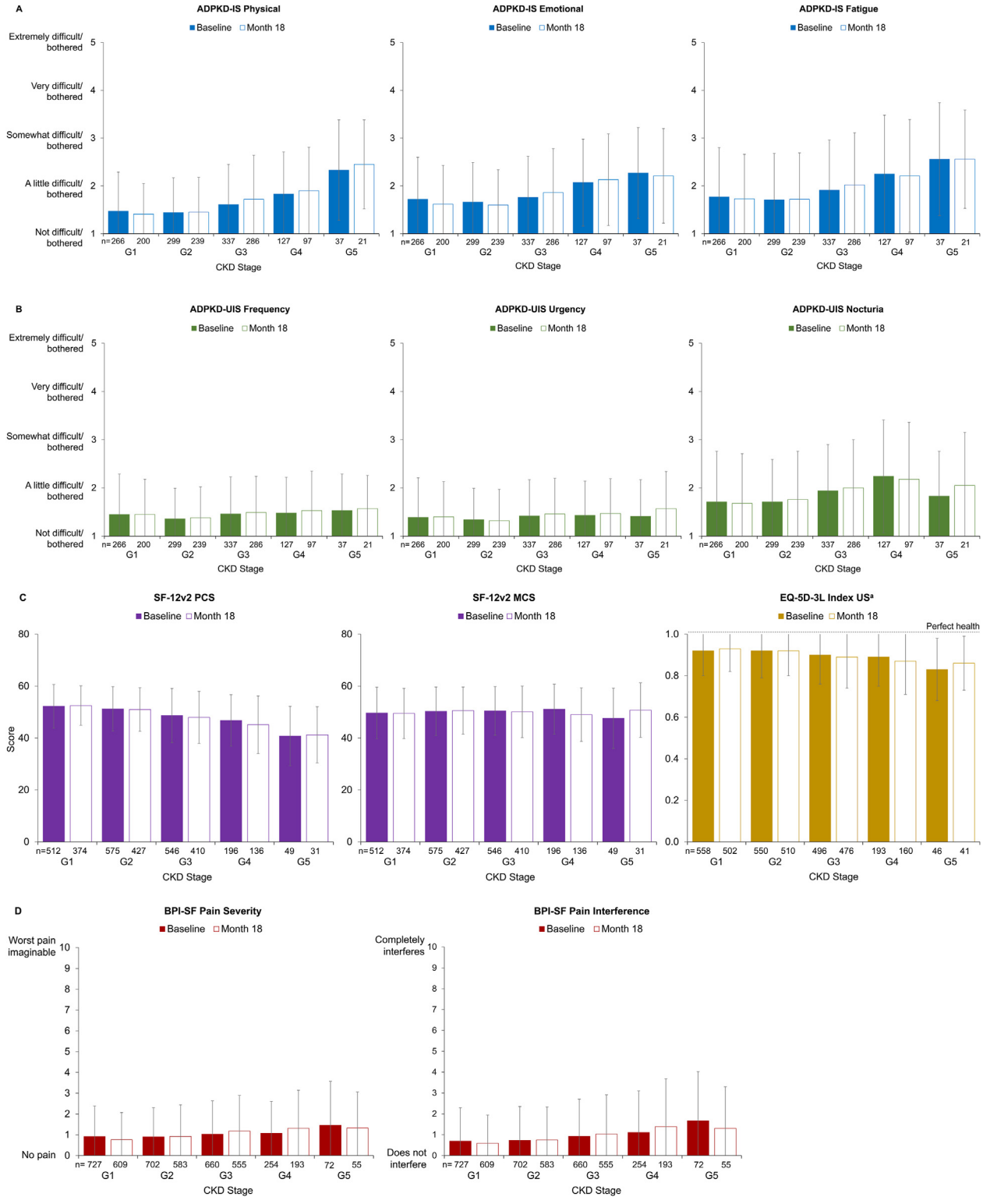

Figure 1. Patient-reported HRQoL scores [mean (SD)] based on baseline chronic kidney disease stage. Abbreviations: ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease-Impact Scale; ADPKD-UIS, Autosomal Dominant Polycystic Kidney Disease-Urinary Impact Scale; BPI-SF, Brief Pain Inventory-Short Form; HRQoL, health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; SD, standard deviation; SF-12v2, Short Form 12-item Health Survey version 2. [a]Scored using reference norms for the US population.

Table 2. Spearman Correlations Between Slow or Rapid Progression (Defined by Baseline CKD Stage with Mayo Risk Subclass) and PRO Scores

Instrument or Parameter	Domain or Outcome	CKD Stage with Mayo Imaging Subclass: Slow Progressor (Mayo Subclasses 1A and 1B)		CKD Stage with Mayo Imaging Subclass: Rapid Progressor (Mayo Subclasses 1C to 1E)	
		N	Correlation Coefficient (95% CI)	N	Correlation Coefficient (95% CI)
ADPKD-IS	Physical	403	0.14 (0.04 to 0.24)	646	0.27 (0.20 to 0.34)
	Emotional	403	0.05 (−0.05 to 0.14)	646	0.22 (0.15 to 0.29)
	Fatigue	403	0.13 (0.03 to 0.22)	646	0.21 (0.13 to 0.28)
ADPKD-UIS	Frequency	403	0.07 (−0.03 to 0.16)	646	0.06 (−0.02 to 0.14)
	Urgency	403	0.08 (−0.02 to 0.17)	646	0.05 (−0.02 to 0.13)
	Nocturia	403	0.19 (0.09 to 0.28)	646	0.17 (0.09 to 0.24)
SF-12v2	Physical Functioning	624	−0.15 (−0.23 to −0.07)	1,225	−0.25 (−0.31 to −0.20)
	Role Physical	624	−0.14 (−0.21 to −0.06)	1,225	−0.22 (−0.27 to −0.16)
	Bodily Pain	624	−0.009 (−0.09 to 0.07)	1,225	−0.13 (−0.18 to −0.07)
	General Health	624	−0.14 (−0.22 to −0.07)	1,225	−0.19 (−0.24 to −0.14)
	Vitality	624	−0.04 (−0.12 to 0.04)	1,225	−0.10 (−0.16 to −0.05)
	Social Functioning	624	−0.04 (−0.12 to 0.03)	1,225	−0.09 (−0.14 to −0.03)
	Role Emotional	624	−0.002 (−0.08 to 0.08)	1,225	−0.06 (−0.12 to −0.01)
	Mental Health	624	−0.006 (−0.08 to 0.07)	1,225	0.04 (−0.01 to 0.10)
	PCS	624	−0.15 (−0.23 to −0.07)	1,225	−0.28 (−0.33 to −0.23)
	MCS	624	0.04 (−0.04 to 0.11)	1,225	0.04 (−0.01 to 0.10)
EQ-5D-3L	Index (US)	602	−0.09 (−0.17 to −0.007)	1,220	−0.11 (−0.17 to −0.06)
BPI-SF	Pain Severity	759	0.03 (−0.04 to 0.10)	1,626	0.07 (0.02 to 0.11)
	Pain Interference	759	0.06 (−0.01 to 0.13)	1,626	0.13 (0.08 to 0.18)
Work Impact	Days Missed	617	−0.05 (−0.13 to 0.03)	1,525	0.04 (−0.01 to 0.09)
	Effectiveness	617	0.02 (−0.06 to 0.09)	1,525	−0.03 (−0.08 to 0.02)

Note: N is the number of patients with data available.
Abbreviations: ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease-Impact Scale; ADPKD-UIS, Autosomal Dominant Polycystic Kidney Disease-Urinary Impact Scale; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; CKD, chronic kidney disease; MCS, Mental Component Summary; PCS, Physical Component Summary; PRO; patient-reported outcome; SF-12v2, Short Form 12-item Health Survey version 2.

htTKV groups, indicating that greater abdominal girth is associated with poorer health and well-being (Table S4).

To further explore the impact of abdominal girth, an analysis of correlations between abdominal girth and htTKV, body mass index (BMI), and percentage weight gain from baseline was conducted (Table S5). Results indicated that abdominal girth was strongly correlated with BMI, moderately correlated with htTKV, and weakly correlated with weight gain.

Subgroup Analysis of Early Stage CKD (G1 or G2) Patients by Good Versus Poor HRQoL at Baseline

A subgroup analysis compared CKD G1 or G2 patients with good (n = 484) versus poor (n = 41) ADPKD-specific HRQoL at baseline. Baseline clinical characteristics of the 2 groups were largely indistinguishable (Table 4). With the exception of the serum urea nitrogen-to-creatinine ratio ($P = 0.04$) and the urine albumin-to-creatinine ratio ($P = 0.04$), all differences were statistically nonsignificant at $P > 0.05$, with small or trivial magnitudes (all effect sizes ≤ 0.34). However, those with poor HRQoL at baseline were significantly more likely to report ADPKD-related signs and symptoms up to 18 months of follow-up, especially those related to kidney pain and urinary disorders (ie, nephrolithiasis, hematuria, and urinary tract infection) compared with those with good HRQoL (Fig 4).

DISCUSSION

In this analysis of data from the prospective, observational OVERTURE study, measures of PROs identified the burden of ADPKD at baseline and in some cases differentiated patients by CKD stage. As reported previously, the disease-specific ADPKD-IS best captured differences in burden across CKD stages, with differences also evident on general HRQoL measures (SF-12v2 PCS and the EQ-5D index).[7] The present study supports nonlinear associations between CKD staging and PROs.[19] Specifically, minimal differences in PRO scores were noted among patients in earlier CKD stages, and not until CKD stages G4 or G5 did PRO measures substantially worsen (Fig 1).

Mayo risk classification, which is an estimate of risk for rapid future progression and not a categorization of disease stage, did not consistently correlate with either disease-specific or general HRQoL PRO scores. Age likely plays a confounding role. Among 2 patients at different ages but the same htTKV, the younger patient will fall into a worse

Table 3. Analysis of Baseline PRO Scores in Slow Versus Rapid Progressors as Defined by Mayo Risk Subclass

Instrument or Parameter	Domain or Outcome	Slow Progressor (Mayo Subclasses 1A and 1B)		Rapid Progressor (Mayo Subclasses 1C to 1E)		Mean Difference (95% CI)	*P* Value
		N	Mean (SD)	N	Mean (SD)		
ADPKD-IS	Physical	403	1.57 (0.87)	646	1.58 (0.83)	−0.02 (−0.12 to 0.09)	0.76
	Emotional	403	1.69 (0.87)	646	1.83 (0.89)	−0.15 (−0.26 to −0.04)	0.008
	Fatigue	403	1.82 (1.05)	646	1.92 (1.10)	−0.10 (−0.24 to 0.03)	0.12
ADPKD-UIS	Frequency	403	1.48 (0.83)	646	1.40 (0.69)	0.08 (−0.01 to 0.17)	0.08
	Urgency	403	1.44 (0.83)	646	1.36 (0.67)	0.09 (−0.01 to 0.18)	0.07
	Nocturia	403	1.85 (1.05)	646	1.83 (0.97)	0.02 (−0.11 to 0.14)	0.78
SF-12v2	Physical Functioning	624	50.04 (9.91)	1,225	50.91 (9.18)	−0.88 (−1.78 to 0.03)	0.06
	Role Physical	624	49.57 (9.71)	1,225	50.00 (9.48)	−0.43 (−1.35 to 0.49)	0.36
	Bodily Pain	624	50.31 (10.26)	1,225	51.30 (9.62)	−0.99 (−1.94 to −0.04)	0.04
	General Health	624	48.43 (9.77)	1,225	47.42 (9.86)	1.01 (0.06 to 1.95)	0.04
	Vitality	624	52.09 (9.92)	1,225	51.26 (9.75)	0.83 (−0.12 to 1.78)	0.09
	Social Functioning	624	50.81 (8.82)	1,225	50.22 (9.15)	0.59 (−0.29 to 1.46)	0.19
	Role Emotional	624	48.92 (10.05)	1,225	48.52 (10.31)	0.39 (−0.59 to 1.38)	0.43
	Mental Health	624	51.69 (9.28)	1,225	50.53 (9.48)	1.16 (0.25 to 2.06)	0.01
	PCS	624	49.46 (10.14)	1,225	50.36 (9.20)	−0.90 (−1.82 to 0.02)	0.06
	MCS	624	51.10 (9.51)	1,225	49.68 (9.57)	1.42 (0.50 to 2.34)	0.003
EQ-5D-3L	Index (US)[a]	602	0.91 (0.13)	1,220	0.91 (0.13)	0.001 (−0.01 to 0.01)	0.91
BPI-SF	Pain Severity	759	1.09 (1.63)	1,626	0.91 (1.45)	0.18 (0.05 to 0.31)	0.008
	Pain Interference	759	0.87 (1.75)	1,626	0.81 (1.72)	0.05 (−0.10 to 0.20)	0.50
Work Impact[b]	Days Missed	617	2.04 (10.45)	1,525	2.88 (14.99)	−0.84 (−2.13 to 0.47)	0.20
	Effectiveness	617	78.05 (39.09)	1,525	77.15 (38.70)	0.90 (−2.73 to 4.53)	0.63

Note: N is the number of patients with data available.
Abbreviations: ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease-Impact Scale; ADPKD-UIS, Autosomal Dominant Polycystic Kidney Disease-Urinary Impact Scale; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; MCS, Mental Component Summary; PCS, Physical Component Summary; PRO; patient-reported outcome; SD, standard deviation; SF-12v2, Short Form 12-item Health Survey version 2.
[a]Scored using reference norms for the US population.
[b]No baseline data available; 6-month data were used.

risk subclass than the older patient.[15] Age and Mayo risk subclass are thus inversely related. As shown previously in the OVERTURE dataset, among patients at the same CKD stage, a patient who is classified as Mayo subclass 1A (least risk) may be decades older than a patient in class 1E (greatest risk).[8] Although older patients in a lesser risk

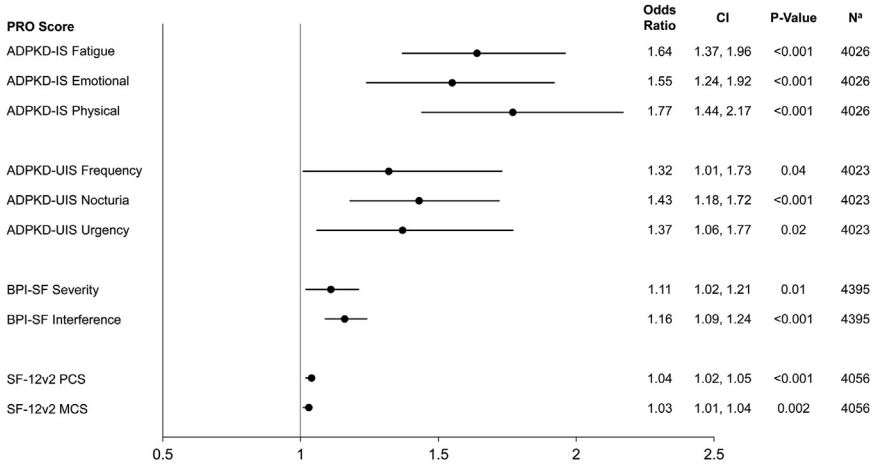

Figure 2. Odds ratios for PRO assessment scores predictive of hospitalization (0 vs ≥1 hospitalizations) over 6-18 months of follow-up. The direction of all associations is increased odds of hospitalization with worse PRO assessment scores (ie, higher scores on ADPKD-IS, ADPKD-UIS, and BPI-SF scales, lower scores on SF-12v2 scales). Abbreviations: ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease-Impact Scale; ADPKD-UIS, Autosomal Dominant Polycystic Kidney Disease-Urinary Impact Scale; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; MCS, Mental Component Summary; PCS, Physical Component Summary; PRO, patient-reported outcomes; SF-12v2, Short Form 12-item Health Survey version 2. [a]The number of assessments available for the PRO score during the follow-up period in participants with hospitalization data.

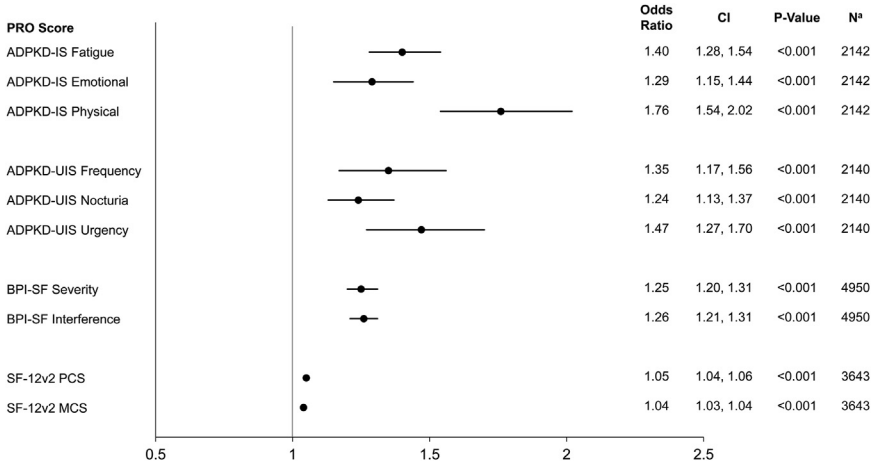

Figure 3. Odds ratios for PRO assessment scores predictive of sick days (0 vs ≥1 sick days) over 6-18 months of follow-up. The direction of all associations is increased odds of sick days with worse PRO assessment scores (ie, higher scores on ADPKD-IS, ADPKD-UIS, and BPI-SF scales, lower scores on SF-12v2 scales). Abbreviations: ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease-Impact Scale; ADPKD-UIS, Autosomal Dominant Polycystic Kidney Disease-Urinary Impact Scale; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; MCS, Mental Component Summary; PCS, Physical Component Summary; PRO, patient-reported outcomes; SF-12v2, Short Form 12-item Health Survey version 2. [a]The number of assessments available for the PRO score during the follow-up period in participants with sick day data.

subclass will have less ADPKD progression than younger patients in a worse risk subclass, patients in the former group may show worse scores given the negative relationship between age and most PRO scores.

Disease-specific PRO instruments predicted hospitalization and work absences. Measures of pain, urinary urgency or frequency, and disease-specific physical burden exhibited the strongest associations with medical resource utilization and impact on employment. These findings underscore the utility and importance of a disease-specific PRO measure in ADPKD, as instruments designed for kidney disease in general do not capture burden before end-stage kidney disease in ADPKD.[7]

In contrast to other key clinical variables, baseline abdominal girth exhibited strong relationships with some measures of PROs, supporting earlier research showing that patient perceptions about the body affect their understanding of their health and well-being.[7] However, there were no consistent associations between abdominal girth growth rate and PRO measures. Analyses of correlations with htTKV, BMI, and weight gain suggested that baseline abdominal girth is an indicator of kidney growth. The location of kidney cysts and presence of other complications, such as liver cysts and obesity, might account for the only moderate association of abdominal girth with htTKV. Abdominal girth correlates best with HRQoL measures that include assessment of physical function or interference with activities, suggesting the impact of body shape on the ability to perform certain activities of daily living.

Patient subgroups with preserved kidney function (CKD stage G1 or G2) with good versus poor HRQoL at baseline on the ADPKD-IS had generally similar baseline characteristics. Those with poor HRQoL did have a significantly higher mean serum urea nitrogen-to-creatinine ratio, which may reflect worse hydration status. Despite the baseline clinical similarity between groups, patients with poor HRQoL were significantly more likely to experience pain and urinary-related disorders at follow-up.

Regarding the SF-12v2, the OVERTURE cohort performed remarkably well, with scores meeting or exceeding the US population norm (50 points). Potential explanations include that approximately 60% of participants with SF-12v2 scores were classified as CKD stages G1 and G2, and 75% were classified as CKD stages G1-G3A. Given that CKD is progressive, most participants were younger, relatively asymptomatic, and possibly with minimal disease impact. Early stage patients are aware that they have a serious chronic condition. However, because they are asymptomatic, they might view what would be normal HRQoL as being above normal when taking into account their condition. Worse PCS scores with worsening CKD stage (and thus older age) were observed. Although older age is generally associated with decreased physical health (and so lower PCS scores), older age is associated with improved mental health.[20] This relationship was consistent with the absence of worse MCS scores by worsening CKD stage in the OVERTURE cohort.

No associations of BPI-SF Pain Severity and Pain Interference with CKD stage were evident. The recall period is "in the last 24 hours" or "right now," which may have resulted in most ADPKD-related pain events being missed, because visits occurred every 6 months. The BPI-SF may not be fit-for-purpose to assess pain in patients with ADPKD. Disease-specific assessments that account for types of pain specific to ADPKD are needed, and the development of measures is ongoing [eg, ADPKD Pain and Discomfort Scale (ADPKD-PDS)].[21]

Table 4. Comparison of Baseline Clinical Markers Between Subgroups at CKD G1 or G2 and With Either Good or Poor HRQoL at Baseline

	Poor HRQoL		Good HRQoL		Mean Difference			
Parameter	N	Mean (SD)	N	Mean (SD)	Difference Value	95% CI	*P* Value	Cohen's d
Kidney volume								
htTKV (mL/m)	41	594.56 (435.60)	481	681.94 (475.67)	−87.37	−238.5 to 63.71	0.26	−0.18
Growth rate of htTKV (mL/m/y)	33	30.25 (67.36)	421	34.36 (112.06)	−4.12	−43.02 to 34.78	0.84	−0.04
Percentage growth rate of htTKV (%/y)	33	0.03 (0.09)	421	0.05 (0.08)	−0.02	−0.05 to 0.01	0.12	−0.28
Abdominal girth (cm)	37	96.71 (19.52)	444	92.77 (15.19)	3.93	−1.30 to 9.17	0.14	0.25
Abdominal girth change	28	0.47 (5.12)	391	1.03 (12.05)	−0.56	−5.07 to 3.95	0.81	−0.05
Abdominal girth percentage change (%)	28	1.12 (5.79)	391	1.69 (14.76)	−0.57	−6.09 to 4.95	0.84	−0.04
Kidney function								
Baseline eGFR (mL/min/1.73 m^2)	41	89.20 (21.68)	484	90.54 (20.64)	−1.35	−7.97 to 5.27	0.69	−0.07
Change rate of eGFR (regression slope in mL/min/1.73 m^2)	34	−2.19 (8.58)	453	−3.07 (9.41)	0.87	−2.40 to 4.14	0.60	0.09
SUN-to-creatinine ratio	41	0.08 (0.22)	483	0.04 (0.11)	0.04	0.002 to 0.08	0.04	0.34
SUN-to-creatinine ratio (natural log transformation for test[a])	41	0.08 (0.22)	483	0.04 (0.11)	0.04	0.002 to 0.08	0.51	0.11
Serum creatinine level (mg/dL)	41	0.89 (0.17)	484	0.90 (0.19)	−0.02	−0.08 to 0.04	0.57	−0.09
Urine creatinine (mg/dL)	41	105.10 (75.71)	483	93.13 (64.91)	11.97	−9.06 to 32.99	0.26	0.18
Urine albumin concentration (mg/dL)	41	10.65 (43.23)	484	4.23 (20.63)	6.42	−0.98 to 13.82	0.09	0.28
Urine albumin concentration (mg/dL; natural log transformation for test[a])	41	10.65 (43.23)	484	4.23 (20.63)	6.42	−0.98 to 13.82	0.21	0.21
Urine albumin-to-creatinine ratio	41	78.8 (222.9)	483	38.7 (106.4)	40.1	1.98 to 78.3	0.04	0.34
Urine albumin-to-creatinine ratio (natural log transformation for test[a])	41	78.8 (222.9)	483	38.7 (106.4)	40.1	1.98 to 78.3	0.51	0.11
Urine osmolality (mOsm/kg)	41	503.56 (222.27)	484	481.96 (229.06)	21.60	−51.43 to 94.63	0.56	0.09

Note: Good HRQoL = a score ≤3 on all 3 ADPKD-IS subscales; poor HRQoL = a score >3 on at least 2 of the 3 ADPKD-IS subscales.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HRQoL, health-related quality of life; htTKV, height-adjusted total kidney volume; SD, standard deviation; SUN, serum urea nitrogen.
[a]Log transformation was used for calculating the *P* value and Cohen's d.

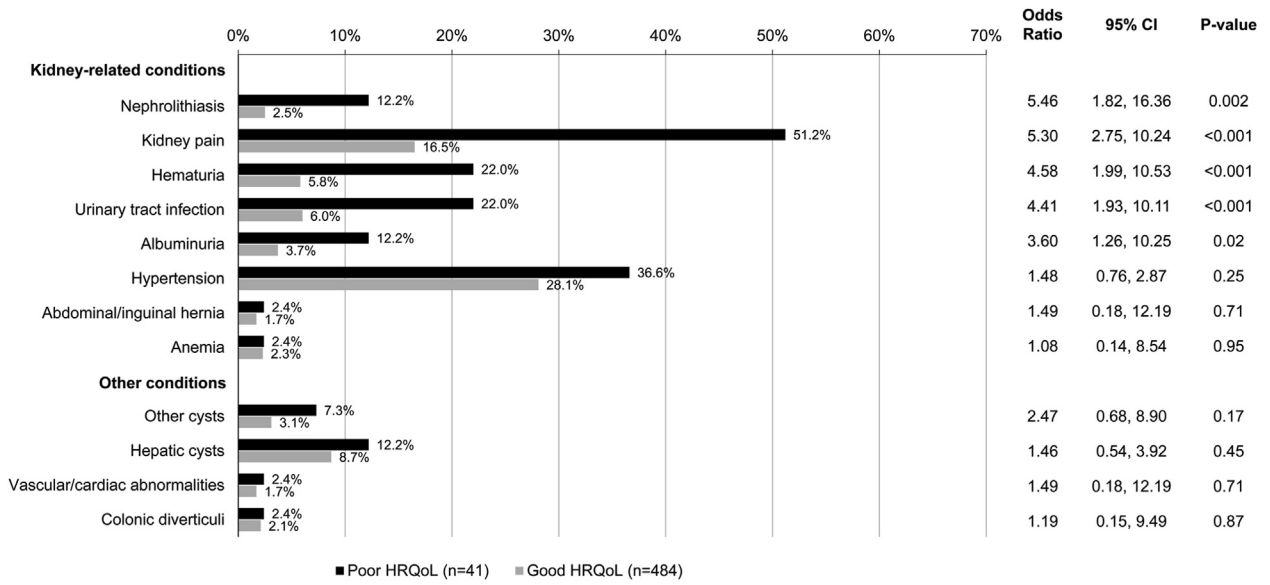

Figure 4. ADPKD-related symptoms and conditions reported during follow-up by early stage (CKD G1-G2) patients with poor HRQoL and good HRQoL at baseline. Good HRQoL = a score ≤3 on all 3 ADPKD-IS subscales; poor HRQoL = a score >3 on at least 2 of the 3 ADPKD-IS subscales. The odds ratio compares the likelihood of the outcome occurring in the poor HRQoL group versus the good HRQoL group. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease-Impact Scale; CI, confidence interval; CKD, chronic kidney disease; HRQoL, health-related quality of life.

Study limitations include the relatively short follow-up, which did not allow for assessment of change measured by PRO instruments or significant decline in kidney function longitudinally. Because of the drop-off in participants and resultant small sample sizes at later assessments, the analyses are limited to 18 months of follow-up. Additionally, visit intervals were 6 months apart, and the recall period was only 1 month or less for the measures used. Thus, events or perspectives falling outside the recall periods may have been missed. Finally, medical resource use and other outcomes were self-reported and therefore subject to recall bias.

In summary, the substantial impact of ADPKD on patients at all stages of disease indicates a need for greater awareness of the burden of illness for patients at earlier stages and supports previous findings that the impact of ADPKD on these individuals is underestimated.[9] Additionally, the burden is specific to each patient, and the same clinical parameter may be experienced differently among individuals. Awareness that a symptom is present in a patient is important, but insufficient to understand the impact. A PRO-specific assessment is necessary to evaluate the burden as experienced in terms of emotions, effects on daily function, and quality of life. In combination with the assessment of abdominal girth and BMI, the inclusion of the ADPKD-IS in routine clinical practice might enable the evaluation of patient needs and anticipation of clinical and health-economic outcomes in addition to its potential utility in ADPKD clinical trials.

Further, although it would be expected that the stage of ADPKD progression will shape the patient's experience of the illness at a given moment, the data presented here indicate that the relationship can also be evaluated conversely, with the question of whether patient-centric outcomes might have predictive value for the later course of the disease. The findings show that it is important for health care providers to assess symptoms and HRQoL to be able to address the physical, psychological, and social consequences of ADPKD. Our results also indicate that patients who perceive an impact of the disease on their lives are more likely to use medical resources and experience effects on their work performance, which in turn may affect their quality of life by introducing financial stressors. Furthermore, given that the ADPKD-IS and ADPKD-UIS ask patients to rate the degree of bother or impact they experience in their daily lives, patients who initially have higher HRQoL scores may be more likely to recognize problems and seek help. However, based on patient discussions during development of the ADPKD-IS, patients who report a low degree of bother might regard problems as part of the expected burden of disease and therefore be less likely to seek help.[7] This could be a topic for further research.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: ADPKD-IS and BPI-SF Scores by Baseline Age and Mayo Risk Subclass.

Table S1: Odds Ratios for PRO Assessment Scores Predictive of Hospitalization (0 vs ≥1 hospitalizations) Over 6-18 Months of Follow-up by Patient Sex.

Table S2: Odds Ratios for PRO Assessment Scores Predictive of Sick Days (0 vs ≥1 Sick Days) over 6-18 Months of Follow-up by Patient Sex.

Table S3: Association of Baseline Abdominal Girth with Patient-Reported Health-Related Quality of Life Scores by Chronic Kidney Disease Stage.

Table S4: Association of Baseline Abdominal Girth with Patient-Reported Health-Related Quality of Life Scores in Patients With and Without ≥5% Increase in htTKV.

Table S5: Correlations of Abdominal Girth With htTKV, BMI, and Percentage Weight Gain.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Dorothee Oberdhan, MS, Aaron Yarlas, PhD, Jakob B. Bjorner, MD, PhD, and Holly Krasa, MS

Authors' Affiliations: Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, MD (DO); QualityMetric Incorporated, Johnston, RI (AY, JBB); and Blue Persimmon Group LLC, Washington, DC (HK).

Address for Correspondence: Dorothee Oberdhan, MS, Otsuka Pharmaceutical Development & Commercialization, Inc., 2440 Research Blvd., Rockville, MD 20850. Email: dorothee.oberdhan@otsuka-us.com

Authors' Contributions: Research idea and study design: DO, HK; data acquisition: DO, HK; data analysis/interpretation: DO, AY, JBB, HK; statistical analysis: AY, JBB. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Data Sharing: To submit inquiries related to Otsuka clinical research or to request access to individual participant data (IPD) associated with any Otsuka clinical trial, please visit https://clinical-trials.otsuka.com/. For all approved IPD access requests, Otsuka will share anonymized IPD on a remotely accessible data sharing platform.

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