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blood advances

Health-related quality of life and fatigue in children and adults with pyruvate kinase deficiency

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Key Points

- The impact of PKD on HRQoL and fatigue is described in 254 children and adults using 6 validated instruments.
- Severe anemia, regular transfusion, iron chelation, and nonmissense mutations are associated with worse patient-reported outcomes.

Pyruvate kinase deficiency (PKD) is the most common cause of congenital nonspherocytic hemolytic anemia. Although recognition of the disease spectrum has recently expanded, data describing its impact on health-related quality of life (HRQoL) are limited. In this prospective international cohort of 254 patients (131 adults and 123 children) with PKD, we used validated measures to assess the impact of disease on HRQoL (EuroQol 5-Dimension Questionnaire, Pediatric Quality of Life Inventory Generic Core Scale version 4.0, and Functional Assessment of Cancer Therapy-Anemia) and fatigue (Patient Reported Outcomes Measurement Information System Fatigue and Pediatric Functional Assessment of Chronic Illness Therapy-Fatigue). Significant variability in HRQoL and fatigue was reported for adults and children, although individual scores were stable over a 2-year interval. Although adults who were regularly transfused reported worse HRQoL and fatigue compared with those who were not (EuroQol-visual analog scale, 58 vs 80; $P = .01$), this difference was not seen in children. Regularly transfused adults reported lower physical, emotional, and functional well-being and more anemia symptoms. HRQoL and fatigue significantly differed in children by genotype, with the worst scores in those with 2 severe *PKLR* mutations; this difference was not seen in adults. However, iron chelation was associated with significantly worse HRQoL scores in children and adults. Pulmonary hypertension was also associated with significantly worse HRQoL. Additionally, 59% of adults and 35% of children reported that their jaundice upset them, identifying this as an important symptom for consideration. Although current treatments for PKD are limited to supportive care, new therapies are in clinical trials. Understanding the impact of PKD on HRQoL is important to assess the utility of these treatments. This trial was registered at www.clinicaltrials.gov as #NCT02053480.

Introduction

Pyruvate kinase deficiency (PKD) is an autosomal recessive hereditary hemolytic anemia resulting from mutations in the *PKLR* gene. Although it is the most common cause of chronic hereditary nonspherocytic

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The full-text version of this article contains a data supplement.

hemolytic anemia, its precise prevalence remains unclear, with estimates ranging between 1:20 000 and 1:300 000 in white populations[1,2] and a higher prevalence in malaria-endemic areas. Pyruvate kinase is the rate-limiting step in erythrocyte adenosine triphosphate production; the shortage of adenosine triphosphate resulting from its deficiency results in a diminished capacity to maintain the erythrocyte membrane and decreased erythrocyte deformability.[3] This leads to chronic hemolytic anemia that is due to decreased erythrocyte lifespan and premature splenic erythrocyte destruction. Hemolysis in PKD ranges from mild and asymptomatic to a severe transfusion-dependent anemia from birth.[4] The sequelae include typical symptoms of anemia (fatigue, reduced exercise tolerance, reduced concentration), iron overload and its complications, extramedullary hematopoiesis, bone disease, endocrinopathies, and venous thromboembolism, among other complications.[5,6]

Although data from the international Pyruvate Kinase Deficiency Natural History Study (PKD NHS)[5] and other cohorts[7-9] have been important in defining the disease spectrum, few objective or quantitative published data have described the impact of PKD on health-related quality of life (HRQoL) or fatigue. A qualitative interview study of 21 adults with PKD described a negative impact of the disease on appearance, emotional and cognitive states, sleep, work and/or school, and the ability to perform physical, social, and leisure activities.[10] Studies published in other hereditary hemolytic anemias, such as sickle cell disease[11] and thalassemia,[12] demonstrated the importance of defining the impact of chronic hemolytic anemia on patient-reported outcomes, underscoring its significance as an outcome measure in the evaluation of treatments. Although treatments for PKD are limited to red blood cell transfusions, splenectomy, and the rare hematopoietic stem cell transplant, oral pyruvate kinase activators[13] and gene therapy[14] are in clinical trials. Understanding the impact of PKD on HRQoL and fatigue is critical to fully characterize the value and utility of these treatments. Therefore, this study aimed to characterize the disease impact on HRQoL and fatigue in an international population of children and adults with PKD.

Methods

Patient population

The PKD NHS (#NCT02053480) was opened at 30 centers in the United States (n = 19), Canada (n = 3), Italy (n = 1), Czech Republic (n = 1), Germany (n = 5), and The Netherlands (n = 1) (supplemental Table 1). The study protocol was in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board and/or Ethics Committee at each site, and all patients and/or their legal guardians gave informed consent. Patients were able to participate from afar by signed medical releases or were primarily followed at a center approved to conduct the study. Patients were eligible to be included in the registry study if they had a genetically confirmed diagnosis of PKD with 2 identified *PKLR* mutations. At the time of enrollment, patients' medical records were reviewed retrospectively, and patients were followed prospectively for 2 years. Data collected from the medical record included medical history, physical examination, and laboratory and radiologic studies. Medical history missing from the medical records was obtained by patient recall, if known. HRQoL was measured at 3 time points: at enrollment and at the 1- and 2-year follow-up in children (<18 years) and adults (≥18 years).

Patient-reported outcome measures

Adult measures. MEASUREMENT OF HRQoL. The EuroQol 5-Dimension Questionnaire (EQ-5D-5L) was used in adults (supplemental Table 2). The EQ-5D is a generic HRQoL instrument that includes 2 primary components: a descriptive system used to generate a EuroQol health index score and the EuroQol-visual analog scale (EQ-VAS), in which respondents mark health status on a vertical scale with end points of 0 (worst health) and 100 (best health). EQ-5D scoring has been validated across multiple chronic diseases and in different countries. The Functional Assessment of Cancer Therapy-Anemia (FACT-An), a validated survey that measures general HRQoL concerns (physical, social, emotional, and functional well-being), as well as items specifically related to anemia and fatigue, was used to measure adult HRQoL. Scores range from 0 to 188; a higher score indicates a higher level of HRQoL (supplemental Table 2).

MEASUREMENT OF FATIGUE. The Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form was used to measure fatigue in adults (adult self-report short-form 7a [SF7a]). PROMIS raw scores are converted to T-scores; a standardized score has a mean of 50 and a standard deviation (SD) of 10. Higher scores indicate greater fatigue. English-speaking adults were asked an additional question for symptom assessment specific to PKD ("I get upset about my jaundice [yellow eyes/skin]"), which used a scale from 0 (not at all) to 5 (very much).

Pediatric measures. MEASUREMENT OF HRQoL. The Pediatric Quality of Life Inventory Generic Core Scale version 4.0 (PedsQL), a validated tool that measures physical, emotional, social, and school functioning, was completed for children and adolescents (supplemental Table 2). Parent proxy forms were completed for children aged 2 to 17 years, whereas patient self-report forms were completed for children aged 5 to 17 years. PedsQL scores have a range of 0 (worst) to 100 (best).

MEASUREMENT OF FATIGUE. The Pediatric Functional Assessment of Chronic Illness Therapy-Fatigue (Peds-FACIT-F) was used to measure fatigue in children aged 8 to 17 years. Scores can range from 0 to 52; a lower score indicates a higher level of fatigue. The PROMIS Fatigue Short Form 10a (SF-10a) was used to measure fatigue in children aged 8 to 17 years (child self-report 10a) and parent proxy forms (parent proxy 10a) were used for children aged 5 to 17 years. Analysis of the child and parent proxy short forms is the same as for the adult forms; higher scores indicate greater fatigue. English-speaking children were asked an additional question for symptom assessment specific to PKD ("I get upset about my jaundice [yellow eyes/skin]"), which used a scale from 0 (none of the time) to 5 (all of the time).

Definitions and statistical analysis

Patient demographics, transfusion status, comorbid diagnoses, and other disease characteristics were described using frequencies, proportions, medians, means, and ranges. Patients were considered regularly transfused if they had received ≥6 red blood cell transfusions in the prior year. Iron overload was defined as elevated ferritin (≥1000 ng/mL) or by the use of iron chelation at any point. Because the Amish population represented a large and similarly managed subset of the cohort, analyses were performed for the entire cohort and for the Amish population separately. Tests of association were performed using the Fisher's exact test for categorical data and the Wilcoxon rank-sum test or the Kruskal-Wallis test for continuous data. Sample

sizes are presented for those with known data available for each variable. Spearman correlations are reported. Data were collected using Inform and analyzed with SAS v9.4 (Cary, NC). Surveys were unavailable in specific languages, which led to more missing data for certain measures (supplemental Table 2). The EQ-5D summary health index score was computed using country-specific value sets. *P* values are 2-sided, and those $<.05$ were considered statistically significant.

Results

PKD NHS demographics

Patients with PKD were enrolled from June of 2014 through April of 2017 at 30 centers in 6 countries. Data are reported for 254 eligible participants (131 adults and 123 adolescents and children). There were 55 patients (21.7%) who identified as part of the Amish community. Baseline demographic information is presented in Table 1. A comprehensive characterization of the complications and laboratory abnormalities associated with PKD in this population is described in a separate publication.[5] Completed HRQoL surveys varied by age and measure (Table 2; supplemental Table 2).

Report of overall HRQoL in adults with PKD

EQ-5D-5L. The EQ-5D Visual Analog Scale was completed by 120 of the 131 adults at enrollment, by 98 at the 1-year follow-up, and by 88 patients at the 2-year follow-up. The median EQ-VAS score was 80, with significant variability in the range of scores reported (20-100). The median EuroQol health index score was 0.88 (range, 0.43-1). The median EQ-VAS and health index scores were unchanged at 1 and 2 years of follow-up.

At the time of enrollment, patients aged $\geq$40 years reported significantly lower EQ-VAS scores compared with adults aged 18 to 39 years (80 vs 85; $P = .02$). Scores were lower in women vs men (80 vs 85; $P = .03$), in non-Amish vs Amish patients (80 vs 85; $P = .04$), regularly transfused vs not regularly transfused patients (58 vs 80; $P = .01$), in patients with iron overload vs no iron overload by chelation requirement (75 vs 84; $P = .02$), and in patients with vs without pulmonary hypertension (40 vs 80; $P = .03$). When the Amish population was excluded from the analysis, there were no longer significant differences by age or history of iron overload by chelation requirement. EQ-VAS scores did not differ based on splenectomy status ($P = .67$), hemoglobin level (<8 g/dL vs >8 g/dL; $P = .97$), bilirubin level (total bilirubin $>$ 4 mg/dL vs <4 mg/dL, $P = .97$), number of lifetime transfusions ($P = .20$), iron overload by ferritin ($P = .12$), or history of extramedullary hematopoiesis ($P = .31$). EQ-VAS scores also did not differ by genotype category: missense/missense (median, 75), missense/nonmissense (median, 83), and nonmissense/nonmissense (median, 80; $P = .28$).

FACT-An. The FACT-An was completed by 126 adults at enrollment, by 98 patients at the 1-year follow-up, and by 88 patients at the 2-year follow-up. The median FACT-An score was 155.6, with high variability between individual patient scores (range, 33.3-181). The median FACT-An score was similar at 1 and 2 years of follow-up.

At enrollment, HRQoL assessed by FACT-An did not vary by age. Significantly lower HRQoL was reported by women vs men (median, 143 vs 159; $P = .008$), non-Amish vs Amish patients (151 vs 163; $P = .04$), regularly vs not regularly transfused patients (113 vs 157; $P = .0003$), patients with iron overload vs no iron overload by chelation requirement (146 vs 157; $P = .006$), and patients with vs without pulmonary hypertension (99 vs 157; $P = .002$). HRQoL did not differ based on splenectomy status ($P = .95$), hemoglobin level (<8 g/dL vs $>$ 8 g/dL; $P = .97$), bilirubin level (total bilirubin $>$ 4 mg/dL vs <4 mg/dL; $P = .4$), number of lifetime transfusions ($P = .18$), or iron overload by ferritin ($P = .12$). There were no significant differences based on *PKLR* genotype ($P = .63$). Differences, or the lack thereof, in FACT-An scores in certain subgroups are shown in Figure 1.

FACT-An subscales. Within the FACT-An, differences were noted in specific subscales across clinical characteristics. Lower scores in the social well-being subscale were reported by patients aged $\geq$40 years vs $<$40 years (22 vs 26; $P = .0006$) and those who had not been splenectomized vs those postsplenectomy (21 vs 25; $P = .004$). Additionally, lower scores in the anemia subscale were reported for females vs males (58 vs 67; $P = .001$). Regularly transfused adults reported significantly lower physical well-being ($P = .002$), emotional well-being ($P = .004$), and functional well-being ($P = .0007$), as well as increased anemia symptoms ($P = .0002$). Those with a history of iron overload by chelation requirement also reported lower physical well-being ($P = .0001$), emotional well-being ($P = .001$), and functional well-being ($P = .0007$), as well as increased anemia symptoms ($P = .02$). In addition, pulmonary hypertension was associated with significantly lower physical well-being ($P = .0004$) and functional well-being ($P = .005$), as well as increased anemia symptoms ($P = .0008$).

Report of fatigue in adults with PKD

PROMIS SF-7a. The PROMIS SF-7a was completed by 60 adults at enrollment and by 47 and 36 adults at 1 and 2 years of follow-up, respectively. The lower number of respondents for this inventory reflects the lack of validated translated forms for some of the participating countries. The median PROMIS SF-7a score was 52.3 (range: 29.4-80.3), and this median was replicated at years 1 and 2.

In adults, fatigue levels using PROMIS SF-7a did not vary by age or by Amish/non-Amish status. Significantly greater levels of fatigue were reported by women vs men (57 vs 51; $P = .004$), regularly vs not regularly transfused patients (68 vs 52; $P = .03$), and patients with vs without pulmonary hypertension (65 vs 52; $P = .04$). Report of fatigue did not differ based on splenectomy status ($P = .59$), hemoglobin level (<8 g/dL vs >8 g/dL; $P = .93$), bilirubin level (total bilirubin $>$ 4 mg/dL vs <4 mg/dL; $P = .28$), number of lifetime transfusions ($P = .37$), history of extramedullary hematopoiesis ($P = .43$), iron overload by ferritin ($P = .12$), or iron overload by chelation ($P = .20$). Reports of fatigue also did not differ by *PKLR* genotype category ($P = .79$).

Other report of symptoms of anemia. English-speaking adults were asked an additional question for symptom assessment specific to PKD (Table 3). Of the 68 adults who completed the questionnaire, 59% (40/68) reported that their jaundice upset them, and 16% (11/68) reported that they felt quite a bit or very much upset.

Report of overall HRQoL in children with PKD

The PedsQL 4.0 survey was completed by 61 of the 124 children at enrollment, by 45 children at the 1-year follow-up, and by 48 children at the 2-year follow-up. The parent proxy was completed by 86 of 124

Table 1. Demographic characteristics of the PKD cohort

Characteristics	All (N = 254)	
	n*	% or median (range)
Male sex	124	48.9
Age at enrollment, y		
Overall	254	19.0 (0.1-69.9)
<18 y old	123	6.4 (0.1-17.7)
≥18 y old	131	36.2 (18.0-69.9)
White race	235	92.5
Hispanic ethnicity	18	7.1
Amish	55	21.7
Splenectomized	150	59.1
Gallstones	112/248	45.2

	Children (<18 y)		Adults (≥ 18 y)	
	n*	% or median (range)	n	% or median (range)
Lifetime transfusions, n	86	18 (1-312)	63	39 (1-516)
Genotype†				
Missense/missense	55/97	57	55/94	58
Missense/nonmissense	26/97	27	25/94	27
Nonmissense/nonmissense	16/97	16	14/94	15
Hemoglobin (g/dL)				
Nonsplenectomized NRT	40	9.1 (6.0-12.5)	30	11.3 (7.6-14.2)
Splenectomized NRT	24	8.5 (4.3-12.8)	52	8.5 (6.1-12.3)
Absolute reticulocyte count ($\times 10^6$ cells/μL)	40	0.30 (0.07-5.36)	42	0.21 (0.09-6.52)
Reticulocytes, %	87	11.2 (0.4-82.9)	54	18.9 (2.5-76)
Bilirubin, mg/dL	80	3.6 (0.1-33.1)	78	4.1 (0.9-17.6)
Lactate dehydrogenase, U/L	46	775 (183-3811)	66	220 (127-1007)
Ferritin, ng/mL	63	917 (22-13409)	72	594 (32-8220)

NRT, not regularly transfused with <6 transfusions per year.
*Sample sizes are those with known data for the given characteristic in the PKD NHS.
†Those from the Amish community (homozygous R479H mutation) were excluded.[5]

parents at enrollment, by 72 parents at the 1-year follow-up, and by 59 parents at the 2-year follow-up. The median child self-report score was 82.6 (range, 33.7-100), and the median parent proxy score was 83.5 (range, 25-100). The median child self-report and parent proxy scores were unchanged at 1 and 2 years of follow-up.

The report of HRQoL in children did not differ by age group (ages 2-4, 5-7, and 8-12 years vs 13-17 years; $P = .34$) or by sex ($P = .69$). Amish children reported higher HRQoL scores (93 vs 80; $P = .007$). HRQoL was significantly lower in children who were more anemic (<8 g/dL vs >8 g/dL, 69 vs 91; $P = .01$), had iron overload by ferritin (34 vs 92; $P = .006$), or had iron overload by chelation requirement (70 vs 88; $P = .007$). HRQoL scores also significantly differed by *PKLR* genotype, with those with a nonmissense/nonmissense genotype reporting a significantly lower HRQoL (missense/missense vs missense/nonmissense vs nonmissense/nonmissense, 83 vs 84 vs 59; $P = .006$). HRQoL did not differ based on splenectomy status ($P = .64$), bilirubin level (total bilirubin > 4 mg/dL vs <4 mg/dL; $P = .69$), receipt of regular transfusions vs not ($P = .21$), total number of lifetime transfusions ($P = .06$), iron status by ferritin ($P = .12$), or history of extramedullary hematopoiesis ($P = .07$). When Amish children were excluded from the analysis, significantly lower HRQoL was reported in children who were splenectomized (76 vs 83; $P = .02$) and in those receiving a higher number of lifetime transfusions (77 vs 82; $P = .02$); however, there was no longer a significant difference in HRQoL by hemoglobin level ($P = .23$).

Report of fatigue in children with PKD

Peds-FACIT-F. Peds-FACIT-F was completed by 47 older children and adolescents at enrollment and by 40 and 36 older children and adolescents at 1 and 2 years, respectively. The median score at enrollment was 45 (range, 16-52), and it was unchanged at 1 and 2 years of follow-up. There was no difference in the report of fatigue by age group ($P = .17$), sex ($P = .46$), splenectomy status ($P = .76$), number of lifetime transfusions ($P = .14$), current transfusion status ($P = .09$), hemoglobin level ($P = .41$), bilirubin level ($P = .54$), or iron overload by ferritin ($P = .83$) in this cohort at enrollment. Amish children reported fatigue that was similar to that of non-Amish children (median, 46 vs 45, respectively; $P = .14$). The report of fatigue varied significantly by *PKLR* genotype, with those with a nonmissense/nonmissense genotype reporting higher levels of fatigue (missense/

Table 2. HRQoL survey results by age group at enrollment

Surveys	n (%)	Median (range)
Adult surveys (n = 131)		
EQ-5D Visual Analog Scale (range 0 [worst] to 100 [best])	120 (92)	80 (20-100)
EQ-5D Health Index Score* (range 0 [worst] to 1 [best])	86 (66)	0.88 (0.43-1)
FACT-An (range 0 [most fatigue] to 188)	126 (96)	156 (33-181)
PROMIS SF-7a (mean, 50; SD, 10; higher is worse)	60 (46)	52.3 (29.4-80.3)†
Pediatric surveys (n = 123)		
PedsQL 4.0 (range 0 [worst] to 100 [best])		
Parent proxy	86 (70.0)	83.5 (25-100)
Child self-report	61 (49.6)	82.6 (33.7-100)
Peds-FACIT-F (range 0 [most fatigue] to 52)	50 (40.7)	70.4 (31-80)
PROMIS Fatigue Child SF-10a (mean, 50; SD, 10; higher is worse)		
Child self-report 10a	36 (29.3)	41.6 (30.3-65.7)
Parent proxy report 10a	48 (39.0)	46.3 (34.1-69.2)

*EQ-5D Health Index Score could only be analyzed for participants from the United States, Germany, and The Netherlands.
†Median T score (range).

missense vs missense/nonmissense vs nonmissense/nonmissense, 46 vs 45 vs 34; $P = .047$). Children with a history of chelation therapy also reported higher levels of fatigue (median, 40 vs 46; $P = .03$). Differences, or the lack thereof, in Peds-FACIT-F scores in certain subgroups are shown in Figure 2.

PROMIS Child SF-10a. The PROMIS Child SF-10a was completed by 36 older children and adolescents with a median score of 41.6 (range, 30.3-65.7). The PROMIS Parent Proxy was completed by 48 parents with a median score of 46.3 (range, 34.1-69.2). The median child self-report and parent proxy reports were unchanged at follow-up. There was no significant difference in the report of fatigue by age ($P = .31$), sex ($P = .82$), splenectomy status ($P = .88$), number of lifetime transfusions ($P = .07$), transfusion status ($P = .06$), hemoglobin level ($P = .18$), bilirubin level ($P = .94$), iron overload by ferritin ($P = .12$), or iron overload by chelation requirement ($P = .19$). There also was no significant difference in the report of fatigue by *PKLR* genotype (median scores for missense/missense vs missense/nonmissense vs nonmissense/nonmissense, 42 vs 44 vs 56; $P = .08$). Although there was no difference in the report of fatigue between Amish and non-Amish children, as measured by PROMIS, when Amish children were excluded from the analysis, a significantly higher level of fatigue was reported in children with a history of iron overload by ferritin (57 vs 32; $P = .008$) and by chelation requirement (57 vs 41; $P = .009$).

Other report of symptoms of anemia. English-speaking children were asked additional questions generated for symptom assessment specific to PKD (Table 3). Of the 40 children who completed the questionnaire, 35% (14/40) reported that their jaundice upset them at least some of the time; 7.5% (3/40) reported that they felt upset most or all of the time.

Discussion

This is the first report of HRQoL and fatigue in patients with PKD using validated instruments. A wide range of scores was reported for general HRQoL, as measured by the EQ-5D in adults and the PedsQL 4.0 in children, and for fatigue using FACIT-F in adults, Peds-FACIT-F in children, and PROMIS in all ages. Consistent correlates were identified between specific clinical characteristics in patients with PKD and worse overall HRQoL and fatigue (Table 4).

The median reported general HRQoL, as measured by EQ-5D in adults and PedsQL 4.0 in children, approximated that of the general population. There are numerous possible explanations for this finding. There is a very wide range of disease spectrum in the analyzed cohort, from asymptomatic individuals with no anemia to individuals who were transfusion dependent since birth.[15] Consistent with the large variation in symptoms and complications, some patients reported very low HRQoL or a high level of fatigue, whereas others reported the best possible HRQoL or no fatigue. In addition, adjustment to chronic anemia and a lack of recognition of its impact on functional status are well described in populations with congenital anemia; this may also be responsible for the observed findings. Another possibility lies with the selected instruments, which, although validated tools, are not validated for use in PKD, hemolytic anemias, or congenital anemias. Therefore, they may be more sensitive to acquired anemia, such as the anemia associated with chronic kidney disease or cancer. The instruments may be insensitive to aspects of lifelong hemolytic anemia that reduce HRQoL, including iron overload, chronic jaundice, and pulmonary hypertension. Finally, there may be specific aspects of PKD that modulate the impact of chronic anemia, such as the elevation in 2,3-diphosphoglycerate (2,3-DPG).[16,17] 2,3-DPG is an important regulator of the oxygen affinity of hemoglobin and is increased in PKD as a result of the metabolic block of glycolysis resulting in an upstream accumulation of glycolytic intermediates. Therefore, enhanced oxygen delivery due to elevated 2,3-DPG may obviate symptoms of anemia in some patients.[6,18]

Although these factors may limit the ability to compare the results of these instruments with other patient populations, comparisons within the population of patients with PKD are informative. Among adults, worse HRQoL and fatigue were consistently reported in patients receiving regular transfusions, those with pulmonary hypertension, and females. In FACT-An subscales, receipt of regular transfusions was associated with significantly lower physical, emotional, and social well-being, as well as with increased symptoms of anemia. Worse HRQoL and fatigue were also generally associated with iron overload in children and adults. Although iron chelation is associated with potential side effects, laboratory monitoring, and costs, this finding may also be a marker of transfusion status. Although symptoms within a patient are typically experienced at a certain hemoglobin level, this level may vary among patients. Therefore, transfusions are not typically initiated based on a specific hemoglobin level across the population, but rather to improve a given individual's fatigue and HRQoL based on their reported symptoms. However, patients who start regular transfusions may be more symptomatic, and transfusions may not significantly improve HRQoL given the burden of time, energy, and cost placed on the patient to undergo the intervention; this emphasizes the need for effective new therapies in this disease. The same overall principle (ie, that more symptomatic patients are more likely to undergo splenectomy) may explain the finding that splenectomy was associated with greater fatigue in adults and worse HRQoL in

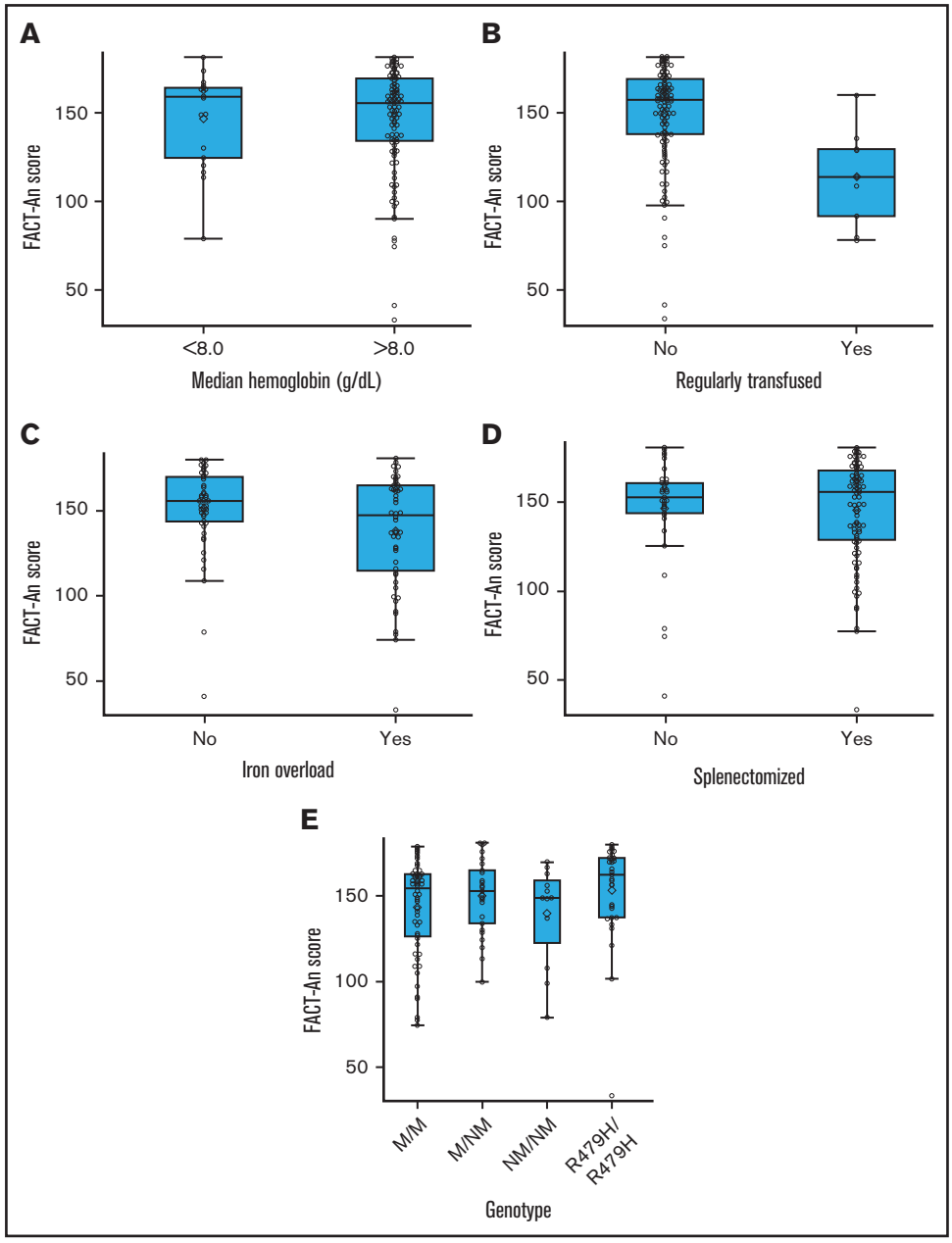

Figure 1. HRQoL as assessed by FACT-An in adults with PKD, by specific relevant subgroupings. Median hemoglobin (A), transfusion status (B), iron overload status (C), splenectomy status (D), and genotype (E). Higher FACT-An scores indicate higher HRQoL. The R479H/R479H genotype is primarily found in the Amish community. M/M, missense/missense; M/NM, missense/nonmissense; NM/NM, nonmissense/nonmissense.

children, despite the fact that this is a 1-time procedure that is performed to improve hemoglobin levels and reduce transfusion needs.

Pulmonary hypertension is a serious and relatively rare complication of PKD affecting 3% of individuals.[5] Patients with this complication reported substantially reduced HRQoL and significantly increased fatigue. Physical and functional well-being were particularly impacted. Therefore, consideration of the possibility of pulmonary hypertension is critical in patients with concerning symptoms and demands aggressive management when identified.

Children, but not adults, reported significantly lower HRQoL with severe anemia (defined as a hemoglobin level $<$ 8 g/dL). In the general PKD population, the relationship between hemoglobin and symptoms is not consistent between patients; however, in individual patients, there is often a relationship between hemoglobin level and symptoms, including fatigue.[6,15] Future studies with paired measurement of HRQoL, in patients before and after therapy to increase their hemoglobin, will help to explore the relationship between hemoglobin and symptoms and capture the impact that improving the hemoglobin level has on HRQoL.

Additional differences in the clinical characteristics associated with reduced HRQoL and fatigue between children and adults included age, sex, and genotype. Older age was associated with reduced HRQoL in adults but not children. Reduced HRQoL with advancing

Table 3. Additional symptom assessment in children and adults with PKD

Age ≥ 18 y	Total, n	Not at all	A little bit	Somewhat	Quite a bit	Very much
I get upset about my jaundice (yellow eyes/skin)	68	28 (41.2)	18 (26.4)	11 (16.2)	5 (7.4)	6 (8.8)
Age < 18 y		**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
I get upset about my jaundice (yellow eyes/skin)	40	26 (65)	7 (17.5)	4 (10)	1 (2.5)	2 (5)
I have trouble walking	40	34 (85)	2 (5)	2 (5)	2 (5)	0
I feel lightheaded (dizzy)	41	26 (63.4)	8 (19.5)	7 (17.1)	0	0
I have been short of breath	40	24 (60)	8 (20)	7 (17.5)	1 (2.5)	0
I have pain in my chest	40	32 (80)	5 (12.5)	3 (7.5)	0	0
I am less motivated to do my usual activities	40	26 (65)	7 (17.5)	7 (17.5)	0	0

Data are n (%) unless otherwise specified.

age is not unexpected in general, especially in the population with PKD, because symptoms of the disease may become more pronounced with age-related declines in cardiopulmonary function, increasing comorbidities, and emergence of time-dependent complications, such as bone disease and iron overload.[6] In addition, female sex was associated with reduced HRQoL and greater fatigue in adults but not in children. Reduced HRQoL in adult females of a given population compared with male counterparts has been reported in a number of other chronic conditions[19] and is not well understood. This may be related to gender-based differences in reporting,[20,21] higher rates of anxiety and depression in women[22] that may result in lower HRQoL, or an inherent fault in the design of the instruments themselves, among other possibilities.

The presence of 2 severe mutations (nonmissense/nonmissense) is associated with worse anemia, more transfusion requirements, and more complications overall[5,23]; therefore, it is expected that this would result in reduced HRQoL and increased fatigue. It is not clear why this correlation between genotype and HRQoL and fatigue was seen in children, but not in adults, because the increased severity imparted by genotype persists throughout life.

Although our study has a number of notable strengths, it also has several limitations. Although the sample size was large for this rare disease, the population was heterogeneous. The follow-up period was just 2 years and assessed patients at 3 time points. The instruments are generic, and cancer-specific measures of HRQoL and fatigue are likely insensitive to many of the unique aspects of PKD and congenital hemolytic anemias more generally.[24] In this study, participants noted a significant impact of jaundice on HRQoL in a disease-specific assessment. This is notably absent from the validated anemia questionnaires but represents an important symptom that future therapies should aim to improve. In patients with a congenital anemia, it may be difficult to assess fatigue or HRQoL except in the setting of a therapeutic intervention, such as pre/postsplenectomy, pre/posttransfusion, or pre/post a novel therapeutic. HRQoL instruments specific to the symptoms and impact of PKD have recently been developed[25] and are being validated in phase 3 clinical trials of a novel therapy. If these new instruments perform well, they may be optimal for future studies evaluating HRQoL in PKD.

In conclusion, this first report of HRQoL and fatigue measurement in a large cohort of patients with PKD using validated standardized instruments found similar HRQoL for patients with PKD and the general population but higher levels of fatigue. Female sex, receipt of regular transfusions, iron overload, and pulmonary hypertension were consistently associated with worse health-related outcomes in adults, whereas

Table 4. Patient characteristics significantly associated with reduced HRQoL or greater fatigue by HRQoL or fatigue instrument in adults and children

	Adults			Children		
Characteristic	**EQ-5D**	**FACT-An**	**PROMIS SF-7a**	**PedsQL 4.0**	**Peds-FACIT-F**	**PROMIS Child SF-10a**
Older age	X					
Female sex	X	X	X			
Non-Amish	X	X		X	X	
Splenectomized		X		A		
Regularly transfused	X	X	X			
Iron overload: any chelation use	X	X		X		A
Iron overload: ferritin > 1000 ng/mL				X		A
Pulmonary hypertension	X	X	X			
Nonmissense/nonmissense genotype				X	X	
Hemoglobin < 8 g/dL				X		
≥18 total transfusions				A		

A, significant only when the Amish population was excluded from analysis; X, significant in entire cohort.

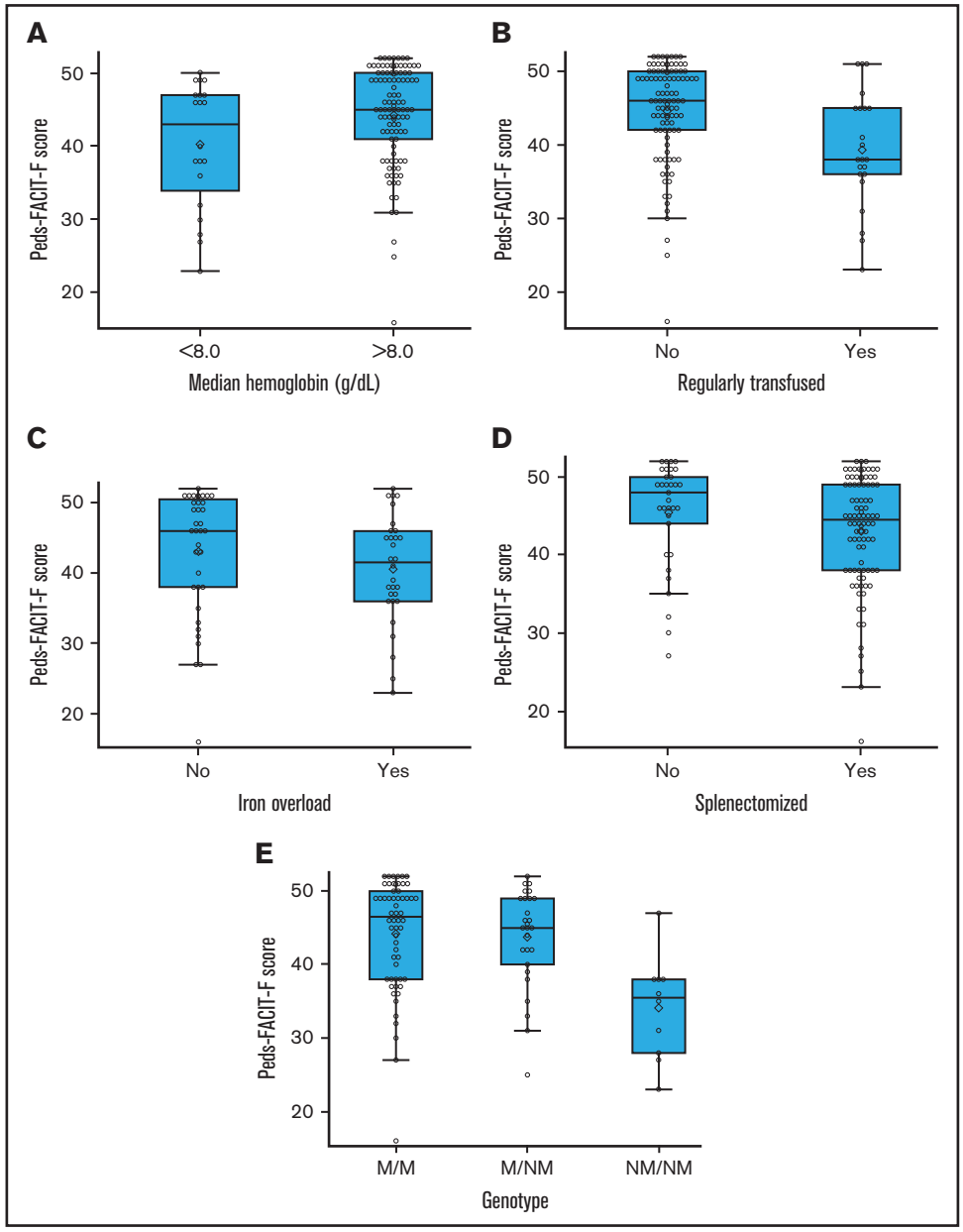

Figure 2. Fatigue as assessed by Peds-FACIT-F in children with PKD, by specific relevant subgroupings. Including median hemoglobin (A), transfusion status (B), iron overload status (C), splenectomy status (D), and genotype (E). Higher Peds-FACIT-F scores indicate less fatigue. M/M, missense/missense; M/NM, missense/nonmissense; NM/NM, nonmissense/nonmissense.

more severe anemia, iron overload, and 2 nonmissense *PKLR* mutations were associated with worse patient-reported outcomes in children. Based on the findings of this study, future studies of HRQoL in patients with PKD should use disease-specific instruments and evaluate the impact of therapeutic interventions on these outcomes.

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Authorship

Contribution: H.A.-S. analyzed data, created tables and figures, wrote the first draft of the manuscript, critically revised the manuscript, and approved its final version; P.W.F. analyzed data, critically revised the

manuscript, and approved its final version. R.F.G. designed the study, collected and analyzed data, created tables and figures, wrote the first draft of the manuscript, critically revised the manuscript, and approved its final version; E.J.v.B., D.H.M., S.W.E., S.C., K.H.M.K., N.K., H.W., V.R.B., S.S., and M.S. collected data, critically revised the manuscript, and approved its final version; and R.J.K. critically revised the manuscript and approved its final version.

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