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ORIGINAL PAPER

Paediatrics

Comorbidities and complications in adult and paediatric patients with pyruvate kinase deficiency: Analysis from the Peak Registry

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Summary

Pyruvate kinase (PK) deficiency, a rare, congenital haemolytic anaemia caused by mutations in the *PKLR* gene, is associated with many clinical manifestations, but the full disease burden has yet to be characterised. The Peak Registry (NCT03481738) is an observational, longitudinal registry of adult and paediatric patients with PK deficiency. Here, we described comorbidities and complications in these patients by age at most recent visit and *PKLR* genotype. As of 13 May 2022, 241 patients were included in the analysis. In total, 48.3% had undergone splenectomy and 50.5% had received chelation therapy. History of iron overload (before enrolment/during follow-up) was common (52.5%), even in never-transfused patients (20.7%). Neonatal complications and symptoms included jaundice, splenomegaly and hepatomegaly, with treatment interventions required in 41.5%. Among adults, osteopenia/osteoporosis occurred in 19.0% and pulmonary hypertension in 6.7%, with median onset ages of 37, 33 and 22 years, respectively. Biliary events and bone health problems were common across *PKLR* genotypes. Among 11 patients who had thromboembolic events, eight had undergone prior splenectomy. Patients with PK deficiency may have many complications, which can occur early in and throughout life. Awareness of their high disease burden may help clinicians better provide appropriate monitoring and management of these patients.

KEYWORDS

adult and paediatric haematology, haemolytic anaemia, iron–clinical iron overload, pyruvate kinase deficiency, red cells–enzyme disorders

INTRODUCTION

Pyruvate kinase (PK) deficiency is a rare, genetic, lifelong haemolytic anaemia that is caused by homozygous or compound heterozygous mutations in the *PKLR* gene.[1] The *PKLR* gene encodes the red blood cell (RBC)-specific form of PK, an enzyme that has a crucial role in the final step of glycolysis.[1,2] Mutations in *PKLR*, more than 350 of which have now been described, cause both impaired glycolysis and adenosine triphosphate production, leading to reduced RBC membrane integrity and lifespan.[3–5]

The prevalence of PK deficiency in Western countries is estimated to be 3.2–8.5 individuals per million, although the true prevalence could be up to 51 cases per million based on genetic population studies.[4,6] This variation in estimates may be explained by the heterogeneous clinical presentation

of the disease and under-recognition of the condition by the medical community.[7,8]

PK deficiency is associated with a spectrum of symptoms and complications, which can be acute and long term, including fatigue, jaundice, iron overload and pulmonary hypertension.[5,9,10] Disease burden is high throughout the age continuum, although the full breadth of clinical presentations and complications is not fully characterised, and reported rates of complications may vary due to differences in collection methods.[11] Iron overload is a serious complication that occurs in patients with PK deficiency, regardless of age or transfusion status, but remains clinically underappreciated despite the potential to cause long-term organ damage.[10,11]

In comparison with an age- and sex-matched cohort from the general US population, adults with PK deficiency had higher lifetime rates of pulmonary hypertension (4.6% vs. 0.3%), osteoporosis (15.6% vs. 0.0%) and liver cirrhosis (5.6% vs. 0.4%), respectively.[10] Previous data suggest that disease complications may be common regardless of genotype.[10,12] The disease burden of PK deficiency often results in a substantial negative impact on health-related quality of life (HRQoL), particularly on patients' physical functioning, level of fatigue and mental health.[13,14]

Before the approval of mitapivat, the management of PK deficiency was supportive only and did not address the underlying enzymatic defect of the disease.[5,10] Mitapivat is a first-in-class, oral, allosteric activator of PK, approved by the US Food and Drug Administration for the treatment of haemolytic anaemia in adults with PK deficiency,[15] in the European Union by the European Medicines Agency and in Great Britain by the Medicines and Healthcare Products Regulatory Agency for the treatment of PK deficiency in adults.[16,17] RBC transfusions, splenectomy, iron chelation therapy and cholecystectomy remain commonly used to treat the symptoms of PK deficiency; however, all are associated with both short- and long-term risks, and, in the cases of transfusions and chelation, may worsen HRQoL.[10,14,18]

The observational PK Deficiency Natural History Study (NHS; NCT02053480) was established in 2013 to increase the understanding of the disease characteristics, treatment patterns and disease burden of PK deficiency.[5] The global, retrospective and prospective Peak Registry (NCT03481738) was subsequently initiated in 2018 to continue and expand upon the NHS using a longitudinal study design, a wider geographic reach and a longer patient follow-up.[19]

The objective of this analysis was to build on previous research describing the comorbidities and complications in patients with PK deficiency, with a particular focus on better understanding their prevalence in neonatal and paediatric patients, along with the distribution of these complications across *PKLR* genotypes. In addition, the age at onset of select comorbidities and complications was examined in all patients participating in the Peak Registry for whom age at onset data were available.

METHODS

Registry information and study population

The Peak Registry is an ongoing, observational, longitudinal, global registry of patients with a genetically confirmed diagnosis of PK deficiency (methodology details previously published).[19] Patients of any age, with a genetically confirmed diagnosis of PK deficiency, are eligible for enrolment. Genetic diagnosis includes the presence of biallelic *PKLR* variants (either compound heterozygous or homozygous state). The full list of Peak Registry sites and investigators is in Table S1. All participants are followed prospectively for at least 2 and up to 9 years.

Data collection

The Peak Registry collects data both retrospectively and prospectively, including relevant data from routine clinical care or assessments associated with a clinical event. Data are obtained from participating registry physicians, participants and, where appropriate, parents/guardians who gave informed consent. All data are submitted to the registry via electronic case report forms (eCRFs) completed by participating sites. Data were collected as clinically available for each patient cohort described below. No specific definitions or criteria were required to be met to confirm diagnosis of any of the comorbidities and complications collected in the eCRFs but rather were reported based on information included in the medical record and the clinicians' judgement.

Patient cohorts

Patients were included in this analysis if they had available age data as of 13 May 2022. Patients were grouped into cohorts by age at most recent visit and *PKLR* genotype, and for some analyses by sex. For age stratification, patients were categorised as paediatric (<18 years of age) or adult (≥18 years of age). Paediatric patients were further separated into three cohorts: <6, 6–<12 and 12–<18 years of age at most recent visit. In the complication onset age analysis, adult patients were also separated into three cohorts: 18–<40, 40–<65 and ≥65 years of age. For genotype stratification, patients with classifiable *PKLR* genotype data were evaluated in the following cohorts: missense/missense (M/M), missense/non-missense (M/NM) and non-missense/non-missense (NM/NM). Non-missense mutations included nonsense, frameshift, in-frame small indels, large deletions and splicing variants (including missense variants directly involved in splicing, such as R479H). Genotype classifications were aligned with those previously reported by the NHS.[11]

Data analyses

Demographics (with the exception of age) and genotype information collected at enrolment in the registry were reported and were assumed to remain unchanged through follow-up. Age at most recent visit was derived by triangulating age at enrolment, date of enrolment and date of most recent visit. For patients who had not yet had any follow-up visits, age at most recent visit was the same as age at enrolment. Laboratory values were taken at the most recent visit.

Medical history data represented lifetime history (from birth through most recent registry visit) and were collected at enrolment and follow-up. Patients were classified as having history of iron overload if they had ever received: (1) chelation therapy; or (2) phlebotomy for removal of iron, collected at enrolment and during follow-up; or within 3 months before enrolment/during follow-up had any of the following: (3) ferritin >1000 ng/mL; (4) liver magnetic resonance imaging (MRI) >3 mg Fe/g dry weight; (5) FerriScan© >3 mg Fe/g dry weight; and (6) cardiac T2* MRI ≤20 ms. Transfusion history (ever vs. never transfused) also represented lifetime history; however, classification of patients as regularly transfused (≥6 transfusions in a 12-month period) or not regularly transfused (<6 transfusions in a 12-month period) was based on the 12-month period before enrolment, as this was the period for which transfusion details were most consistently reported.

Categories of symptoms, comorbidities and complications with high clinical significance to the PK deficiency population were identified in collaboration with Peak Registry Steering Committee members and based on evidence previously reported in the literature.[4,10,11] Table S2 contains the full list of comorbidities and complications collected. The age of onset of select comorbidities and complications were reported for all patients with available age of onset data.

Data on demographics, medical history, laboratory values, comorbidities and complications were summarised descriptively. Continuous variables were summarised using mean, standard deviation, median and range. Categorical variables were summarised using number and per cent of patients within a category. All data analyses were performed using SAS software version 9.4 (SAS Institute, Inc.).

RESULTS

A total of 241/243 patients (104 [43.2%] <18 years and 137 [56.8] ≥18 years) were included in the analysis (two patients were excluded because their ages were missing). Among them, 199 (82.6%) patients had classifiable genotype data and were included in the genotype stratification.

Median age (range) at enrolment was 19 years (0–77), median age (range) at most recent visit was 21 years (0–78) and 54.4% of patients were female. Median (range) haemoglobin at most recent assessment was 9.5 g/dL (5.8–18.3) and median (range) indirect bilirubin was 3.3 mg/dL (0.0–14.7) (Table 1).

In terms of their medical history, most patients across age groups and genotypes had received ≥1 transfusion in their lifetime. Approximately half of patients had ever (at time of enrolment and during follow-up) received chelation therapy (50.5%), with median (range) ferritin of 452 µg/L (2–7050); 48.3% had ever undergone splenectomy, at a median (range) age of 6 years (1–57). Of the 166 patients who had received a transfusion before enrolment or during follow-up, 66.9% had a history of iron overload, as did 20.7% of patients who had never received a transfusion (Table S3). An additional 12 patients who did not meet the criteria for history of iron overload had ferritin between 500 and 1000 µg/L, suggesting probable iron overload. Demographic characteristics, medical history and laboratory values for patients by age group and *PKLR* genotype are shown in Table 1 and by *PKLR* genotype and sex in Table S4.

Paediatric comorbidities and complications

Among the 104 paediatric patients, 35 were < 6 years of age at most recent visit, 35 were 6–<12 years and 34 were 12–<18 years. For these age groups, the proportions of patients ever having a splenectomy were 0.0%, 40.0% and 61.8%, respectively; the proportions of patients who ever received chelation therapy were 40.0%, 62.9% and 55.9%, respectively (Table 1). Median (range) haemoglobin in the <6 years, 6–<12 years and 12–<18 years of age cohorts were 9.1 g/dL (5.8–12.0), 8.5 g/dL (6.8–11.3) and 9.2 g/dL (7.1–14.4), respectively.

Eighty-five paediatric patients had classifiable genotype information; 57.6% were classified as M/M, 31.8% as M/NM and 10.6% as NM/NM. Ever having splenectomy was most common in the NM/NM cohort. Splenectomy had been performed in 28.6% of the M/M cohort, 33.3% of the M/NM cohort and 66.7% of the NM/NM cohort, at median (range) age of 6 (2–10), 5 (3–10) and 5 (4–10) years, respectively. Treatment with chelation was common across paediatric age groups (Table 1).

The most common neonatal comorbidities, complications or symptoms were jaundice (64.2%), splenomegaly (18.9%) and hepatomegaly (17.9%). These complications occurred regardless of genotype (neonatal jaundice: M/M: 63.0%, M/NM: 79.2% and NM/NM: 50.0%; neonatal splenomegaly: M/M: 15.2%, M/NM: 37.5% and NM/NM: 25.0%; neonatal hepatomegaly: M/M: 17.4%, M/NM: 33.3% and NM/NM: 12.5%) (Table S2). Other neonatal complications included thrombocytopenia (15.8%), preterm delivery (15.8%) and pulmonary hypertension (5.3%). Neonatal management was required in 62.4% of patients, which included phototherapy (52.9%), exchange transfusion (21.2%) and in utero transfusions (1.2%).

Other comorbidities and complications in the paediatric cohort are shown in Figures 1 and 2A and Table S2. Notable complications in those with genotype data were history of biliary events (overall: 19.8%; M/M: 17.0%; M/NM: 23.1%; NM/NM: 25.0%), extramedullary haematopoiesis (overall:

TABLE 1 Demographics, medical history and laboratory parameters for patients with PK deficiency stratified by age at most recent visit and by *PKLR* genotype.

	All patients	Patients by age		
		<6 years	6–<12 years	12–<18 years
	N = 241	*N* = 35	*N* = 35	*N* = 34
Demographics				
Age at enrolment, median (range), years	19 (0–77)	2 (0–5)	7 (2–11)	12 (8–17)
Age at most recent visit, median (range), years	21 (0–78)	4 (0–5)	9 (6–11)	14 (12–17)
Female, *n*/*N*′ (%)	131/241 (54.4)	19/35 (54.3)	11/35 (31.4)	23/34 (67.6)
Medical history				
Age at PK deficiency diagnosis,[b] *n*	233	35	34	32
Median (range), years	3 (–1 to 68)[c]	0 (–1 to 3)[c]	1 (–1 to 9)[c]	4 (0–14)
Never transfused,[d] *n*/*N*′ (%)	58/227 (25.6)	3/35 (8.6)	6/35 (17.1)	3/33 (9.1)
Ever had splenectomy,[d] *n*/*N*′ (%)	111/230 (48.3)	0/35 (0.0)	14/35 (40.0)	21/34 (61.8)
Age at splenectomy, *n*	110	0	14	20
Median (range), years	6 (1–57)	NA	5 (2–10)	6 (3–10)
Ever had chelation therapy,[d] *n*/*N*′ (%)	112/222 (50.5)	14/35 (40.0)	22/35 (62.9)	19/34 (55.9)
Laboratory values, median (range)				
Haemoglobin, *n*	184	23	33	26
g/dL	9.5 (5.8–18.3)	9.1 (5.8–12.0)	8.5 (6.8–11.3)	9.2 (7.1–14.4)
Reticulocyte percentage, *n*	93	15	20	15
%	8.7 (1.6–76.5)	6.0 (1.8–45.0)	6.5 (1.6–65.0)	20.8 (4.6–76.5)
Absolute reticulocytes, *n*	83	12	13	6
10^9/L	290 (25–1630)	168 (78–408)	236 (51–1425)	639 (143–1400)
Indirect bilirubin, *n*	108	13	26	17
mg/dL	3.3 (0.0–14.7)	3.0 (0.5–9.2)	3.6 (0.0–9.7)	4.7 (0.4–14.7)
Lactate dehydrogenase, *n*	110	13	18	17
U/L	250 (119–3820)	864 (528–3139)	595 (186–3820)	434 (143–2808)
Ferritin, *n*	123	14	18	18
µg/L	452 (2–7050)	736 (15–1761)	442 (26–3547)	332 (17–1993)

Note: The number of patients with known results (denoted as *N*′) was used as the denominator in calculation of percentage. Patients with data missing or with response as 'Not Reported' or 'Not Done' were excluded from the denominator.

Abbreviations: M/M, missense/missense; M/NM, missense/non-missense; NA, not available; NM/NM, non-missense/non-missense; PK, pyruvate kinase.

[a]Includes only patients with available *PKLR* genotype data.

[b]Age at PK deficiency diagnosis = year of PK deficiency diagnosis – year of birth.

[c]Age at diagnosis of –1 represents patients diagnosed in utero.

[d]Data as of most recent visit.

12.8%; M/M: 10.9%; M/NM: 20.8%; NM/NM: 0.0%), bone health problems (overall: 8.9%; M/M: 8.9%; M/NM: 7.7%; NM/NM: 12.5%) and cardiac complications (overall: 6.4%; M/M: 8.7%; M/NM: 4.2%; NM/NM: 0.0%). History of iron overload was reported in 55.3% of paediatric patients, 44.9% of patients with M/M genotype, 59.3% with M/NM genotype and 100.0% with NM/NM genotype. More females than males had iron overload in the <6 years (52.6% vs. 25.0%) and 6–<12 years (81.8% vs. 54.2%) age groups, but proportions were similar among patients aged 12–<18 years (60.9% vs. 63.6%; Table S4).

History of cholecystitis was not reported in any patients <6 years old, but cholecystitis had occurred in 6.1% of patients aged 6–<12 years and 23.3% of patients aged 12–<18 years (Table S2). History of thromboembolic events was reported in one paediatric patient, who was <6 years of age, had an M/NM genotype and had not had a prior splenectomy (Table S5). Sepsis was reported in eight paediatric patients, including three with documented or suspected neonatal sepsis. Two of these eight patients had undergone splenectomy and, in both cases, sepsis occurred postsplenectomy, one 39 months postsplenectomy and one 24 days postsplenectomy (Table S6). Both patients had received the pneumococcal conjugate (PCV13), pneumococcal polysaccharide (PPSV23), quadrivalent meningococcal and *Haemophilus influenzae* type B (HIB) vaccines (one patient had also received the meningococcal B vaccine, but this was unknown in the other patient). There were five paediatric

	Paediatric patients by genotype[a]			Adult patients by genotype[a]		
≥18 years	M/M	M/NM	NM/NM	M/M	M/NM	NM/NM
N = 137	*N* = 49	*N* = 27	*N* = 9	*N* = 74	*N* = 31	*N* = 9
33 (16–77)	6 (0–16)	6 (0–15)	11 (3–17)	36 (16–77)	26 (18–77)	27 (16–50)
34 (18–78)	9 (0–17)	7 (1–16)	13 (5–17)	38 (18–77)	27 (18–78)	28 (18–53)
78/137 (56.9)	25/49 (51.0)	12/27 (44.4)	6/9 (66.7)	44/74 (59.5)	17/31 (54.8)	5/9 (55.6)
132	47	26	9	73	30	8
14 (0–68)	1 (−1 to 14)[c]	0 (0–11)	3 (−1 to 11)[c]	15 (0–68)	15 (0–54)	3 (0–22)
46/124 (37.1)	5/48 (10.4)	3/27 (11.1)	0/9 (0.0)	26/67 (38.8)	12/29 (41.4)	0/9 (0.0)
76/126 (60.3)	14/49 (28.6)	9/27 (33.3)	6/9 (66.7)	42/68 (61.8)	17/31 (54.8)	8/9 (88.9)
76	14	8	6	42	17	8
6 (1–57)	6 (2–10)	5 (3–10)	5 (4–10)	9 (2–57)	5 (1–18)	6 (1–12)
57/118 (48.3)	21/49 (42.9)	15/27 (55.6)	9/9 (100.0)	28/60 (46.7)	11/31 (35.5)	8/9 (88.9)
102	38	19	8	57	24	9
9.9 (5.9–18.3)	9.2 (6.2–12.1)	8.4 (5.8–12.0)	7.7 (7.1–14.4)	10.3 (6.8–13.3)	10.3 (6.7–15.5)	7.5 (5.9–18.3)
43	27	10	2	19	10	4
7.3 (2.7–66.3)	11.3 (2.0–76.5)	8.8 (1.6–48.5)	17.9 (6.0–29.8)	5.3 (3.1–66.3)	10.4 (4.7–33.4)	18.4 (2.7–26.6)
52	13	7	3	33	9	4
377 (25–1630)	236 (77–1400)	190 (51–1425)	263 (144–980)	447 (25–1630)	268 (122–1090)	814 (470–1327)
52	26	14	6	26	13	6
2.5 (0.7–11.0)	3.5 (0.0–9.2)	3.7 (0.5–12.5)	5.2 (0.3–13.9)	2.3 (0.8–11.0)	2.3 (0.8–9.1)	2.5 (0.7–5.5)
62	25	11	6	35	14	5
199 (119–1096)	721 (143–2255)	631 (184–3820)	361 (166–3139)	178 (119–625)	207 (147–318)	225 (140–411)
73	27	12	3	45	15	5
452 (2–7050)	379 (15–1993)	472 (102–2997)	1436 (874–1617)	376 (2–2700)	735 (83–3244)	4271 (2–7050)

patients who had documented neonatal pulmonary hypertension, and three whose pulmonary hypertension was suspected to be neonatal.

Adult comorbidities and complications

Of 137 adult patients, 114 had classifiable genotype information; 64.9% were classified as M/M, 27.2% as M/NM and 7.9% as NM/NM. Most adults with an NM/NM genotype had ever had a splenectomy (88.9%), and median haemoglobin levels in this subgroup were numerically lower than in the M/M and M/NM subgroups, where splenectomy rates were 61.8% and 54.8%, respectively (Table 1).

The percentages of adult patients who had select complications across genotypes are shown in Figure 2B. Jaundice (including neonatal jaundice), a consequence of long-term haemolysis, was common for adult patients across genotypes (overall: 52.4%; M/M: 55.7%; M/NM: 48.3%; NM/NM: 33.3%), as were biliary events (overall: 35.6%; M/M: 36.8%; M/NM: 30.0%; NM/NM: 50.0%) and bone health problems (overall: 29.1%; M/M: 26.5%; M/NM: 33.3%; NM/NM: 40.0%). Overall, osteopenia/osteoporosis was not uncommon, reported in 19.0% of patients, despite the overall median (range) age at most recent visit for the adult cohort of 34 years (18–78) (Table 1; Table S2).

Extramedullary haematopoiesis was reported across genotypes (overall: 11.0%; M/M: 7.7%; M/NM: 13.3%;

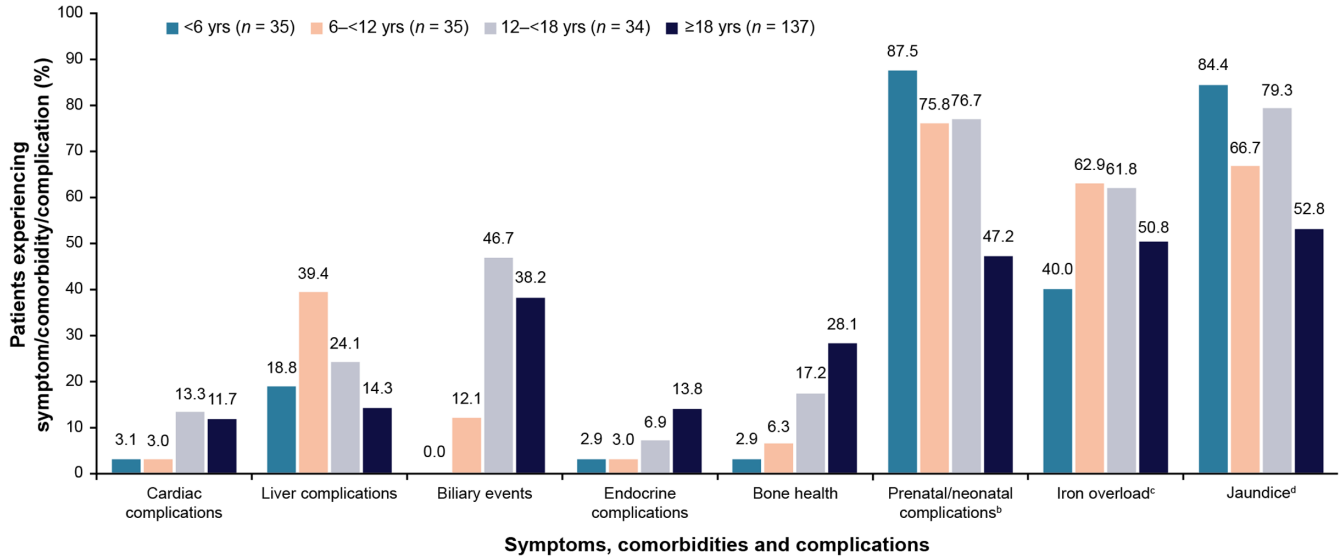

FIGURE 1 Lifetime history of symptoms, comorbidities and complications[a] in patients with PK deficiency stratified by age at most recent visit. MRI, magnetic resonance imaging; PK, pyruvate kinase; yrs, years. [a]Symptoms, comorbidities and complications are derived from enrolment and follow-up data. [b]The substantially lower proportions of prenatal/neonatal complications experienced by patients who are now ≥18 years of age compared with paediatric cohorts suggests recall bias in the ≥18 years cohort. [c]Iron overload defined as ever having received (up to date): (1) chelation therapy; or (2) phlebotomy for removal of iron collected at enrolment and during follow-up; or within 3 months of enrolment or during study follow-up period had any of: (3) ferritin >1000 ng/mL; (4) liver MRI (including FerriScan®) >3 mg Fe/g dry weight; and (5) cardiac T2* MRI ≤20 ms. [d]Includes neonatal jaundice.

NM/NM: 40.0%) (Table S2). History of liver complications was reported in 14.9% of adults and cardiac complications had occurred in 12.7%. Arrhythmia (8.3%) and pulmonary hypertension (6.7%) were the most common cardiac complications. History of iron overload occurred in 50.5% of adults overall, and 49.3% of M/M, 41.9% of M/NM and 88.9% of NM/NM patients. Numerically more males than females had iron overload in the adult cohort (61.4% vs. 42.7%); this was consistent across genotypes. Median (range) ferritin levels were also higher in males than females (756 µg/L [112–6208] vs. 355 µg/L [2–7050]; Table S4). Of adult patients who had never received a transfusion, 30.8% of M/M patients and 16.7% of M/NM patients had a history of iron overload (no NM/NM patients had ever been transfused) (Table S3).

Among the 10 adult patients with documented thromboembolic events, nine had previously undergone splenectomy, of whom eight had thromboembolic events postsplenectomy (one patient had not had a splenectomy up to data cut-off, and the timing of the thromboembolic event relative to splenectomy was uncertain for one patient; Table S5). In one of these eight patients, the thromboembolic event was perioperative (i.e. the thromboembolic event occurred within 1 month of the splenectomy procedure). In addition, among the three adults with a diagnosis of sepsis, all had a splenectomy, of whom one had sepsis 25 years postsplenectomy (they had received the PCV13 and quadrivalent meningococcal vaccines, but it was unknown if they had received the PPSV23, HIB or meningococcal B vaccines), one had sepsis 42 years postsplenectomy (it was unknown if they had received any of these vaccines) and one had sepsis 3 years presplenectomy (they had received the PCV13, HIB and PPSV23 vaccines, but not the quadrivalent meningococcal or the meningococcal B vaccines; Table S6).

Age of onset of comorbidities and complications

The age of onset of select comorbidities and complications is shown in Table 2. Iron overload often began at an early age (71.0% were aged <18 years), with a median (range) age of onset of 5 years (0–68). Onset age was similar in males and females, regardless of transfusion status (Table S7). Median (range) age of onset was 37 years (9–76) for osteopenia and 33 years (9–68) for osteoporosis. Liver disease also generally occurred early, with 47.6% of the 21 patients with known age of onset being under 2 years of age, with a median (range) age of onset of 1 year (0–57).

Jaundice affected 41.6% of patients with age at onset data, of whom 71.7% had ongoing jaundice. Among the patients with ongoing jaundice, overall median (range) age was 19 years (0–51), and 43.9% were aged 18–<40 years.

DISCUSSION

This study, the first using data from the Peak Registry, a large, global, real-world patient registry, evaluated the prevalence and age of onset of comorbidities and complications in patients with PK deficiency. We report that adult and paediatric patients have serious comorbidities and complications across multiple systems, regardless of *PKLR* genotype.

The results presented here support previously reported data, showing that iron overload occurs in a substantial

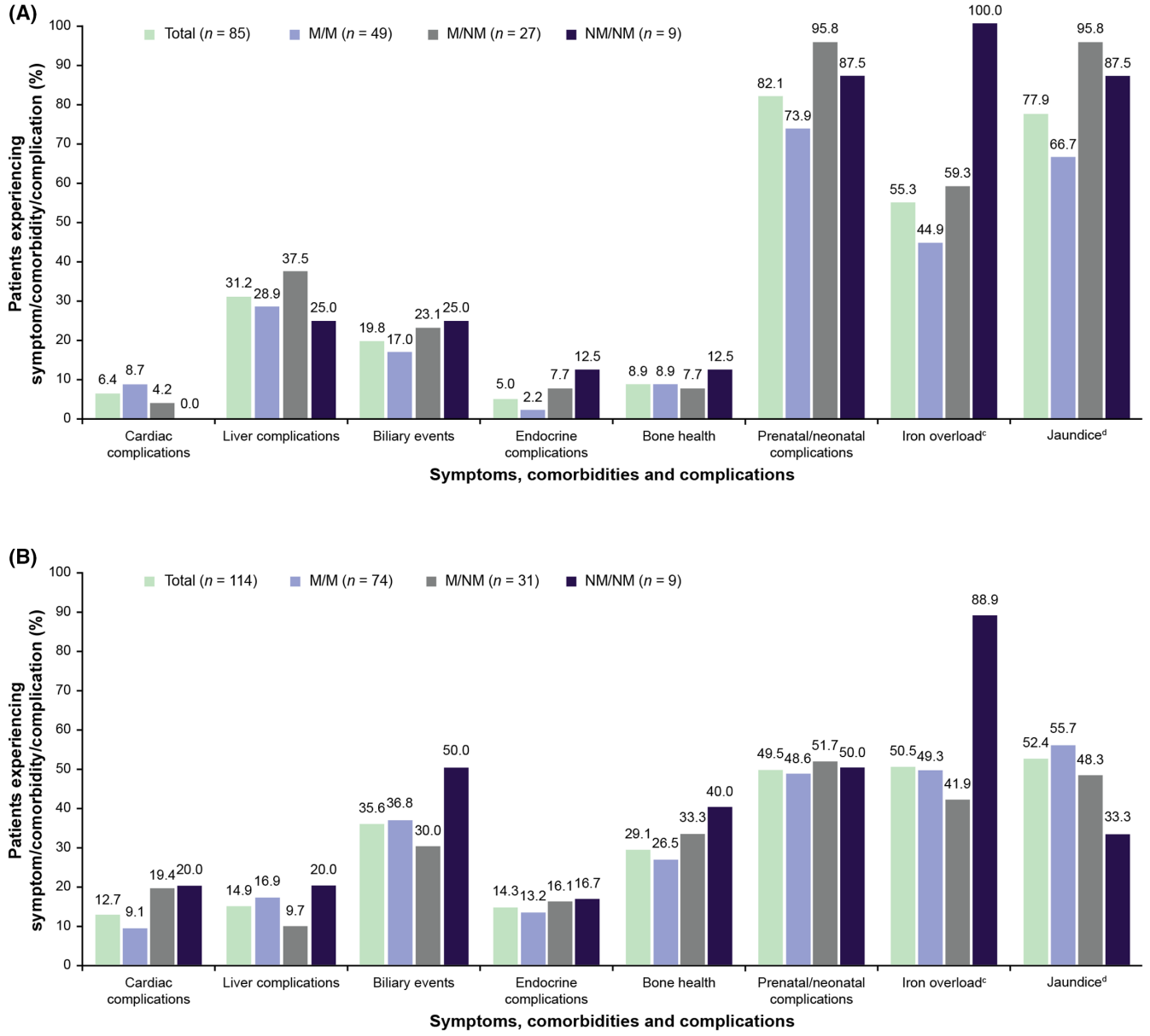

FIGURE 2 Lifetime history of symptoms, comorbidities and complications[a] in patients with PK deficiency stratified by *PKLR* genotype. (A) Lifetime history of symptoms, comorbidities and complications in paediatric patients by genotype.[b] (B) Lifetime history of symptoms, comorbidities and complications in adult patients by genotype.[b] M/M, missense/missense; M/NM, missense/non-missense; MRI, magnetic resonance imaging; NM/NM, non-missense/non-missense; PK, pyruvate kinase. [a]Symptoms, comorbidities and complications are derived from enrolment and follow-up data. [b]Low NM/NM patient numbers make the true prevalence of complications difficult to assess. [c]Iron overload defined as ever having received (up to date): (1) chelation therapy; or (2) phlebotomy for removal of iron collected at enrolment and during follow-up; or within 3 months of enrolment or during study follow-up period had any of: (3) ferritin >1000 ng/mL; (4) liver MRI (including FerriScan®) >3 mg Fe/g dry weight; and (5) cardiac T2* MRI ≤20 ms. [d]Includes neonatal jaundice.

number of patients in the Peak Registry and the NHS (55% vs. 48% in paediatric patients and 51% vs. 62% in adults, respectively).[11,12] However, it should be noted that 74/241 (31%) patients enrolled in the Peak Registry were also previously enrolled in the NHS, meaning some patients are represented in both databases. Iron overload was common across all ages and *PKLR* genotypes, and even occurred in patients who had never received a transfusion, demonstrating that iron overload is part of the underlying pathophysiology of PK deficiency. Appropriate monitoring and management of this complication is therefore important in patients with PK deficiency, regardless of transfusion status. In addition, over half (62/112, 55%) of patients in the analysis who did not meet the criteria for history of iron overload did not have available ferritin or MRI liver iron concentration data, suggesting a possible underestimation of iron overload in this population. Furthermore, as the registry only captures ferritin levels and MRI liver iron concentration data in the 3 months before enrolment, it is likely that patients who have never been chelated or phlebotomised are missed from this estimate of iron

TABLE 2 Age of onset of select complications and comorbidities in patients with PK deficiency.

Comorbidity or complication	Number of patients with known age of onset, *n* *N* = 241	Number of patients by age of onset, *n* 0–<2 years	2–<12 years	12–<18 years	18–<40 years	40–<65 years	≥65 years	Age of onset, median (range), years
Liver disease[a]	21	10	5	0	1	5	0	1 (0–57)
Hepatitis B	9	0	3	0	5	1	0	29 (4–51)
Hepatitis C	3	0	2	0	1	0	0	5 (2–21)
Sepsis	11	5	4	0	1	1	0	2 (0–47)
Pulmonary hypertension	9	3	0	1	1	3	1	22 (0–77)
Pulmonary embolism	4	0	0	0	3	1	0	31 (18–55)
Deep vein thrombosis	5	0	0	0	3	1	1	35 (29–66)
Portal vein thrombosis	3	0	0	0	3	0	0	24 (23–26)
Osteopenia	16	0	1	1	7	6	1	37 (9–76)
Osteoporosis	7	0	1	0	3	2	1	33 (9–68)
Cholecystitis	25	0	8	8	6	3	0	15 (3–58)
Cholangitis	1	0	1	0	0	0	0	7 (7–7)
Mental health (including depression and anxiety)	26	0	2	4	13	4	3	27 (9–74)
Iron overload[b,c]	100	9	55	7	16	12	1	5 (0–68)
Among patients never transfused	8	1	0	0	1	5	1	49 (1–68)
Among patients regularly transfused[d]	33	2	26	3	1	1	0	3 (1–45)
Among patients not regularly transfused[e]	67	7	29	4	15	11	1	10 (0–68)
Splenectomy	109	2	89	11	6	1	0	6 (1–57)

Abbreviations: MRI, magnetic resonance imaging; PK, pyruvate kinase.

[a]Liver disease combines the terms 'Cirrhosis', 'Non-alcoholic fatty liver disease' and 'Non-alcoholic steatohepatitis'.

[b]For lifetime prevalence, iron overload defined as ever having received: (1) chelation therapy; or (2) phlebotomy for removal of iron collected at enrolment and during follow-up; or within 3 months of enrolment or during study follow-up period had any of: (3) ferritin >1000 ng/mL; (4) liver MRI (including FerriScan®) >3 mg Fe/g dry weight; and (5) cardiac T2* MRI ≤20 ms.

[c]For age distribution, iron overload defined as a history of 'ever chelation' or 'ever phlebotomy'.

[d]≥6 transfusions in the 12 months before enrolment.

[e]0–5 transfusions in the 12 months before enrolment.

overload prevalence, thereby potentially further underestimating the burden of iron overload.

Our finding that more adult than paediatric patients have never been transfused is noteworthy. However, these data should be interpreted with caution because they reflect real-life diagnosis patterns, including delayed diagnosis. Indeed, it is entirely plausible that more paediatric patients with PK deficiency have a history of never having been transfused, but are absent from the registry data due to not yet having a PK deficiency diagnosis. In addition, although there appeared to be a decrease in lactate dehydrogenase with age, this finding may be because adult patients in the registry are collectively clinically different to paediatric patients; for example, paediatric patients may have to be more clinically severe in order to present with symptoms that lead to a PK deficiency diagnosis at an early age, whereas a subset of the adult population may not have been diagnosed as young children as they are phenotypically different. Indeed, as shown in Table 1, the median age for PK deficiency diagnosis among adults was 14 years, whereas, in children, the median age was 0 for those younger than 6 years of age, 1 year for those aged 6–<12 years and 4 years for those aged 12–<18 years.

Other management strategies and complications were reported in similar proportions in the Peak Registry compared with the NHS: splenectomy in children (34% vs. 42%), pulmonary hypertension in adults (7% vs. 5%) and liver cirrhosis in adults (3% vs. 6%).[11,12] Osteopenia and osteoporosis were common among adults in the Peak Registry (19%), while the median age of onset of osteopenia was greater (37 years) than for osteoporosis (33 years), in contrast to what might be expected clinically (i.e. osteopenia occurring earlier than osteoporosis). For all but one of the patients, osteopenia or osteoporosis was reported, and not both. Thus, the median values for each condition were calculated based on two distinct subsets and influenced by the distribution of age at onset data in each group. These events were not frequently observed in paediatric patients, and they were reported at lower levels than previously shown at baseline in the DRIVE-PK (NCT02476916), ACTIVATE (NCT03548220) and ACTIVATE-T (NCT03559699) clinical trials, which required baseline dual-energy X-ray absorptiometry scans and reported osteopenia or osteoporosis in 43% of patients.[20] The lower levels of osteopenia/osteoporosis diagnosis observed here suggest that patients in the Peak Registry may not be routinely screened for bone health problems, resulting in underdiagnosis and potentially suboptimal management.

This analysis also shows that patients with PK deficiency, particularly neonates, have varied disease presentations (e.g. hyperferritinaemia, thrombocytopenia and pulmonary hypertension) that may be difficult to recognise as being due to PK deficiency, potentially leading to initial misdiagnosis and unnecessary or inappropriate interventions. Clinicians should be aware of all manifestations of PK deficiency to ensure patients receive appropriate diagnosis, monitoring and management.

Splenectomy had been performed in approximately half of all patients in this analysis, and in most adults and adolescents. Although splenectomy can increase haemoglobin levels and reduce transfusion burden in patients with PK deficiency, the improvement in anaemia is only partial and is not effective for all patients.[21] In addition, most thromboembolic events and 4/11 sepsis events observed in the Peak Registry occurred postsplenectomy. PK deficiency may increase the risk of sepsis, however, in contrast to sickle cell anaemia, loss of spleen function is not thought to be intrinsic to PK deficiency.[22] If this were the case, one would expect a high incidence of sepsis throughout the age continuum, rather than only in children.

Onset of osteopenia/osteoporosis, liver disease and cholecystitis tended to be observed at younger-than-expected ages than in the general population.[23–25] These findings indicate that the disease burden associated with PK deficiency starts early in life. In addition, jaundice is a common consequence of the long-term haemolytic process observed in PK deficiency. It occurred throughout the lifespan of patients, starting in the neonatal period in many. However, approximately half of adults also had ongoing jaundice. Clinicians should therefore be aware that this symptom, which can negatively impact patients' HRQoL, can be present in all age groups.[14]

A limitation of the study was the low number of NM/NM patients, although this is expected due to the intrinsic nature of PK deficiency.[9] Furthermore, although the eCRFs require inputting of lifetime medical history, for many adult patients, recall bias or incomplete medical histories may result in medical records inadequately reflecting conditions that they may have had as children or young adults; frequencies of historic conditions reported, particularly neonatal complications, could be understated. Finally, prevalence rates and age of onset for comorbidities and complications in this analysis represent only diagnosed prevalence, so may exclude complications that have not yet been diagnosed or have been misdiagnosed.

Enrolment and follow-up for the Peak Registry is ongoing until 2025.[19] Participants in the Peak Registry who were originally included in the NHS from 2014 to 2017 and for whom data are integrated within the Peak Registry may have a cumulative follow-up exceeding 11 years.[19] Further analyses with merged data from the NHS and the Peak Registry are currently underway and active involvement from the patient community will continue to help shape the reporting and analyses that are undertaken in the registry. The longitudinal design of the Peak Registry will allow for continued monitoring and follow-up of comorbidities and complications in patients with PK deficiency. In addition, the current analysis focuses on description of patients with PK deficiency and a wide spectrum of their comorbidities and complications. Some interesting findings could be investigated in subsequent research to further improve understanding. For example, a higher proportion of patients 'never transfused' was observed in the adult population (37.1% [95% confidence interval: 28.6%, 46.2%]) than in the paediatric population (11.7% [6.2%, 19.5%]), which may not be consistent with common understanding. Future research

on this observed difference (e.g. statistical inference using rigorous statistical approaches) and on the reasons leading to such differences can be considered.

This analysis shows that PK deficiency is associated with multiple, serious, long-term comorbidities and complications. Both adult and paediatric patients with PK deficiency have a high disease burden, and early monitoring and management by clinicians is indicated.

AUTHOR CONTRIBUTIONS

Rachael F. Grace, Eduard J. van Beers, Bertil Glader, Yan Yan and Paola Bianchi contributed to the conception and design of the registry. Andreas Glenthøj, Rachael F. Grace, Carl Lander, Eduard J. van Beers, Bertil Glader, Kevin H. M. Kuo, Yan Yan, Bryan McGee, Audra N. Boscoe, Junlong Li and Paola Bianchi helped to draft and revise the manuscript and read and approved the final manuscript. Andreas Glenthøj is responsible for the overall content as guarantor.

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CONFLICT OF INTEREST STATEMENT

Andreas Glenthøj: Consultant/advisory committee member for Agios Pharmaceuticals, Inc., Bristol Myers Squibb, Novartis Pharmaceuticals, Novo Nordisk A/S, Pharmacosmos UK Ltd. and Vertex Pharmaceuticals, Inc. Received research support from Agios Pharmaceuticals, Inc., Bristol Myers Squibb, Novo Nordisk A/S, Saniona and Sanofi. Rachael F. Grace: Received research funding from Agios Pharmaceuticals, Inc., Novartis Pharmaceuticals and Sobi. Consultant for Agios Pharmaceuticals, Inc. and Sanofi. Carl Lander: Received payment as a patient representative on the Agios Pharmaceuticals, Inc. PK Deficiency Patient Advocacy Advisory Council. Eduard J. van Beers: Advisory committee member for Agios Pharmaceuticals, Inc. Received research funding from Agios Pharmaceuticals, Inc., Novartis Pharmaceuticals, Pfizer, Inc. and RR Mechatronics International B.V. Bertil Glader: Consultant for Agios Pharmaceuticals, Inc. Kevin H. M. Kuo: Consultant for Agios Pharmaceuticals, Inc., Alexion Pharmaceuticals, Inc., Apellis Pharmaceuticals, bluebird bio, Inc., Celgene Corporation, Novartis Pharmaceuticals and Pfizer, Inc. Received honoraria from Alexion Pharmaceuticals, Inc. and Novartis Pharmaceuticals. Member of the Data Safety Monitoring Board of Bioverativ, Inc. Received research funding from Pfizer, Inc. Yan Yan, Bryan McGee, Audra N. Boscoe, Junlong Li: Employees of Agios Pharmaceuticals, Inc. and own shares in the company. Paola Bianchi: Scientific advisor for Agios Pharmaceuticals, Inc.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to related clinical study documents. Send your data-sharing requests to data-sharing@agios.com. The following considerations will be taken into account as part of the review: (1) Ability for external researchers to re-identify trial participants such as small rare disease trials or single-centre trials; (2) Language used in data and requested documents (e.g. English or other); (3) Informed consent language with respect to allowance for data sharing; (4) Plan to re-evaluate safety or efficacy data summarised in the approved product labelling; (5) Potential conflict of interest or competitive risk.

ETHICAL APPROVAL STATEMENT

The protocol and informed consent form were approved by an Institutional Review Board/Independent Ethics Committee at each study site and the study was performed in accordance with the ethical principles of the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

Written informed consent and assent, when appropriate, will be/have been obtained from all enrolled patients and/or their guardians.

CLINICAL TRIAL REGISTRATION NUMBER

Peak Registry; NCT03481738.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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