Comorbidities and complications in adults with pyruvate kinase deficiency according to hemoglobin strata: A descriptive analysis from the Peak Registry

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BACKGROUND

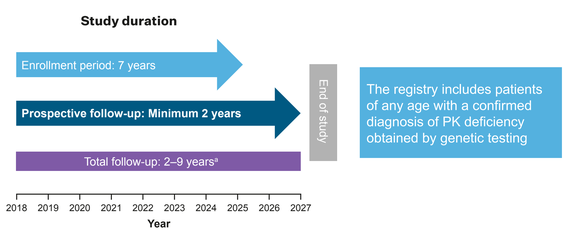
- Pyruvate kinase (PK) deficiency is a rare, congenital, hemolytic anemia caused by mutations in the *PKLR* gene[1]
- Hemoglobin (Hb) levels are an important assessment of disease, but patients with less pronounced anemia (Hb >10 g/dL) may still experience symptoms and complications due to the underlying pathophysiology of PK deficiency[1]
- The Pyruvate Kinase Deficiency Global Longitudinal (Peak) Registry (NCT03481738), which began in 2018, was designed to address the gaps in knowledge of PK deficiency and allows for investigation into treatment outcomes, the variability and severity of complications, and disease burden of patients with PK deficiency, including those with Hb >10 g/dL[2]
- The Peak Registry is a global, retrospective and prospective, observational study of patients with PK deficiency,[2] with 261 patients meeting eligibility criteria and enrolled as of 27Mar2023

OBJECTIVE

- **To describe the comorbidities and complications of adults with PK deficiency and average Hb >10 g/dL enrolled in the Peak Registry**

METHODS

Figure 1. Peak Registry study design and duration[2]



[a]Participants in the Peak Registry who were originally included in the PK Deficiency Natural History Study from 2014 to 2017 and for whom data are integrated within the Peak Registry may have a cumulative follow-up exceeding 11 years; PK, pyruvate kinase

- The Peak Registry will continue enrolling until early 2025[2]
- All participants are followed prospectively for at least 2 years and for up to 9 years[2] **(Figure 1)**
- This analysis included adult patients (≥18 years at enrollment) with Hb data available as of the data cutoff date of 13May2022
  - Hb data were collected within 3 months prior to enrollment and during follow-up
  - All Hb data collected ≤61 days post-transfusion were considered ineligible
- Patients were grouped into 2 cohorts based on mean Hb value across eligible data: >10 g/dL and ≤10 g/dL
- Data on demographics, clinical characteristics, medical history, and selected medical complications were collected at study enrollment and during follow-up via electronic case report forms
  - Data on markers of hemolysis were only collected for 3 months prior to enrollment and during follow-up
  - These data were summarized descriptively for all patients and for each cohort
- All comorbidities and complications included as clinically relevant to patients with PK deficiency are presented in **Supplemental Tables 1–5 (QR code)**

RESULTS

Demographics at enrollment

- 93 patients were included in the analysis, of whom 48 (51.6%) had mean Hb >10 g/dL
  - 8 patients were excluded as all their Hb measurements were taken ≤61 days post-transfusion
- Age and sex were similar between cohorts **(Table 1)**
- Patients from 13 different countries were included in the analysis **(Supplemental Figure 1 [QR code])**

Medical history

- Of patients with Hb >10 g/dL and patients with Hb ≤10 g/dL, 34.9% and 83.3%, respectively, had received a transfusion within their lifetime **(Table 1)**
- 36.4% of patients with Hb >10 g/dL had undergone splenectomy by most recent follow-up, at a median (range) age of 14 years (2–58), compared with 81.8% of patients with Hb ≤10 g/dL, at a median (range) age of 7 years (2–20) **(Table 1)**

Table 1. Demographics and medical history

	Patients by average Hb level at enrollment	
	Hb >10 g/dL N=48	Hb ≤10 g/dL N=45
Demographics		
Age at enrollment, median (range), years	36 (18–70)	33 (18–71)
Female, n (%)	27 (56.3)	25 (55.6)
Medical history		
Age at PK deficiency diagnosis, median (range), years	20 (0–60)	6 (0–55)
PKLR mutation class, n/N' (%)		
M/M	29/44 (65.9)	24/37 (64.9)
M/NM	13/44 (29.5)	9/37 (24.3)
NM/NM	2/44 (4.5)	4/37 (10.8)
Never transfused, n/N' (%)	28/43 (65.1)	7/42 (16.7)
Ever transfused, n/N' (%)	15/43 (34.9)	35/42 (83.3)
Lifetime transfusion status		
Regularly transfused (≥6 transfusions in any 12-month period), n/N' (%)	8/45 (17.8)	17/41 (41.5)
Non-regularly transfused (no more than 5 transfusions in any 12-month period), n/N' (%)	37/45 (82.2)	24/41 (58.5)
Ever had chelation therapy, n/N' (%)	12/44 (27.3)	25/41 (61.0)
Ever had splenectomy, n/N' (%)	16/44 (36.4)	36/44 (81.8)
Age at splenectomy, median (range), years	14 (2–58)	7 (2–20)

N' represents the number of patients with data available. Range represents the minimum and maximum values within the group; Hb, hemoglobin; M/M, missense/missense; M/NM, missense/non-missense; NM/NM, non-missense/non-missense; PK, pyruvate kinase

Hematologic and iron markers

- The median (range) Hb value for patients with Hb >10 g/dL was 11.6 g/dL (10.1–18.3) and 8.8 g/dL (6.4–10.0) for patients with Hb ≤10 g/dL **(Table 2)**
- The median (range) hematologic and iron marker values (collected 3 months prior to enrollment and during follow-up) for patients with Hb >10 g/dL and Hb ≤10 g/dL, respectively, were **(Table 2)**:
  - Reticulocyte percentage: 6% (3–41) and 28% (4–43)
  - Indirect bilirubin: 1.8 mg/dL (0.7–10.8) and 3.2 mg/dL (1.9–8.1)
  - Ferritin: 304 µg/L (35–6208) and 735 µg/L (17–7050)

Table 2. Enrollment and follow-up hematologic and iron markers

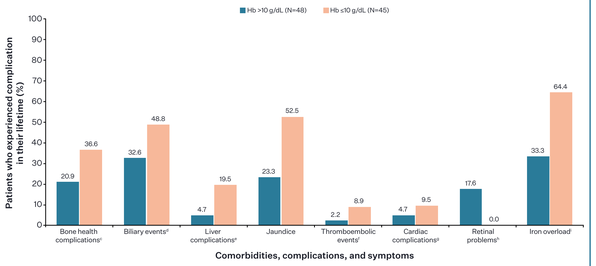
	Patients by average Hb level at enrollment	
	Hb >10 g/dL N=48	Hb ≤10 g/dL N=45
Hb,[a] median (range), g/dL	11.6 (10.1–18.3)	8.8 (6.4–10.0)
Reticulocyte percentage, median (range), %	6 (3–41)	28 (4–43)
Indirect bilirubin, median (range), mg/dL	1.8 (0.7–10.8)	3.2 (1.9–8.1)
Lactate dehydrogenase, median (range), U/L	180 (133–625)	220 (114–770)
Ferritin, median (range), µg/L	304 (35–6208)	735 (17–7050)

Range represents the minimum and maximum values within the group; [a]Hb data collected ≤61 days post-transfusion were considered ineligible, per the cohort definition. Values were not excluded for other hematologic and iron markers, as these were summarized by visit; Hb, hemoglobin

Comorbidities, complications, and symptoms of PK deficiency

- Bone health complications (fracture, osteopenia, osteoporosis, and bone pain) occurred in 20.9% of patients with Hb >10 g/dL and 36.6% of patients with Hb ≤10 g/dL **(Figure 2)**
  - Within both cohorts, high proportions of patients experienced osteopenia/osteoporosis (Hb >10 g/dL: 18.6%; Hb ≤10 g/dL: 17.1%) **(Supplemental Table 1 [QR code])**
- Biliary events (cholecystitis, cholangitis, asymptomatic gallstones, and bile duct stones) were common in both cohorts, affecting 32.6% of patients with Hb >10 g/dL and 48.8% of patients with Hb ≤10 g/dL **(Figure 2)**
  - Cholecystitis occurred in 20.9% of patients with Hb >10 g/dL and 26.8% of patients with Hb ≤10 g/dL **(Supplemental Table 1 [QR code])**
- Jaundice occurred in 23.3% of patients with Hb >10 g/dL and 52.5% of patients with Hb ≤10 g/dL **(Figure 2)**
- Of patients with Hb >10 g/dL, 33.3% had experienced iron overload, compared with 64.4% of patients with Hb ≤10 g/dL **(Figure 2)**
- Other complications included extramedullary hematopoiesis (Hb >10 g/dL: 2.3%; Hb ≤10 g/dL: 15.0%), reticulocytopenia (Hb >10 g/dL: 2.3%; Hb ≤10 g/dL: 2.5%), hemolytic crisis (Hb >10 g/dL: 7.0%; Hb ≤10 g/dL: 10.0%), and hemochromatosis (Hb >10 g/dL: 11.6%; Hb ≤10 g/dL: 20.0%) **(Supplemental Table 2 [QR code])**

Figure 2. Lifetime history of comorbidities, complications, and symptoms of PK deficiency in each Hb group[a,b]



The number of patients with known results 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; [a]Comorbidities and complications were derived from baseline and/or follow-up data; [b]Not all specific conditions collected under these terms were necessarily observed in the registry; [c]Bone health complications were fracture, osteoporosis, osteopenia, and bone pain; [d]Biliary events were cholecystitis, cholangitis, asymptomatic gallstones, and bile duct stones; [e]Liver complications were non-alcoholic steatohepatitis, non-alcoholic fatty liver, hepatic cirrhosis, and hepatomegaly; [f]Thromboembolic events were deep vein thrombosis, pulmonary embolism, venous embolism, cerebral venous thrombosis, portal vein thrombosis, and ischemic stroke; [g]Cardiac complications were pulmonary hypertension, arrythmia, left ventricular hypertrophy, and congestive cardiac failure; [h]Retinal problems were reported as 'Other, please specify' in the case report forms; [i]Iron overload defined as ever having received: (1) chelation therapy; (2) phlebotomy for removal of iron; or within 3 months of enrollment or during study follow-up had any of: (3) ferritin >1000 ng/mL; (4) liver MRI (including FerriScan®) >3 mg Fe/g dry weight; (5) cardiac T2* MRI ≤20 ms; Hb, hemoglobin; MRI, magnetic resonance imaging; PK, pyruvate kinase

Comorbidities, complications, and symptoms of PK deficiency by splenectomy status

- Comorbidities, complications, and symptoms in adult patients with PK deficiency appear to occur regardless of splenectomy status **(Table 3)**
- For patients with Hb >10 g/dL, numerically higher proportions of splenectomized patients experienced bone health complications, biliary events, liver complications, jaundice, and retinal problems compared with non-splenectomized patients
- In patients with Hb ≤10 g/dL, numerically more patients who were splenectomized experienced bone health complications, biliary events, and liver complications compared with those who had not been splenectomized, in this group
  - The proportion of patients who experienced jaundice were similar between splenectomized and non-splenectomized patients in this group
- This analysis could not determine if these complications were caused by splenectomy or occurred as a result of the patients' disease severity

Table 3. Lifetime history of comorbidities, complications, and symptoms of PK deficiency in each Hb group by splenectomy status[a,b]

	Patients by average Hb level at enrollment			
	Hb >10 g/dL N=48		Hb ≤10 g/dL N=45	
Complications, n/N' (%)	Splenectomized (n=16)	Non-splenectomized (n=28)	Splenectomized (n=36)	Non-splenectomized (n=8)
Bone health complications[c]	7/15 (46.7)	2/26 (7.7)	13/33 (39.4)	2 (25.0)
Biliary events[d]	9 (56.3)	5/25 (20.0)	18/32 (56.3)	1 (12.5)
Liver complications[e]	2/15 (13.3)	0/26 (0.0)	7/33 (21.2)	1 (12.5)
Jaundice	6/14 (42.9)	2/26 (7.7)	17/32 (53.1)	4 (50.0)
Thromboembolic events[f]	1 (6.3)	0/24 (0.0)	3/33 (9.1)	1 (12.5)
Cardiac complications[g]	0/15 (0.0)	2/26 (7.7)	2/34 (5.9)	2 (25.0)
Retinal problems[h]	4/14 (28.6)	2/18 (11.1)	0/21 (0.0)	0/4 (0.0)
Iron overload[i]	6 (37.5)	22 (78.6)	8 (22.2)	7 (87.5)

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 unknown splenectomy status were excluded from the denominator and this subanalysis; [a]Comorbidities and complications were derived from baseline and/or follow-up data; [b]Not all specific conditions collected under these terms were necessarily observed in the registry; [c]Bone health complications were fracture, osteoporosis, osteopenia, and bone pain; [d]Biliary events were cholecystitis, cholangitis, asymptomatic gallstones, and bile duct stones; [e]Liver complications were non-alcoholic steatohepatitis, non-alcoholic fatty liver, hepatic cirrhosis, and hepatomegaly; [f]Thromboembolic events were deep vein thrombosis, pulmonary embolism, venous embolism, cerebral venous thrombosis, portal vein thrombosis, ischemic stroke, and other; [g]Cardiac complications were pulmonary hypertension, arrythmia, left ventricular hypertrophy, and congestive cardiac failure; [h]Retinal problems were reported as 'Other, please specify' in the case report forms; [i]Iron overload defined as ever having received: (1) chelation therapy; (2) phlebotomy for removal of iron; or within 3 months of enrollment or during study follow-up had any of: (3) ferritin >1000 ng/mL; (4) liver MRI (including FerriScan®) >3 mg Fe/g dry weight; (5) cardiac T2* MRI ≤20 ms; Hb, hemoglobin; MRI, magnetic resonance imaging; PK, pyruvate kinase

CONCLUSIONS

- **Patients with PK deficiency and less pronounced anemia (Hb >10 g/dL) experienced a wide range of comorbidities and complications**
- **As with patients with lower Hb levels, patients with Hb >10 g/dL also had hemolysis, iron overload, transfusion requirements, and the need for chelation therapy**
- **Furthermore, patients with Hb >10 g/dL experienced serious complications and symptoms of PK deficiency, such as bone health complications, biliary events, and jaundice**
- **A limitation of this study is that, as splenectomy improves Hb, this analysis cannot establish whether the complications observed in these patients occurred prior to or after splenectomy and the subsequent increase in Hb**

All patients with PK deficiency, regardless of Hb levels, may benefit from careful monitoring to reduce the risk of long-term complications

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DP: nothing to disclose. **RFG:** Agios, Novartis, Sobi – research funding; Agios, Sanofi – consulting. **AG:** Agios, bluebird bio, Bristol Myers Squibb, Novartis, Novo Nordisk, Pharmacosmos – consultancy/advisory board; Agios, Saniona, Sanofi – research support. **CL:** Agios PK Deficiency Patient Advocacy Advisory Council – patient representative. **EJvB:** Agios – advisory board member; Agios, Novartis, Pfizer, RR Mechatronics – research funding. **BG:** Agios – consultancy. **DML:** Agios, Novartis – consultancy; Agios, Cerus, Novartis – membership of an entity's Board of Directors or advisory committees. **KHMK:** Agios, Alexion, Apellis, bluebird bio, Celgene, Novartis, Pfizer – consultancy; Alexion, Novartis – honoraria; Agios, Bioverativ – membership on an entity's Board of Directors or advisory committees; Agios, Pfizer – research funding. **J-LVC:** nothing to disclose. **YY:** Agios – employee and shareholder. **BM:** Agios – employee and shareholder. **SH:** Agios – employee and shareholder. **PB:** Agios – scientific advisor.

References: 1. Grace RF et al. *Blood* 2018;20:2183–92. **2.** Grace RF et al. *BMJ Open* 2023;3:e063605.