Comorbidities and complications in adults with pyruvate kinase deficiency

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare congenital disorder caused by autosomal recessive mutations in the *PKLR* gene.
  - A glycolytic defect causes reduced adenosine triphosphate levels and leads to hemolytic anemia.
- A previously published analysis characterized the rates of comorbidities and complications among 254 pediatric and adult patients with PK deficiency.[1]

OBJECTIVES

- The objectives of this study were to:
  - Compare rates of comorbidities and complications between adults with PK deficiency and the general population.
  - Assess the impact of transfusion frequency on the prevalence of comorbidities and complications in adults with PK deficiency.

METHODS

Data sources

- The PK Deficiency Natural History Study (NHS):
  - Longitudinal cohort study that evaluated 254 patients with genetic confirmation of PK deficiency at 31 centers in six countries from June 2014 through April 2017.
- US-based IBM MarketScan® claims databases:
  - Inpatient, outpatient, and prescription drug claims for a representative sample of approximately 10% of the US population insured commercially or as part of the national Medicare or Medicaid (government health insurance) programs.
- Individuals from the general population were matched 10:1 to patients with PK deficiency on the basis of age, gender, and year of enrollment in the PK Deficiency NHS.

Study population and inclusion criteria

Patients with PK deficiency

- Age ≥18 years.
- Two confirmed mutations in the *PKLR* gene.
- Sufficient data on transfusion history to enable classification into one of three mutually exclusive cohorts:
  - Ever Regularly Transfused (ERT): Received transfusions, ≥6 in any year
  - Never Regularly Transfused (NRT): Received transfusions, ≤4 per year
  - Never Transfused (NT): Never received a transfusion

General population

- No hemolytic anemia diagnoses.
- ≥5 years of continuous enrollment in the MarketScan® databases.

Data analysis

- The PK Deficiency NHS reported lifetime history, whereas claims data were limited to what is clinically relevant and reported during the period of health plan enrollment.
- To minimize the risk of understating the occurrence of conditions and events in the matched general population, comparisons were limited to certain conditions, and three different analytic approaches were used:
  1. A focus on chronic conditions that require ongoing management and thus are likely to appear in claims data regardless of diagnosis date (osteoporosis, liver cirrhosis, and pulmonary hypertension)
  2. Medications for which the "current status" was reported in both datasets; medications (anticoagulants, prophylactic antibiotics, antidepressants, and antianxiety medications) were considered proxy indicators of comorbidities and complications
  3. A narrowing of the observation window for the PK deficiency population to be aligned with the average 8-year observation window for the general population with a focus only on conditions for which a diagnosis/procedure date was available in the PK Deficiency NHS population, so that events that occurred prior to the narrowed observation window could be distinguished and excluded from the analysis (splenectomy, cholecystectomy, and gallstones).

RESULTS

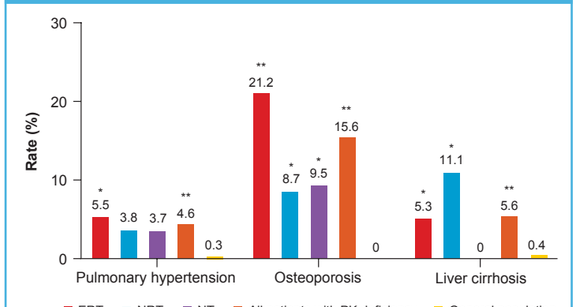
Table 1. Transfusion status and demographics of the PK deficiency cohort (N=122)

Parameter	ERT (n=65)	NRT (n=30)	NT (n=27)	p-value ERT vs NRT	p-value ERT vs NT
Male, n (%)	30 (46.2)	17 (56.7)	16 (59.3)	0.383	0.360
Age, mean (SD), years	34.2 (11.0)	39.5 (14.7)	37.2 (16.3)	0.083	0.383
White, n (%)	63 (96.9)	30 (100)	27 (100)	>0.999	>0.999
Hispanic or Latino, n (%)	2 (3.1)	1 (3.3)	1 (3.7)	>0.999	>0.999
Genotype, n (%)				0.085	0.003
Amish (R479H/R479H)	20 (30.8)	4 (13.3)	3 (11.1)		
Missense/missense	21 (32.3)	14 (46.7)	19 (70.4)		
Non-missense/missense	11 (16.9)	8 (26.7)	5 (18.5)		
Non-missense/non-missense	12 (18.5)	2 (6.7)	0 (0)		
Unknown	1 (1.5)	2 (6.7)	0 (0)		

The general population (N=1220) was matched by age and gender to the PK deficiency population
For sex, race, and ethnicity, the p-value is based on a two-sided Fisher's exact test; for age, the p-value is based on a two-sample t-test; for genotype, the p-value is based on a Chi-square test

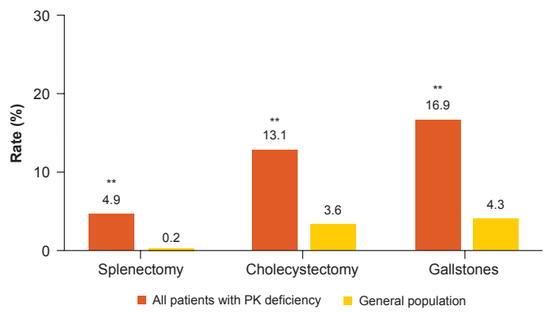
Comparisons with the general population

Figure 1. Adults with PK deficiency had higher lifetime rates of pulmonary hypertension, osteoporosis, and liver cirrhosis



All comparisons are based on a two-sided Fisher's exact test
*p<0.05 for PK Deficiency NHS population versus matched general population
**p<0.001 for PK Deficiency NHS population versus matched general population

Figure 2. Adults with PK deficiency had higher rates of splenectomy, cholecystectomy, and gallstones over the preceding 8 years



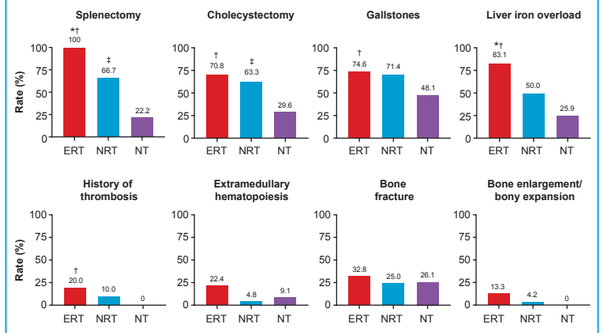
All comparisons are based on a two-sided Fisher's exact test
**p<0.001 for PK Deficiency NHS population versus matched general population

- Rates of current prophylactic antibiotic and anticoagulant use were also significantly higher among patients with PK deficiency (not shown).
- There were no differences in rates of antidepressant and anti-anxiety medication use.

Comparisons within the PK deficiency population by cohort

- For conditions for which fair and balanced comparisons with the general population could not be made, we show the lifetime prevalence rates just for the PK deficiency population, stratified by transfusion cohort (**Figure 3**).

Figure 3. Rates of many complications varied by transfusion cohort



All comparisons are based on two-sided Fisher's exact test
*p<0.05 for ERT versus NRT
†p<0.05 for ERT versus NT
‡p<0.05 for NRT versus NT

- No significant differences were found for bone enlargement/expansion, sepsis, thyroid disease, arrhythmia, congestive heart failure, and leg ulcers.

CONCLUSIONS

- Patients with PK deficiency, regardless of transfusion status, have higher rates of select comorbidities and complications than age- and gender-matched individuals from the general population.
- For many conditions, a gradient is seen across PK deficiency transfusion cohorts, with the highest rates observed for ERT patients.
- Even patients with PK deficiency who have never been transfused are at increased risk of complications of the disease and its treatment.

Disclosures

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ANB: Agios – employment and stockholder. YY: Agios – consultant. EH: IBM Watson Health – employment. EJvB: Agios – advisory committee member and research funding; Novartis – consultant and research funding; Pfizer, RR Mechatronics – research funding. HA: Agios, Dova – consultant and research funding; Moderna – consultant. WB: Agios, Apellis, Bioverativ, Incyte – consultant; Novartis – speakers bureau member; Alexion – consultant and speakers bureau member. SWE: Agios –consultant. BG: Agios – consultant, advisory committee member, and research funding. HMY, MS, NK, CMK, YDP, AAT, HW, VRB, MAM, MJR, and DP: no conflict of interest to disclose. SC: Agios, Alexion – advisory board member. JAR: Agios, Novartis – honoraria and research funding; Pfizer – consultant, honoraria, and research funding. KHMK: Agios, Apellis, Bluebird Bio, Celgene, Pfizer – consultant; Alexion, Novartis – consultant and honoraria; Bioverativ – data safety monitoring board member. JLK: Agios, Celgene – consultant; Bluebird Bio – consultant and research funding; Apopharma, Novartis, Terumo – research funding. YR: Agios –investigator and research funding. EJN: Celgene, NHLBI/NIH – research funding; Octapharma – consultant, research funding, and investigator; Novo Nordisk, Shire – consultant and research funding; Acceleron, Agios, Apopharma, Bayer Healthcare, CSL Behring, Genentech, Grifols, Novartis, Pfizer – consultant. SH: Agios – consultant. MMV: Vertex – consultant; Sickle Cell Disease Association of Canada – advisory committee member and research funding; Canadian Haemoglobinopathy Association and Sickle Cell Awareness Group of Ontario – advisory committee member. JBK: Novartis – advisory committee member. SS: Celgene – consultant; CRSPR/Vertex – clinical trial steering committee member; Apopharma – data safety monitoring board member. JMD: Novartis – research funding; Dova – honoraria. RFG: Agios – consultant, advisory committee member, and research funding; Novartis – research funding.

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Reference

1. Grace RF et al. *Blood* 2018;131:2183-92.

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