The clinical characteristics and overall survival of patients with pyruvate kinase deficiency in the UK: a real-world study

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, inherited red blood cell enzyme disorder that causes chronic hemolysis and anemia, which lead to a spectrum of complications including biliary events, iron overload, aplastic crises, osteopenia/bone fragility, extramedullary hematopoiesis, and pulmonary hypertension, among other complications[1–4]
- It has been reported that these severe clinical complications are associated with lower health-related quality of life amongst patients with PK deficiency[5]
- The estimated prevalence of diagnosed PK deficiency in western populations has been reported to be between 3.2 and 8.5 per million[4]
- Due to the rarity of PK deficiency, its inherited nature, and its common misdiagnosis, the understanding of its burden is limited

OBJECTIVES

- **To describe clinical characteristics of patients with PK deficiency**
- **To compare overall survival (OS) between patients with PK deficiency and matched non-PK deficiency controls**

METHODS

Study design

- This was a retrospective cohort study, using data from Clinical Practice Research Datalink (CPRD) linked to the Hospital Episode Statistics (HES) database and Office of National Statistics (ONS)
  - CPRD is a longitudinal primary care data source, covering 20% (CPRD Aurum) and 4% (CPRD GOLD) of the United Kingdom (UK) population[6]
  - HES is a secondary care data source containing details of public hospital data in England for all admissions, outpatient appointments including outpatient specialty types, and attendances for accident and emergency; these are recorded within HES Admitted Patient Care (APC), Outpatient (OP), and Accident and Emergency (A&E) datasets[7]
  - CPRD-HES linkage is available for only English practices consenting to participate in the linkage scheme; therefore, this study included only patients who visited or were admitted to hospitals in England

Selection criteria

- Patients with PK deficiency of all ages were eligible for study inclusion if they had ≥1 PK deficiency diagnosis code in CPRD, as shown in **Table 1**
- Controls with no PK deficiency and no acquired/congenital anemia codes were matched 5:1 using exact matching without replacement to patients with PK deficiency based on:
  - Birth year
    - Using calendar year (e.g., if date of birth was 20 Mar 2006 for the patient, matched birth year was 2006)
  - Sex
  - Availability of medical records in the CPRD GOLD or CPRD Aurum databases
    - For instance, a patient from CPRD Aurum was matched with controls from CPRD Aurum
  - Registered general practitioner (GP)
  - Having at least one medical record in the same calendar year as the first occurrence of a PK deficiency diagnosis code for the matched patient with PK deficiency

Table 1. CPRD Medcodes used to identify patients with PK deficiency

CPRD Aurum database	Description
4363551000006119	Deficiency of pyruvate kinase
294000010	Haemolytic anaemia due to pyruvate kinase deficiency
4761371000006119	Hemolytic anemia due to pyruvate kinase deficiency
4363581000006110	PK - Pyruvate kinase deficiency
4363591000006113	Pyruvate kinase deficiency
3714051000006113	Pyruvate kinase deficiency anemia
3714071000006115	Pyruvate kinase deficiency anaemia
3714041000006111	HNSHA due to pyruvate kinase deficiency
3714111000006111	Hereditary nonspherocytic hemolytic anemia due to pyruvate kinase deficiency
3714091000006119	Hereditary nonspherocytic hemolytic anemia (HNSHA) due to pyruvate kinase deficiency
3714101000006113	Hereditary nonspherocytic haemolytic anaemia (HNSHA) due to pyruvate kinase deficiency
3714061000006110	PK deficiency anemia
3714081000006117	PK deficiency anaemia
CPRD GOLD database	**Description**
55561	Haemolytic anaemia due to pyruvate kinase deficiency

CPRD: Clinical Practice Research Datalink; HNSHA: Hereditary Nonspherocytic Hemolytic Anemia; PK: Pyruvate Kinase

METHODS (contd.)

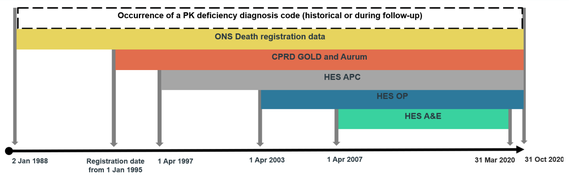
Matching dates (used for OS analysis and follow-up)

- The matching date for patients with PK deficiency was the first occurrence of a PK deficiency diagnosis code, which could appear at any time in the patient's records, either prior to or after CPRD registration
  - Records might be found prior to CPRD registration if the GP recorded historical diagnosis codes before CPRD registration date. These patients were included in the study to maximize patient numbers. In these cases, the date of the first historical diagnosis code was used as the matching date
  - Matching date for matched controls was the first medical record in the same calendar year as the first diagnosis code for the patient with PK deficiency

Index dates (used for clinical characteristics analyses)

- Although historical PK deficiency diagnosis codes prior to CPRD registration could be used for the OS analysis, the level of detail required for clinical characteristics analyses could only be gathered from timepoints after HES/CPRD registration. A separate set of index dates was created for these analyses
  - For patients with PK deficiency, index date was defined as the earliest of:
    - CPRD registration (from 1995 onwards) or;
    - HES database collection start date or date of birth if born after the start of the database (dates shown in **Figure 1**)
- The total data period was from the earliest data availability from CPRD or HES, which could include records found in the databases prior to registration date if the GP recorded historical data, until 31 Oct 2020

Figure 1. Data collection periods of CPRD GOLD, CPRD Aurum, HES APC, HES OP, HES A&E, and ONS Death data



Note: For CPRD, patient registration was from 1995. Some records might be found prior to registration date if the GP recorded historical data. For context, earliest occurrence of a PK deficiency diagnosis code in this study occurred in 01 Nov 1988

A&E: Accident and Emergency; APC: Admitted Patient Care; CPRD: Clinical Practice Research Datalink; HES: Hospital Episode Statistics; ONS: Office of National Statistics; OP: Outpatient

- **Follow-up time**
  - Clinical characteristics: Follow-up time in years from index
  - OS: Follow-up time in years from matching date

Variable definition

- **Clinical characteristics**
  - Iron chelation, iron overload, gallstones, and cholecystectomy from index to end of follow-up
    - Iron chelation was obtained using CPRD codes indicating use of deferasirox, deferiprone, and/or deferoxamine, or presence of a PK deficiency code within 6 months of a X90.2 Classification of Surgical Operations (OPCS) code (Hypoplastic hemolytic and renal anemia drugs Band 2)
    - Iron overload was obtained using CPRD clinical codes for elevated ferritin (>1000 mcg/L), iron chelation as defined previously, or iron overload diagnostic codes
    - Gallstones was obtained using CPRD, International Classification of Diseases tenth revision (ICD-10), and OPCS clinical codes indicating gallstone presence
    - Cholecystectomy was obtained using OPCS procedure codes
    - Codes for clinical characteristics are not listed due to the large number of codes
- **OS**
  - OS was evaluated from matching date until death or censoring
    - Mortality data were captured using CPRD death date and linked death registration data from the ONS, which contain information on the official date and cause of death (using ICD codes)[7]
    - Censoring was defined as earliest of de-registration from practice, last collection date from practice/hospital, or study end date (31 Oct 2020)

METHODS (contd.)

Statistical analysis

- **Continuous variables** were summarized using mean, standard deviation (SD), median, and first and third quartiles (Q1 and Q3) values
- **Categorical variables** were summarized using number and percentage (%)
- **OS** was estimated using the Kaplan-Meier method and was compared using the log-rank test between patients with PK deficiency and matched controls

RESULTS

Study population

- A total of 89 patients with PK deficiency met the inclusion criteria, and were matched with 445 non-PK deficiency controls
- Patient demographics and follow-up statistics are presented in **Table 2**

Table 2. Demographics and follow-up time for patients with PK deficiency and matched controls

Variables	PK deficiency cohort	Matched non-PK deficiency cohort
	N=89	N=445
Demographics		
Age at matching date, mean (SD), in years	24.7 (21.4)	24.5 (21.3)
Male, recorded at any time, n (%)	50 (56.2%)	250 (56.2%)
White, recorded at any time, n (%)	69 (77.5%)	283 (63.6%)
Follow-up period		
From index, median (Q1-Q3), in years	23.6 (21.3–23.6)	-
From matching date, median (Q1-Q3), in years	15.7 (7.2–22.3)	14.6 (7.8–21.1)

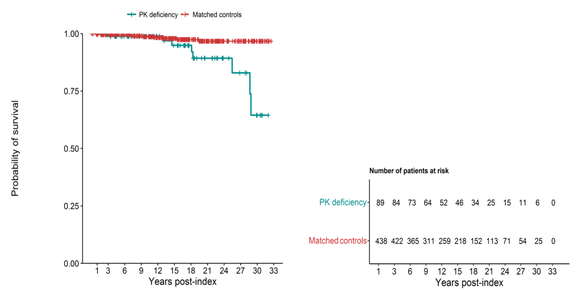
Note: Patients with PK deficiency were matched with controls by birth year, sex, availability of medical records in the CPRD GOLD or CPRD Aurum databases, registered GP, and having at least one medical record in the same calendar year as the first occurrence of a PK deficiency diagnosis code for the matched patient with PK deficiency. Matching by race was not undertaken, hence the differences in white %s

PK: Pyruvate Kinase; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

Clinical characteristics for patients with PK deficiency

- In the PK deficiency group, 14 (15.7%) patients had iron overload, 6 (6.7%) patients had iron chelation, 23 (25.8%) patients had gallstones, and 19 (21.3%) patients had cholecystectomy from index to end of follow-up

Figure 2. OS for patients with PK deficiency and matched controls



Note: OS was evaluated from matching date. 30-year OS is observed due to capturing the follow-up of patients with a historical diagnosis and their matched controls

OS: Overall Survival; PK: Pyruvate Kinase

RESULTS (contd.)

OS (Figure 2) for patients with PK deficiency and matched controls

- There were statistical differences in OS between patients with PK deficiency and matched controls (p=0.001)
- OS at 15 years was similar between patients with PK deficiency and matched controls
  - Probability of survival (95% CIs): 95% (89–100%) vs 98% (96–99%), respectively
- However, at 30 years, OS for patients with PK deficiency was significantly lower compared to matched controls
  - Probability of survival (95% CIs): 64% (44–95%) vs 97% (94–99%), respectively
- During the follow-up period, 8 (9%) patients in the PK deficiency group died while 9 (2%) in the control group died

LIMITATIONS

- The first occurrence of a PK deficiency diagnosis code in this study should not be considered as the true diagnosis date since diagnosis may have occurred prior to when the database started collecting data
- Procedures such as cholecystectomy may have occurred prior to the start of HES data collection and could thus be under-reported in this study
- This study only reports on gallstones, cholecystectomy, and iron overload/chelation. Due to General Data Protection Regulations and small sample size, some observed complications are not reported. Other clinical manifestations for PK deficiency that have been reported in past literature include aplastic crises, osteopenia/bone fragility, extramedullary hematopoiesis, pulmonary hypertension, and leg ulcers[2–4]
- For the clinical characteristics observed, data capture was additionally limited to available codes. For instance, T2* magnetic resonance imaging codes that are used to investigate iron overload, were not available in CPRD or HES[8]

CONCLUSIONS

- **To our knowledge, this is the first study evaluating the OS of patients with PK deficiency in the UK**
- **Findings from this study provide insight into the real-world disease burden of PK deficiency in England, UK**
- **Patients with PK deficiency had a statistically higher mortality compared to matched controls**

Early intervention may help mitigate serious medical complications and premature mortality amongst patients with PK deficiency

Disclosures: This study was funded by Agios Pharmaceuticals, Inc.

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