Patient characteristics and healthcare resource utilization of patients with pyruvate kinase deficiency in a United States electronic health record database

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, congenital, chronic hemolytic anemia with an estimated prevalence of 3.2 – 8.5 per million patients among Western populations[1]
- The most frequently reported symptoms are those related to anemia (e.g. fatigue, dizziness, and dyspnea), as well as jaundice and cardiac symptoms[2]
- Many patients with PK deficiency experience significant long-term complications, including gallstones, pulmonary hypertension, thrombotic complications, osteoporosis, and iron overload[3]
  - Iron overload occurs in over 60% of patients with PK deficiency[4,5]
- Until recently, with the FDA approval of mitapivat in February 2022, available treatments were supportive only and included blood transfusions and iron chelation therapy[6,7]
- Real-world data for patients with PK deficiency are limited because of the rarity of the disease and the lack of a specific diagnostic code for the condition before October 2021, when the Centers for Disease Control and Prevention (CDC) issued the new code 55.21 (Anemia due to pyruvate kinase deficiency)[8]

OBJECTIVE

- To identify and characterize patients with PK deficiency and summarize their healthcare resource utilization (HCRU), using Optum's US electronic health record (EHR) database

METHODS

Database

- Optum's Clinical EHR Database is an open system database containing fields derived from the medical records of over 100 million lives with an average of 45 months of observed patient data
- It is enhanced by natural language processing (NLP) of free-text electronic clinical notes that add additional fields to the EHR tables
- Optum's Clinical EHR Database can deliver a longitudinal record that covers a comprehensive spectrum of patient health, medical information, and treatment decisions

Sample identification

- Patients with a presence of select hemolytic anemia diagnoses, provider notes with PK deficiency-related NLP terms, or evidence of relevant signs, symptoms, laboratory tests, and procedures, and with no acquired or congenital hemolytic anemias were considered part of the general hemolytic anemia population (**Figure 1**)

Figure 1. Sample identification of patients with PK deficiency from Optum EHRs

General hemolytic anemia population
≥1 diagnosis code for hemolytic anemia; or ≥1 provider note with PK deficiency-related NLP term; or evidence of relevant signs, symptoms, laboratory tests, and procedures; and no acquired or congenital hemolytic anemias[a]

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Likely PK deficiency patients
PK deficiency-related hemolytic anemia: ≥1 diagnosis code for hemolytic anemia more specific to PK deficiency (282.3, 282.9, D55.2, D55.8, D55.9, D58.9, E74.4) during identification period[b]; and
PK deficiency notes – multiple terms: ≥1 provider note with any of the following NLP terms: "pyruvate kinase deficiency" or "deficiency of pyruvate kinase" during identification period[b]

→

Confirmed patients with PK deficiency
Clinical expert review of provider notes with an abnormal PK enzyme or molecular genetic genotype

Affirmed patients with PK deficiency
No evidence of abnormal PK enzyme or molecular genetic genotype but with ≥2 references to having 'a history of PK deficiency' in EHR provider notes

[a]Acquired or congenital anemias included diagnosis codes for hereditary spherocytosis and elliptocytosis, hemoglobinopathic, thalassemia, and sickle cell disease during identification period; [b]Identification period was 01Jan2007 to 30Sept2019
EHR, electronic health record; NLP, natural language processing; PK, pyruvate kinase

- Of the general hemolytic anemia population, patients with ≥1 PK deficiency-related diagnosis code (International Classification of Diseases [ICD]-9: 282.3, 282.9; ICD-10: D55.2, D55.8, D55.9, D58.9, E74.4) and ≥1 provider note during identification period (01Jan2007 to 30Sept2019) were reviewed and patients with ≥12 months of follow-up after the index date (defined as the earliest date with a PK deficiency-related diagnosis code) were included
- Analyses were conducted on the cohort of confirmed and affirmed patients
- Outcomes included: demographics and patient characteristics, HCRU (defined as the number of ambulatory, emergency room (ER), and inpatient medical encounters), provider visits, procedures, laboratory testing, and medications
- Patient characteristics and HCRU were analyzed descriptively:
  - Categorical variables were summarized using frequencies and percentages
  - Continuous variables were summarized using descriptive statistics (including mean, standard deviation [SD], median, and range)
- Results are reported over two time horizons:
  - 12-month follow-up, defined as the 12 months after the index date (same duration for all patients)
  - Total follow-up, defined as the period starting one day after the index date until the earliest of study cut-off (30Sept2019), end of clinical activity, or death (utilizes all available follow-up data; some patients have longer follow-up and more years of data than others)

RESULTS

Patient characteristics

- 40 patients met inclusion criteria, 6 (15.0%) with confirmed PK deficiency and 34 (85.0%) with affirmed PK deficiency
- Median age at index date (defined as the earliest date with a PK deficiency-related diagnosis code) was 23.0 years, 60.0% of patients were male, and patients had a mean (SD) follow-up of 5.1 (2.7) years in the Optum Clinical EHR Database (**Table 1**)
- The majority of patients (67.5%) had some form of commercial insurance

Table 1. Characteristics of patients with PK deficiency in the Optum Clinical EHR Database

Characteristic	Cohort size (N=40)
Age at index, mean (SD), years	26.8 (22.3)
Range, years	0–74
Age, n (%)	
<6 years	8 (20.0)
6–11 years	6 (15.0)
12–17 years	1 (2.5)
18–64 years	22 (55.0)
65+ years	3 (7.5)
Female, n (%)	16 (40.0)
Race, n (%)	
African American/Black	2 (5.0)
Caucasian/White	27 (67.5)
Unknown	11 (27.5)
Follow-up, mean (SD), years	5.1 (2.7)
Range, years	1.2–12.3
Follow-up, n (%)	
<2 years	4 (10.0)
2–6 years	21 (52.5)
>6 years	15 (37.5)
Payer type, n (%)	
Commercial only	24 (60.0)
Medicaid only	2 (5.0)
Medicare only	1 (2.5)
Commercial + Medicaid	1 (2.5)
Commercial + Medicare	2 (5.0)
Unknown/missing/invalid/other	10 (25.0)

EHR, electronic health record; PK, pyruvate kinase; SD, standard deviation

HCRU

- Of patients who had ≥1 ambulatory care visit over the 12-month follow-up period (80.0%), the median (range) number of visits was 8 (1–61) (**Table 2**)
- Almost one-quarter of patients (22.5%) had ≥1 ER visit over the 12-month follow-up period, with a median (range) of 1 visit (1–2)
- The median (range) length of stay in hospital was 6 days (1–400) among patients who had ≥1 hospital admission during the 12-month follow-up period (17.5%)
- All hospitalized patients were <30 years old
- The most common reason for hospital admission was hereditary hemolytic anemias (3 [42.9%])

Table 2. Inpatient and outpatient HCRU in patients with PK deficiency in the Optum Clinical EHR Database

HCRU	Cohort size (N=40) 12-month follow-up	Total follow-up
Ambulatory Visits		
Patients with ≥1 visit, n (%)	32 (80.0)	36 (90.0)
Ambulatory visits among patients with ≥1 visit, mean (SD)	12.8 (14.2)	–[a]
Median visits (range)	8 (1–61)	–[a]
ER Visits		
Patients with ≥1 visit, n (%)	9 (22.5)	16 (40.0)
ER visits among patients with at ≥1 visit, mean (SD)	1.2 (0.4)	–[a]
Median visits (range)	1 (1–2)	–[a]
Inpatient Admissions		
Patients with ≥1 admission, n (%)	7 (17.5)	16 (40.0)
Inpatient admissions among patients with ≥1 admission, mean (SD)	2.3 (2.2)	–[a]
Median admissions (range)	1 (1–7)	–[a]
Inpatient length of stay among those with ≥1 admission, mean (SD), days	63 (148.7)	–[a]
Median length of stay (range), days	6 (1–400)	–[a]

12-month follow-up was defined as the one-year (365 days) period starting one day after the index date. Total follow-up was defined as the period starting one day after the index date until the earliest of study cut-off (30Sept2019), end of clinical activity, or death. With variable observation time in the total follow-up period, apply caution in interpretation
[a]Number of visits/admissions over total follow-up is not meaningful given the variable length of follow-up available for each patient
EHR, electronic health record; ER, emergency room; HCRU, healthcare resource utilization; PK, pyruvate kinase; SD, standard deviation

Provider visits

- Almost three-quarters of patients (72.5%) had visited a primary care provider over the 12-month follow-up period (**Table 3**)
- Oncologists were the most visited specialists during the 12-month (25.0%) and total follow-up (47.5%) periods

Table 3. Provider visits of patients with PK deficiency in the Optum Clinical EHR Database

Visits	Cohort size (N=40) # of patients with ≥1 visits (12-month follow-up), n (%)	# of patients with ≥1 visits (total follow-up), n (%)
Primary care	29 (72.5)	35 (87.5)
Hematologist	3 (7.5)	5 (12.5)
Oncologist	10 (25.0)	19 (47.5)
Hepatologist	1 (2.5)	1 (2.5)
Nephrologist	1 (2.5)	2 (5.0)

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EHR, electronic health record; PK, pyruvate kinase

Procedures

- Over total follow-up, 35.0% of patients had ≥1 monitoring-related procedure (**Table 4**)
- 20.0% of patients received ≥1 transfusion over the 12-month follow-up period, half of whom were considered regularly transfused (received ≥6 transfusions in the 12-month follow-up period)
- During the total follow-up period, patients receiving ≥1 transfusion had numerically increased from 20.0% to 32.5%
- Among those patients who were transfused, the median (range) transfusions received in the 12-month follow-up period was 5 (1–9)

Table 4. Procedures in patients with PK deficiency in the Optum Clinical EHR Database

Procedures	Cohort size (N=40) # of patients with ≥1 visits (12-month follow-up), n (%)	# of patients with ≥1 visits (total follow-up), n (%)
Monitoring-related procedure	3 (7.5)	14 (35.0)
Liver MRI	0 (0)	2 (5.0)
Echocardiogram	2 (5.0)	7 (17.5)
Gallbladder ultrasound	1 (2.5)	7 (17.5)

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EHR, electronic health record; MRI, magnetic resonance imaging; PK, pyruvate kinase

Laboratory testing

- Of the 23 patients (57.5%) with available hemoglobin (Hb) over the 12-month follow-up, approximately half (47.8%) had Hb levels indicative of moderate to severe anemia (<10 g/dL) (**Table 5**)
- Over total follow-up, around half of patients (46.7%) also had Hb levels that were <10 g/dL
- These data may underestimate levels of anemia as Hb results within 61 days following a transfusion were not excluded

Table 5. Laboratory testing in patients with PK deficiency in the Optum Clinical EHR Database

Hemoglobin	Cohort size (N=40) 12-month follow-up	Total follow-up
Hemoglobin result available, n (%)	23 (57.5)	30 (75.0)
Result, mean (SD), g/dL	9.9 (2.7)	10.3 (2.8)
Median (range)	10.3 (5.3–15.1)	10.4 (5.3–16.1)
Result <10 g/dL, n (%)	11/23 (47.8)	14/30 (46.7)
Result ≥10 g/dL, n (%)	12/23 (52.2)	16/30 (53.3)

12-month follow-up was defined as the one-year (365 days) period starting one day after the index date. Total follow-up was defined as the period starting one day after the index date until the earliest of study cut-off (30Sept2019), end of clinical activity, or death. With variable observation time in the total follow-up period, apply caution in interpretation
EHR, electronic health record; PK, pyruvate kinase; SD, standard deviation

Medication use

- The percentages of patients who had ever taken iron chelation, folic acid supplements, antithrombotic agents, antibiotics, antidepressants, and antianxiety medications at 12-month and at total follow-up are shown in **Table 6**
- The higher percentages observed over total follow-up reveal that it is not uncommon for patients to be taking these medications at some point during their lifetime
- Over the average of 5.1 years of follow-up, over half of patients reported having taken antibiotics and approximately one-quarter reported having taken anticoagulants and anti anxiety medications
- The medications with the largest increases in usage during both the 12-month and total follow-up periods were iron chelation, folic acid supplements, and antibiotics

Table 6. Medication use in patients with PK deficiency in the Optum Clinical EHR Database

Medications	Cohort size (N=40) # of patients with ≥1 prescriptions (12-month follow-up), n (%)	# of patients with ≥1 prescriptions (total follow-up), n (%)
Iron chelation	1 (2.5)	6 (15.0)
Folic acid supplements	8 (20.0)	15 (37.5)
Antithrombotic agents		
Anticoagulants	6 (15.0)	10 (25.0)
Antiplatelets	1 (2.5)	4 (10.0)
Thrombolytics	1 (2.5)	3 (7.5)
Antibiotics	13 (32.5)	23 (57.5)
Antidepressants	2 (5.0)	4 (10.0)
Antianxiety medications	3 (7.5)	9 (22.5)

12-month follow-up was defined as the one-year (365 days) period starting one day after the index date. Total follow-up was defined as the period starting one day after the index date until the earliest of study cut-off (30Sept2019), end of clinical activity, or death. With variable observation time in the total follow-up period, apply caution in interpretation
EHR, electronic health record; PK, pyruvate kinase

SUMMARY

- **This is the first study to describe the HCRU of patients with PK deficiency using EHR data in the US**
- **In the 12 months after index, 17.5% of patients had ≥1 hospital admission (median length of stay of 6 days), 22.5% had ≥1 ER visit, and 80% had ≥1 (median of 8) ambulatory visit**
  - **All patients admitted to hospital over the 12-month follow-up period were young (<30 years old)**
- **Over the total follow-up, only 5% of patients had received an MRI for liver iron. Similarly, despite being diagnosed with a hemolytic anemia, only 57.5% had Hb results in the 12 months post-index and 75% over the total follow-up period**
  - **Further investigations into disease management and monitoring practices are warranted, given the long-term complications associated with chronic hemolytic anemia and iron overload**
- **Given the cross-sectional design of the study and the open system nature of the database, results may be an underestimation of HCRU in patients with PK deficiency**
- **The number and percentage of events observed in the total follow-up period should be interpreted with caution as patients were followed for a variable length of time**

Overall, using Optum's large US EHR database, these data show high HCRU for patients with PK deficiency

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