Mortality among veterans with a diagnosis of pyruvate kinase deficiency: A real-world study using US Veterans Health Administration data

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, underrecognized inherited disorder caused by autosomal recessive mutations in the *PKLR* gene
  - The *PKLR* gene encodes red blood cell (RBC) PK (PKR), which is critical for maintaining RBC energy levels and morphology[1,2]
  - A glycolytic defect causes reduced adenosine triphosphate levels and leads to hemolytic anemia[1,2]
  - Defects in PKR cause chronic hemolysis, which leads to other long-term complications[3,4]
    - These include gallstones, pulmonary hypertension, extramedullary hematopoiesis, osteoporosis, and iron overload and its sequelae[3–5]
  - PK deficiency can also cause quality of life problems, including challenges with work and school activities, social life, and emotional health[6]
- Current management strategies for PK deficiency, including RBC transfusions and splenectomy, are associated with both short- and long-term risks[3,7]
- Population-based studies of PK deficiency using claims or electronic health record databases are limited
  - Identifying PK deficiency in real-world data is challenging due to a lack of diagnosis codes and treatments that are specific to the disease
- Data on mortality in this patient population are lacking and limited to a few individual case reports[8–16]
- The US Veterans Health Administration (US VHA) database was selected for this research because of its long length of follow-up and availability of death data

OBJECTIVES

- Identify patients with a PK deficiency diagnosis as documented by physicians
- Compare their rates of mortality to an age- and gender-matched cohort of individuals without PK deficiency

METHODS

PK deficiency cohort

- Patients with ≥ 1 diagnosis code related to PK deficiency between January 1995 and July 2019 were selected from the US VHA database
  - Anemia due to disorders of glycolytic enzymes (ICD-10-CM: D55.2), other hemolytic anemias due to enzyme deficiency (ICD-9-CM 282.3), or unspecified hereditary hemolytic anemia (ICD-9-CM 282.9, ICD-10-CM D58.9)
- To be considered for inclusion in this research, physicians' notes were required to contain the words "pyruvate", "kinase", and "deficiency"
- A manual review of these physicians' notes was performed to identify patients with a physician-documented diagnosis of PK deficiency
- The index date for the PK deficiency cohort was defined as the date of the first medical record with a diagnosis code related to PK deficiency

Non-PK deficiency cohort

- Each patient in the PK deficiency cohort was matched 1:5 by age at index, sex, and index year (± 1 year) to patients from the general US VHA population with no diagnosis codes related to PK deficiency
- The index date for the non-PK deficiency cohort was defined as a random visit date during their match's index year

Patient characteristics

- Demographic and clinical characteristics were compared between the PK deficiency cohort and their non-PK deficiency cohort matches

Survival analysis

- Survival time from the index date between the PK deficiency cohort and their non-PK deficiency cohort matches was summarized using Kaplan–Meier survival estimates and compared using a univariate Cox proportional hazards model with robust standard error estimation

RESULTS

Patient characteristics

- A total of 18 patients met inclusion criteria for the PK deficiency cohort and were matched to 90 individuals in the non-PK deficiency cohort
- Baseline characteristics for both cohorts are shown in **Table 1**
- For both cohorts, the mean age at index was 56.8 years
- There were no significant differences between age, sex, race, or mean Charlson Comorbidity Index
- Imbalances remained between the two cohorts with regard to region (South) and body mass index (higher BMI in the non-PK deficiency cohort)

Table 1. Patient characteristics

	PK deficiency cohort (N = 18)	Matched non-PK deficiency cohort (N = 90)
Age at index year, mean ± SD [median]	56.8 ± 13.6 [59.0]	56.8 ± 13.1 [59.0]
Category, years, n (%)		
> 20 to ≤ 30	1 (5.6)	5 (5.6)
> 30 to ≤ 40	0 (0.0)	0 (0.0)
> 40 to ≤ 50	5 (27.8)	25 (27.8)
> 50 to ≤ 60	4 (22.2)	20 (22.2)
> 60 to ≤ 70	7 (38.9)	35 (38.9)
> 70 to ≤ 80	0 (0.0)	0 (0.0)
> 80	1 (5.6)	5 (5.6)
Male, n (%)	17 (94.4)	85 (94.4)
US region, n (%)		
South	6 (33.3)	6 (6.7)
Midwest	2 (11.1)	4 (4.4)
North East	7 (38.9)	48 (53.3)
West	3 (16.7)	32 (35.6)
White, n (%)	15 (83.3)	77 (85.6)
Weight (lbs), mean ± SD [median]	190.0 ± 42.4 [189.2]	206.2 ± 47.5 [195.0]
Height (inches), mean ± SD [median]	69.3 ± 2.8 [69.9]	69.0 ± 2.9 [69.9]
BMI, mean ± SD [median]	27.6 ± 5.0 [26.7]	30.5 ± 6.7 [28.8]
20–25, n (%)	7 (38.9)	11 (12.2)
26–30, n (%)	5 (27.8)	37 (41.1)
> 30, n (%)	6 (33.3)	39 (43.3)
Charlson comorbidity index score, mean ± SD [median]	0.4 ± 1.2 [0]	0.5 ± 1.2 [0]

BMI = body mass index; PK = pyruvate kinase; SD = standard deviation.

Survival analysis

- The number of observed deaths over the follow-up period, and years until death for both cohorts are highlighted in **Table 2**

Table 2. Differences in observed deaths and years until death between cohorts

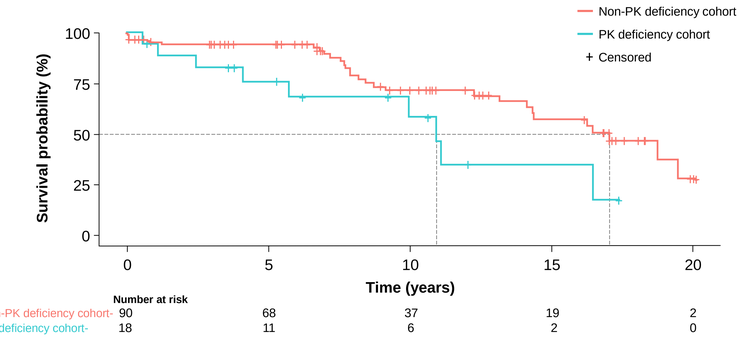
	PK deficiency cohort (N = 18)	Non-PK deficiency cohort (N = 90)
Years of follow-up, mean ± SD [median]	7.3 ± 5.2 [6.0]	9.2 ± 5.8 [8.0]
Observed deaths over follow-up period, n (%)	9 (50%)	28 (31%)
Years until death, median	10.9	17.1

PK = pyruvate kinase; SD = standard deviation.

RESULTS (CONTINUED)

- Patients in the non-PK deficiency cohort had a significantly longer time to death than the PK deficiency cohort (hazard ratio: 2.3; p = 0.0306; **Figure**)
- 10 years after index, 42% of patients in the PK deficiency cohort had died compared with 28% of those in the non-PK deficiency cohort

Figure. Kaplan–Meier survival estimates



PK = pyruvate kinase.

Study strengths:

- The patients in the PK deficiency cohort had a manually-confirmed, physician-documented diagnosis
- This study is the first to compare mortality between patients with (physician-documented) PK deficiency and the general population

Study limitations:

- Females, pediatric, and adolescent population are underrepresented in this study
- Due to the rare and heterogeneous nature of PK deficiency, results of this study may not be generalizable

CONCLUSIONS

- **The results of this study suggest that patients with PK deficiency may be at an increased risk of mortality**
- **Further research is warranted to:**
  - **Understand cause of death among patients with PK deficiency**
  - **Examine mortality using larger sample sizes and other real-world data sources that better represent females and younger age groups**

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