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

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This study was funded by Agios Pharmaceuticals, Inc.

Introduction

Background

- Pyruvate kinase (PK) deficiency is a rare, inherited disorder caused by autosomal recessive mutations in the *PKLR* gene
  - A glycolytic defect causes reduced adenosine triphosphate levels and leads to hemolytic anemia
- 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[1–9]
- The US Veterans Health Administration (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

Study Design

PK deficiency cohort

- Patients with ≥ 1 diagnosis code[a] related to PK deficiency between January 1995 and July 2019 were selected from the US VHA database
- To be considered for inclusion, 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 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

[a]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).
PK = pyruvate kinase; US = United States; VAH = Veterans Health Administration.

Data Analysis

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

PK = pyruvate kinase.

Results

Patient characteristics

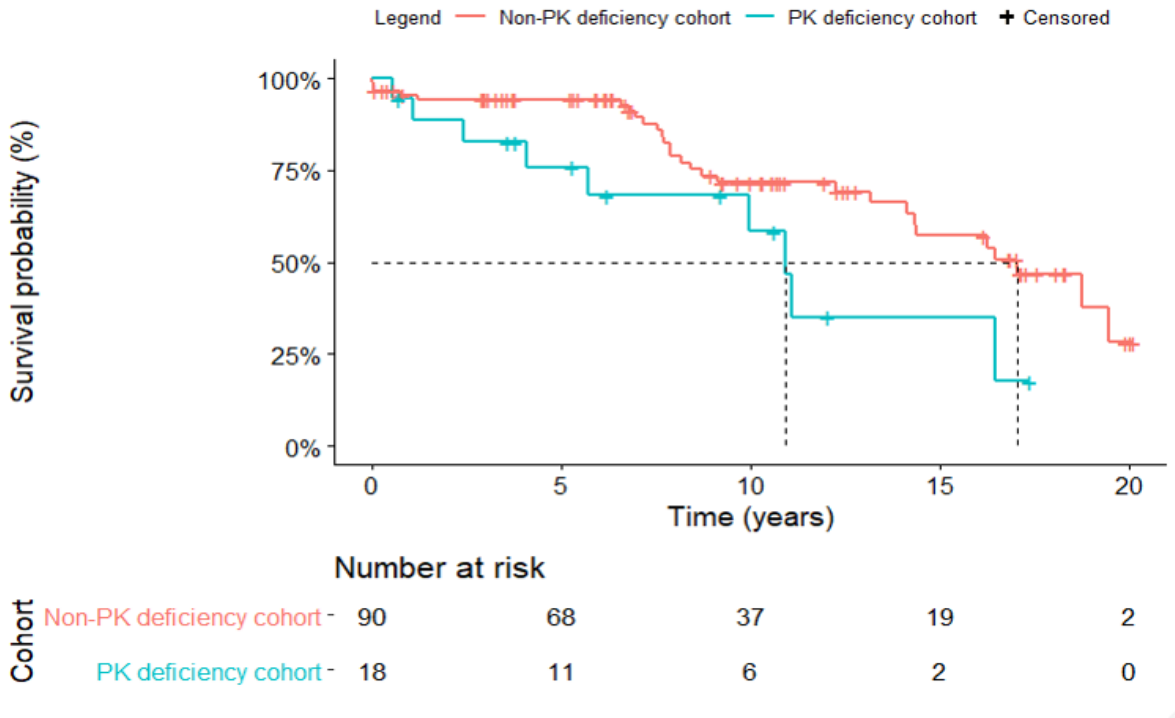
	PK deficiency cohort (N = 18)	Matched non-PK deficiency cohort (N = 90)
Age at index year, mean ± SD [median]	56.8 ± 13.6 [59.0]	56.8 ± 13.1 [59.0]
Category, n (%)		
20–30 years	1 (5.6)	5 (5.6)
30–40 years	0 (0.0)	0 (0.0)
40–50 years	5 (27.8)	25 (27.8)
50–60 years	4 (22.2)	20 (22.2)
60–70 years	7 (38.9)	35 (38.9)
70–80 years	0 (0.0)	0 (0.0)
80+ years	1 (5.6)	5 (5.6)
Male, n (%)	17 (94.4)	85 (94.4)
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 (in), 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]

- 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
- The mean age at index was 57 years
- Imbalances remained between the two cohorts with regard to region (South) and body mass index (higher BMI in the non-PK deficiency cohort)

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

Results

Survival analysis



	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

- 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)
- 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

PK = pyruvate kinase; SD = standard deviation.

Conclusion

- 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

PK = pyruvate kinase.

References

1. Alli N, Coetzee M, Louw V, van Rensburg B, Rossouw G, Thompson L, Pissard S, Thein SL. Sickle cell disease in a carrier with pyruvate kinase deficiency. *Hematology.* 2008;13:369–72.
2. Nagai H, Takazakura E, Oda H, Tsuji H, Terada Y, Makino H, Yamauchi H, Saitoh K. An autopsy case of pyruvate kinase deficiency anemia associated with severe hemochromatosis. *Internal Medicine.* 1994;33:56–9.
3. Pérez-Albert P, Guillen M, Prudencio M, Gonzalez-Vicent M, Sevilla J. Trasplante de progenitores hematopoyéticos en déficit de piruvato cinasa: ¿cuándo indicarlo? *An Pediatr (Barc).* 2018;88:106–7.
4. Pissard S, Max-Audit I, Skopinski L, Vasson A, Vivien P, Bimet C, Goossens M, Galacteros F, Wajcman H. Pyruvate kinase deficiency in France: a 3-year study reveals 27 new mutations. *British Journal of Haematology*. 2006;133:683–9.
5. Raphaël MF, Van Wijk R, Schweizer JJ, Schouten-van Meeteren NA, Kindermann A, van Solinge WW, Smiers FJ. Pyruvate kinase deficiency associated with severe liver dysfunction in the newborn. *American Journal of Hematology*. 2007;82:1025–8.
6. Rider NL, Strauss KA, Brown K, Finkenstedt A, Puffenberger EG, Hendrickson CL, Robinson DL, Muenke N, Tselepis C, Saunders L, Zoller H. Erythrocyte pyruvate kinase deficiency in an old-order Amish cohort: Longitudinal risk and disease management. *American Journal of Hematology.* 2011;86:827–34.
7. Zahid MF, Bains AP. Rapidly fatal Klebsiella pneumoniae sepsis in a patient with pyruvate kinase deficiency and asplenia. *Blood*. 2017;130:2906.
8. Zanella A, Berzuini A, Colombo MB, Guffanti A, Lecchi L, Poli F, Cappellini MD, Barosi G. Iron status in red cell pyruvate kinase deficiency: study of Italian cases. *British Journal of Haematology*. 1993;83:485–90.
9. Zanella A, Fermo E, Bianchi P, Chiarelli LR, Valentini G. Pyruvate kinase deficiency: the genotype-phenotype association. *Blood Reviews*. 2007;21:217–31.

Disclosures

- **Erin Zagadailov** – Agios – employee and stockholder; **Audra N. Boscoe** – Agios – employee and stockholder; **Viviana Garcia-Horton**, **Sherry Shi** – employed by Analysis Group, Inc., which received payment from Agios for participation in this research; **Shuqian Liu** – has a research contract and received consulting fees from Analysis Group, Inc., which received payment from Agios for participation in this research; **Lizheng Shi** – has a research contract and received consulting fees from Analysis Group, Inc., which received payment from Agios for participation in this research; **Dendy Macaulay** – employed by Analysis Group, Inc., which received payment from Agios for participation in this research.