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Short Communication

# Survival of propionic acidemia patients with liver transplant

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ABSTRACT

Propionic acidemia (PA) is a rare metabolic disorder affecting amino acid metabolism. Liver transplantation improves some outcomes, but the impact on long-term survival remains unclear. A systematic literature review and survival analysis, identifying 94 PA patients who underwent transplantation, revealed a survival probability of 62% at age 33; while median survival was estimated at 40 years. These findings highlight a substantial survival deficit of PA patients compared to the general population despite liver transplantation.

## 1. Introduction

Propionic acidemia (PA) is a rare and serious metabolic disorder characterized by the deficiency of propionyl-CoA carboxylase. This disorder leads to impaired metabolism of certain amino acids (isoleucine, valine, methionine, and threonine), odd-chain fatty acids, and cholesterol side chains. PA can lead to severe complications and patients require a special dietary regimen [1].

Liver transplantation (LT) has proven effective in restoring enzyme activity, allowing for a more liberal diet, and preventing severe complications such as metabolic decompensations [2]. However, evidence regarding the impact of transplantation on long-term survival remains limited. To address this gap, the survival of PA patients who have undergone liver transplants was estimated based on a systematic literature review (SLR) and survival analysis. The survival of PA patients was compared with that of the general population as a reference to understand the potential contribution of disease.

## 2. Methods

An SLR was performed in February 2023 across relevant scientific databases (PubMed, Scopus and Cochrane Database). English language publications reporting on liver or combined liver and kidney transplant patients were considered relevant without a publication date limit. Individual-level data on patients with PA were collected from studies reporting original data (e.g., case studies, case series, cohort studies with individual data, etc.). Outcomes extracted from the identified articles included the age at loss of follow-up, length of follow-up, age at death, and survival/mortality data of patients with PA. When age at loss of follow-up and age at death were not reported explicitly, these measures were calculated based on individual-level follow-up times and survival/mortality data. In certain cases, the age at loss of follow-up and age at death were estimated based on age at transplantation and length of follow-up or survival since transplantation. In order to exclude patients who may have been double-reported across studies, a rigorous evaluation was performed by assessing the reporting clinical centers, year of birth and age at transplantation for each patient.

The details of the systematic literature review, including the PRISMA flow diagram can be found in the Online supplement.

To illustrate the survival of transplanted PA patients, a Kaplan-Meier (KM) curve was constructed using the collected or calculated data on age at death and age at loss of follow-up. To evaluate the difference in survival between transplanted PA patients and the general population, the survival probability for the United States (US) general population was calculated using US life tables [4].

To estimate the survival probability beyond the time horizon of the

*Abbreviations:* CI, Confidence interval; IQR, Interquartile Range; KM, Kaplan-Meier; LT, Liver transplantation; PA, Propionic acidemia; SD, Standard Deviation; SLR, Systematic literature review; US, United States of America.

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created KM curve, disease-specific excess mortality rates were calculated as the difference in the mortality of PA patients with a transplant and the general population. Mortality rates were calculated as the number of events divided by the total person-time of observation during each period. The excess mortality due to PA was calculated until the end of the KM curve in four age bands: 0–1 years, >1–5 years, >5–10 years, and >10–33 years. It was assumed that the latter also holds for patients with PA after 33 years (end of KM curve). By adding these estimated excess mortality rates to the age-specific mortality rates in the general population at each time point (age), a survival curve was created for transplanted PA patients. To address the uncertainty in the KM curve and the model fit, 95% confidence intervals (CIs) were calculated. The estimated median survival was compared to that of the general population.

## 3. Results

The current SLR found data on a total of 94 transplanted PA patients from 34 different articles published between 1999 and 2023. Papers published between 1999 and 2014 reported 19 patients, while articles published between 2015 and 2019, and those after 2019, reported 40 and 35 cases, respectively. Although not reported for all cases, the vast majority of the transplantations in our dataset were performed after the year 2000. However, the earliest transplantation was reported from the Birmingham Children's Hospital, Birmingham, United Kingdom in 1991 [3]. 45 male and 34 female patients were identified; gender information was not available for 15 patients. Transplantations published included 22 from hospitals in the UK, 15 from the US, and 11 from Japan. An additional 27 transplantations were performed in other Western European countries, while China reported ten and India also six procedures.

The extracted data and the list of included publications can be found in the Online supplement.

In the identified studies 17 deaths were reported between the age of 3 months and 19 years. Observing the patients alive at the end of the study follow-up periods the oldest patient was 33 years old. When reported, liver transplantation was performed between the ages of 2 months and 22 years. The mean age of transplantation was 4.4 years (SD: 4.1), while the median age was 2.8 years (IQR: 5.2).

The KM curve showed a substantial difference between the survival of transplanted PA patients and the US general population. At 33 years of age the survival probability was only 62% among PA patients and 98% in the general population. Based on the survival extrapolation applying disease-specific excess mortalities, the point estimate of the median survival was 40 years in PA patients with a 95% confidence interval of 12–70 years. The median survival in the US general population is 78 years. The survival curves can be seen in Fig. 1.

## 4. Discussion

To the best of our knowledge, this study represents one of the most comprehensive literature reviews and survival analyses of PA patients with a liver transplant. A key strength of our study is the inclusion of a large number of individual patients, achieved through a rigorous assessment of duplicate reporting to reduce bias. Additionally, we employed a sophisticated method for survival extrapolation beyond the reported observation periods, enabling us to estimate median survival time of the patients. However, the study has limitations. The literature search was restricted to a limited number of databases, English language only, and conference abstracts were not considered, potentially omitting relevant published studies or cases. The dispersion of cases published indicates that an equal or greater number of cases have been reported over the time frame of this literature review. Between 1999 and 2014, 19 patients were reported, while articles published between 2015 and 2019, and those after 2019, reported 40 and 35 cases, respectively. Nevertheless, there is the potential for publication bias due to potentially less transplant cases and outcomes being published as a proportion

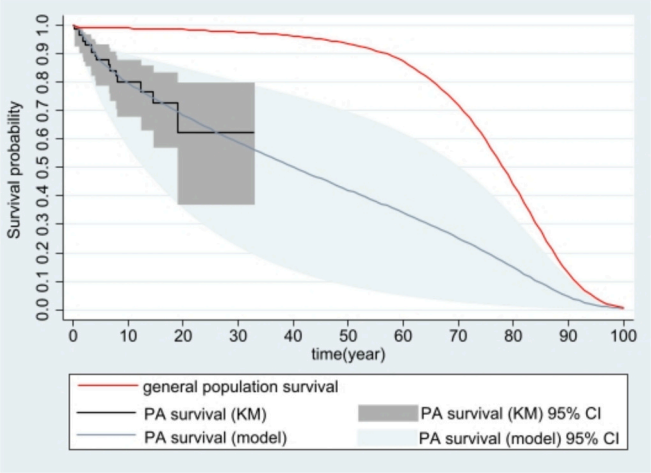


**Fig. 1.** Kaplan-Meier curve of transplanted PA patients (black line) (95% confidence interval indicated with grey zone), the model-based estimates of survival of PA patients with a liver transplant (blue line) (95% confidence interval indicated with light blue zone) and the survival probability of general population in the US (red line).

of all transplants performed, since transplantation has become more routine. Another limitation is that the calculated confidence interval for the median survival time indicates considerable uncertainty, limiting the interpretation of the results beyond the age of 33, despite robust modeling.

Liver transplantation has emerged as an effective therapeutic approach for selected PA patients. However, recent disease management guidelines emphasize the importance of several other factors and advances in acute and chronic care when assessing survival outcomes [5,6]. Improved treatment strategies and patient monitoring, particularly focusing on metabolic stability, play a crucial role in determining long-term outcomes for transplanted PA patients as well and may continue to improve survival post-transplant. However, a limitation of this analysis is that patients who underwent transplantation recently may not have been followed for a sufficient duration to accurately assess their long-term survival rates, which constrains our ability to demonstrate the impact of recent advances in pre- and post-transplant care.

## 5. Conclusion

In severe cases of PA, liver transplantation offers an effective treatment option, significantly improving symptoms and slowing disease progression. However, despite great advances in liver transplantation, the findings of our systematic literature review (SLR) and survival analysis document a pooled survival rate that indicates a substantial survival deficit in PA patients. This highlights a high unmet medical need, underscoring the necessity for developing new and innovative therapeutic approaches for PA.

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## CRediT authorship contribution statement

**Tamás Zelei:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Zoltán Vokó:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Formal analysis,

Conceptualization. **Bertalan Németh:** Writing – review & editing, Writing – original draft, Resources, Project administration, Data curation. **Zsuzsanna Petykó:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Data curation. **Geetanjoli Banerjee:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Vanja Sikirica:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Tamás Zelei and Bertalan Németh are employees of Syreon Research Institute. Zoltán Vokó is an employee of Semmelweis University, and an employee and partner at Syreon Research Institute. Zsuzsanna Petykó is a PhD Candidate at Semmelweis University, and an employee of Syreon Research Institute. Geetanjoli Banerjee and Vanja Sikirica are employees of Moderna Therapeutics, Inc. and own stock/options in Moderna. The content of this paper, as well as the views and opinions expressed therein are those of the Authors and not the organizations that employ them.

## Data availability

Data can be found in the Supplementary File.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101093.

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