Association Between Homocysteine and Clinical Outcomes in Patients With Classical Homocystinuria: A Systematic Literature Review

Mehul Shah[1]; Marissa Betts[2]; Sophie Yoon[2]; Lionel Pinto[1]; Sarah Ronnebaum[2]

[1]Travere Therapeutics, Inc., San Diego, CA, United States; [2]Evidera, Inc., Bethesda, MD, United States

Poster #68

TRAVERE THERAPEUTICS

RESULTS

- From 4,377 unique records identified, 13 studies describing 854 patients with classical HCU were ultimately included in the SLR (**Table 1, Figure 1)**:
  - Study designs included retrospective (n=9), prospective observational (n=3), and randomized trials (n=1)
  - The mean or median patient age ranged 8.5 to 33.5 years
  - 40% to 70% of patients were male
  - Sample sizes ranged from five to 328; the majority of studies had <50 patients
  - Studies described patients from Europe (n=5), North America (n=3), South America (n=2), Eastern Mediterranean (n=2), and Western Pacific (n=1)
  - Data collection began before 2000 for the majority of studies (n=8); for the remaining studies, data collection started after 2000 (n=3) or was unclear (n=2)
  - Study follow-up was <2 years (n=1), two to 10 years (n=6), >10 years (n=2), or was not reported (n=4)
- Four studies reported a significant relationship between high tHcy or being pyridoxine non-responsive and increased risk of adverse clinical outcomes (**Table 2**):
  - Almuqbil et al. 2019: tHcy and medical complications (including dislocated lens, osteoporosis, stroke, scoliosis, deep venous thrombosis, and/or other complications)[3]
  - Kožich et al. 2021: pyridoxine responsiveness and individual central nervous system, vascular, ocular, and skeletal complications/abnormalities[8]
  - Poloni et al. 2018: pyridoxine responsiveness and ocular complications[11]
  - Weber et al. 2016: tHcy and lumbar bone marrow density[11]
- Other studies reported patient-level data only (n=4), outcomes based on different diagnostic/treatment subgroups (n=2), or outcomes based on the entire study population (n=3).
- Newborn screening was significantly[1,3] or qualitatively[4,12] associated with improved clinical outcomes compared to patients with later diagnoses (**Table 2**).
  - In Al-Dewik et al., IQ and quality of life (via PedsQL 4.0) were significantly higher, and tHcy and methionine levels were significantly lower in the newborn-diagnosed group.[1]
  - In Almuqbil et al., psychiatric symptoms (such as anxiety, depression, attention deficit±hyperactivity, anger, drug abuse, and social isolation) were statistically less frequent in the newborn-diagnosed group.[3]
  - In Burke et al., no patients identified in newborn screening developed ectopia lentis, while all later-diagnosed patients experienced ectopia lentis, despite good biochemical control.[4]
  - In Yap & Naughten, no patients identified in newborn screening who were diet-compliant experienced complications, while newborn-screened patients who were diet non-compliant or later-diagnosed patients experienced ocular issues and/or intellectual disabilities.[12]

Table 1. Characteristics of Included Studies

Author, Year	Study Design	Country/ Region	Study Period	Follow-up, Y	Sample Size, N	Mean Age, Y	Median Age, Y	Male, %
Al-Dewik et al. 2019[1]	Prospective observational	Qatar	2016 to 2017	≥2	126	17.4	NR	57
Allen et al. 2019[2]	Retrospective observational	Ireland	1971 to NR	1	36	26.6	NR	47
Almuqbil et al. 2019[3]	Retrospective observational	United States	1962 to NR	NR	25	33.5	29.0	52
Burke et al. 1989[4]	Prospective observational	Ireland	NR	Mean: 8.2 (HCU detected on newborn screening), 9 (HCU detected later)	19	9.4	8.5	53
Gahl et al. 1988[5]	Randomized controlled trial	United States	NR	2	5	17.6	16.0	60
Gus et al. 2021[6]	Retrospective observational	Brazil	NR	NR	10	26.3	NR	70
Karaca et al. 2014[7]	Retrospective observational	Turkey	1981 to 2012	NR	26	NR	NR	54
Kožich et al. 2021[8]	Retrospective observational	Europe (19 countries)	1962 to 2018	Median: 3.7	328	NR	26.0	53
Lim & Lee 2013[9]	Prospective observational	Korea	2007 to 2011	3.4	5	NR	NR	40
Poloni et al. 2018[10]	Cross-sectional survey and retrospective observational	Brazil	NR	Median: 6	72	NR	19.0	55
Weber et al. 2016[11]	Retrospective observational	United States	2002 to 2010	NR	19	11.5	NR	47
Yap & Naughten 1998[12]	Retrospective observational	Ireland	1971 to 1996	Mean: 14.3 (HCU detected on newborn screening), 14.7 (HCU detected later)	25	NR	NR	52
Yap et al. 2001[13]	Retrospective observational	Ireland, Australia, the Netherlands, and United Kingdom	NR to 1998	Mean: 17.9	158	29.4	NR	NR

Abbreviations: HCU = homocystinuria; NR = not reported

Table 2. Relationships Between Clinical Outcomes, tHcy, and Screening

Author, Year	Sample Size, N	tHcy, µmol/L	Outcome Types	Association with tHcy and/or Screening
Within-study tHcy-outcome relationship				
Almuqbil et al. 2019[3]	25	NR	Medical complications	Fisher's exact P=0.047
			Psychiatric symptoms	χ^2/Fisher's exact P=0.733 Newborn screening group was less likely to have psychiatric symptoms than late diagnosis group (P=0.048)
Kožich et al. 2021[8]	328	Median at diagnosis: 230 Categorized as pyridoxine non-responder, partial, full, or extreme responder	Neurologic disease, developmental delay/learning difficulties, thromboembolic complication, DVT, PE, ocular complication, lens dislocation	Fisher's exact P<0.05 for each outcome listed Skeletal abnormalities were also significant via linear-by-linear association test
Poloni et al. 2018[10]	72	Pyridoxine responder, median: 19 Pyridoxine non-responder, median: 212	Ocular complications	χ^2 P=0.013
Weber et al. 2016[11]	19	Median (IQR): 105.2 (48.7-141.7)	Lumbar bone marrow density	Spearman's rho = 0.499; P=0.05 Multiple linear regression (adjusted for age, sex, and height): β=3.04 (1.35, 4.72), R^2=0.64; P=0.01
Patient-level outcome data				
Burke et al. 1989[4]	19	<10 µmol/L: 12 (63%) 10-15 µmol/L: 3 (16%) >15 µmol/L: 4 (21%)	Ocular	Authors state that patients identified through early screening had better ocular outcomes; significance not assessed
Gahl et al. 1988[5]	5	Placebo: 36 Betaine: 8	Various	NR
Gus et al. 2021[6]	5	<50 µmol/L: 3 (30%) >50 µmol/L: 7 (70%)	Ocular	NR
Karaca et al. 2014[7]	26	Mean: 293	Various	NR
tHcy and outcome prevalence based on diagnostic/treatment subgroups				
Al-Dewik et al. 2019[1]	126	Newborn screening, median: 52 Family screening, median: 77.6 Late diagnosis, median: 108	Various	Newborn screening group had increased likelihood of higher IQ and better quality of life than late diagnosis group (P<0.001)
Yap & Naughten 1998[12]	25	HCU detected on screening, range: 4-48 HCU detected on screening but non-compliant, range: 5.5-58 HCU missed on screening, range: 4.5-8.5	Various	Authors state that patient identified on screening had no HCU-related complications, while non-compliant and late-diagnosed patients had HCU complications; significance not assessed
tHcy and outcome prevalence reported for entire study population				
Allen et al. 2019[2]	36	Mean: 78	Hypermethioninemia encephalopathy	NR
Lim & Lee 2013[9]	5	Median: 50.2	Bone/joint	NR
Yap et al. 2001[13]	158	NR	Cardiovascular	NR

Note: pyridoxine response refers to tHcy <50 µmol/L; see individual studies for additional categorization.
Abbreviations: DVT = deep venous thrombosis; HCU = homocystinuria; IQ = intelligence quotient; IQR = interquartile range; NR = not reported; PE = pulmonary embolism; tHcy = total homocysteine

LIMITATIONS AND CONCLUSIONS

- Thirteen studies describing classical HCU and tHcy were included in the SLR.
- Limited data were identified to quantify the association between tHcy accumulation and clinical complications (most studies lacked the appropriate design, sufficient sample size and follow-up duration, and/or statistical assessments to estimate associations).
- Despite these limitations, the evidence demonstrates that outcome risk is related to tHcy levels, and supports the importance of early diagnosis and intervention to minimize the risk of complications.

DISCLOSURES

MS and LP: Employees and stockholders of Travere Therapeutics, Inc. **MB, SY, and SR:** Employees of Evidera, a business unit of PPD, part of Thermo Fisher Scientific, which was contracted by Travere Therapeutics to conduct this study.

ACKNOWLEDGMENTS

This study was supported by Travere Therapeutics, Inc. (San Diego, CA). Editorial and graphic design support were provided by Fritz Hamme and Shani Berger, of Evidera, a business unit of PPD, part of Thermo Fisher Scientific, and were funded by Travere Therapeutics, Inc.

REFERENCES

1. Al-Dewik N, Ali A, Mahmoud Y, et al. *J Inherit Metab Dis.* 2019;42(5):818-830. **2.** Allen J, Power B, Abedin A, Purcell O, Knerr I, Monavari A. *JIMD Rep*. 2019;47(1):41-46. **3.** Almuqbil MA, Waisbren SE, Levy HL, Picker JD. *Genet Med*. 2019;21(8):1827-1831. **4.** Burke JP, O'Keefe M, Bowell R, Naughten ER. *Br J Ophthalmol.* 1989;73(6):427-431. **5.** Gahl WA, Bernardini I, Chen S, Kurtz D, Horvath K. *J Inherit Metab Dis*. 1988;11(3):291-298. **6.** Gus PI, Donis KC, Marinho D, et al. *Ophthalmic Genet.* 2021;42(1):71-74. **7.** Karaca M, Hismi B, Ozgul RK, et al. *Gene.* 2014;534(2):197-203. **8.** Kožich V, Sokolová J, Morris AAM, et al. *J Inherit Metab Dis.* 2021;44(3):677-692. **9.** Lim JS, Lee DH. *Osteoporos Int.* 2013;24(9):2535-2538. **10.** Poloni S, Hoss GW, Sperb-Ludwig F, et al. *J Inborn Erro Met Screen*. 2018;6. **11.** Weber DR, Coughlin C, Brodsky JL, et al. *Mol Genet Metab.* 2016;117(3):351-354. **12.** Yap S, Naughten E. *J Inherit Metab Dis.* 1998;21(7):738-747. **13.** Yap S, Boers GH, Wilcken B, et al. *Arterioscler Thromb Vasc Biol.* 2001;21(12):2080-2085.

To obtain a PDF of this poster:

Scan the QR code OR visit traverepublications.com/SIMD2024/68/

No personal information is stored.

INTRODUCTION

Background

- Classical homocystinuria (HCU) is a rare metabolic disorder associated with a significant clinical burden—particularly thromboembolic complications, developmental delay, neurological disorders, ocular issues, and skeletal events and abnormalities (e.g., osteoporosis, fracture). Classical HCU is characterized by elevated plasma levels of total homocysteine (tHcy). Guidelines recommend early intervention in patients with HCU, with a methionine-restricted diet and treatments (such as betaine and pyroxidine) to lower tHcy levels. However, the broad clinical spectrum and rarity of HCU have hindered understanding the incremental relationship between tHcy and manifestation of clinical complications.

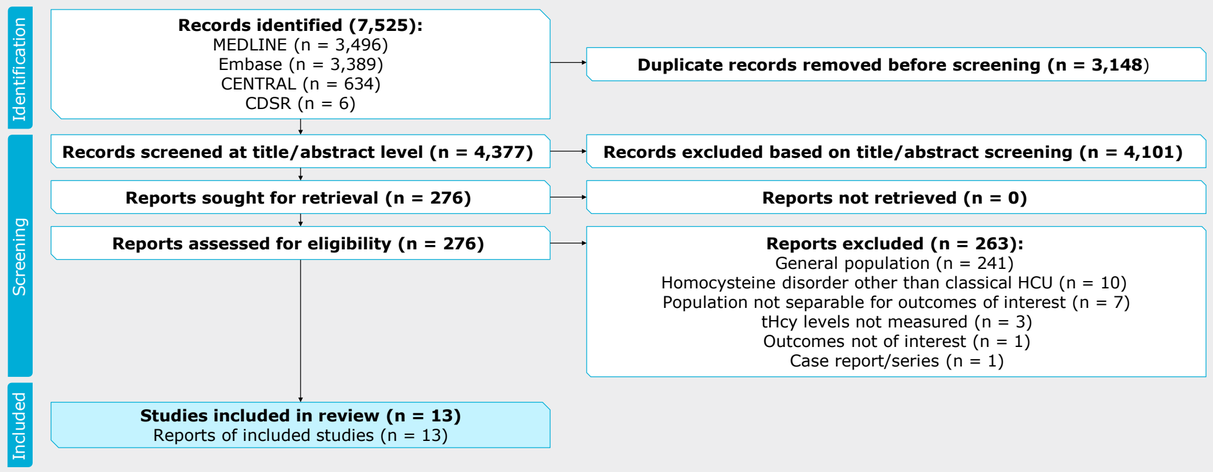
Objective

- To comprehensively identify evidence from studies describing the relationship between tHcy and clinical outcomes in HCU.

METHODS

- A systematic literature review (SLR) was performed on May 22, 2022, in Embase, MEDLINE, and the Cochrane Library for articles published at any time, and conference abstracts published from 2020 to the present, using comprehensive search strings.
- Studies of interest included interventional trials and observational studies of patients with classical HCU that reported any clinical outcomes and tHcy levels.
- Two independent reviewers screened all records, first as title/abstracts and then as full texts. A third reviewer adjudicated any screening decisions as necessary.

Figure 1. PRISMA Diagram



Abbreviations: CDSR = Cochrane Database of Systematic Reviews; HCU = homocystinuria; tHcy = total homocysteine

Contact information: Medinfo@Travere.com
MA-PE-24-0065, August 2024

Presented at the Society for Inherited Metabolic Disorders (SIMD) 45th Annual Meeting; April 14–17, 2024; Charlotte, NC, USA