Dimension Analysis of EQ-5D in Patients With Acute Hepatic Porphyria Categorized by Annualized Attack Rate to Assess Any Relationship With Symptoms Occurring Between Attacks

Manisha Balwani[1]; Manish Thapar[2]; Susana Monroy[3]; Weiming Du[4]; Teresa L Kauf[4]; Marianne T Sweetser[4]; Jamie L Weiss[4]; Paolo Ventura[5]; Bruce Wang[6], on behalf of the study investigators

[1]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Thomas Jefferson University, Philadelphia, PA, USA; [3]Instituto Nacional de Pediatría, Mexico City, Mexico; [4]Alnylam Pharmaceuticals, Cambridge, MA, USA; [5]Internal Medicine Unit, University of Modena and Reggio Emilia, Modena, Italy; [6]University of California, San Francisco, CA, USA

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Correspondence: Manish Thapar – manish.thapar@jefferson.edu

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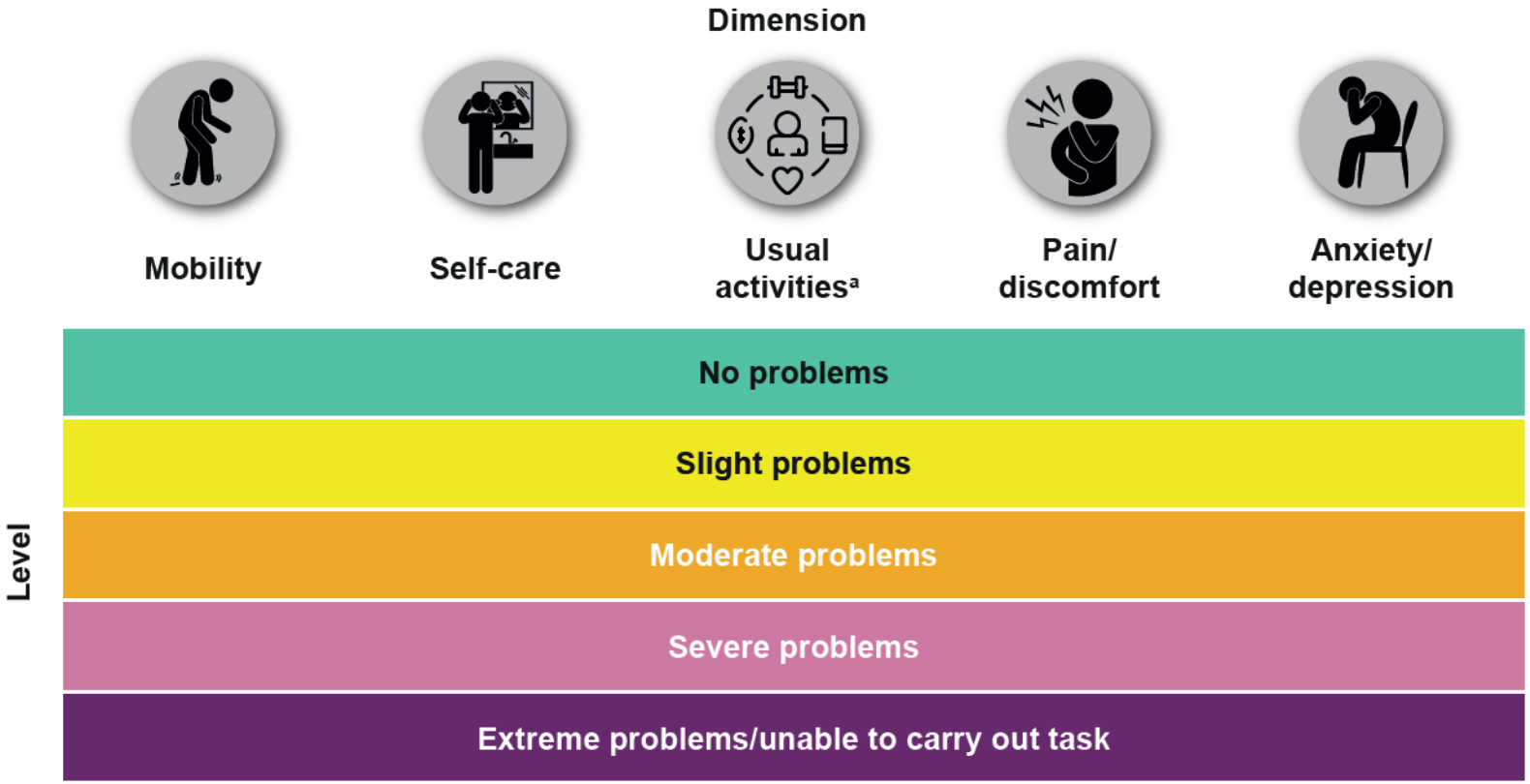
Introduction

- Acute hepatic porphyria (AHP) are a group of four rare, genetic, multisystemic disorders caused by defects in the heme biosynthesis pathway[1]
  - The four types of porphyria comprising AHP are acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and δ-aminolevulinic acid dehydratase-deficiency porphyria (ADP)[1]
  - Patients with AHP experience acute attacks, characterized by pain, neurological symptoms, and altered mental status[1]
- AHP severity is typically measured by attack frequency via annualized attack rate (AAR)
- In clinical studies of AHP,[2-6] AAR is defined by requiring hospitalization, urgent care, or intravenous hemin administration
- Emerging data suggest that patients with AHP also have chronic symptoms that may occur between acute attacks[7,8]

1. Wang B, et al. *Hepatol Commun.* 2019;3:193-206. 2. Kuter DJ, et al. *J Hepatol.* 2023;79:1150-1158. 3. Balwani M, et al. *N Engl J Med.* 2020;382:2289-2301. 4. Gouya L, et al. *Hepatology.* 2020;71:1546-1558.
5. Cassiman D, et al. *J Inherit Metab Dis.* 2022;45:1163-1174. 6. Guida CC, et al. *Mol Genet Metab Rep.* 2024;40:101111. 7. Wheeden K, et al. *Adv Ther.* 2022;39:4330-4345. 8. Simon A, et al. *Patient.* 2018;11:527-537.

EQ-5D Questionnaire



[a]The usual activities dimension asks respondents to evaluate the severity of problems in carrying out their usual activities, such as work, study, housework, family, or leisure activities.

- The EQ-5D is a concise, self-reported, standardized, generic questionnaire designed to evaluate health-related quality of life (HRQoL) across five dimensions[1-5]
  - In the EQ-5D, each dimension has five possible severity levels[5,6]

1. Kuter DJ, et al. *J Hepatol.* 2023;79:1150-1158. 2. Balwani M, et al. *N Engl J Med.* 2020;382:2289-2301. 3. Gouya L, et al. *Hepatology.* 2020;71:1546-1558. 4. Cassiman D, et al. *J Inherit Metab Dis.* 2022;45:1163-1174.
5. Devlin NP et al. 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK565678/ (Accessed October 22, 2024). 6. Herdman M et al. *Qual Life Res.* 2011;20:1727-36.
EQ-5D, EuroQol-5D.

Objective

- The objective of this post hoc analysis is to examine if there was any relationship between AAR and the burden of symptoms, occurring between attacks, as assessed by the EQ-5D survey in the ENVISION study

AAR, annualized attack rate; EQ-5D, EuroQol-5D.

Methods

- ENVISION is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study (NCT03338816) investigating the effects of givosiran in patients with AHP[1,2]
  - Baseline was defined as the assessment period before randomization and givosiran dosing (study day −60 to −1)
- During their baseline assessment, patients with AHP aged ≥12 years and with a historical AAR ≥4 completed the EQ-5D survey to describe their health on that day
  - Baseline assessments were performed at a clinic site and thus it was assumed that patients were not experiencing an acute attack during the visit
- Historical AAR was calculated based on the number of attacks requiring hospitalization, urgent care, or hemin administration at home in the 6 months before study randomization
- For this analysis, data from the givosiran and placebo groups were pooled, and patients were categorized into quartiles by historical AAR
- The relationship between EQ-5D dimension level at baseline and historical AAR was determined by Spearman correlation coefficients and logistic regression
  - As these post hoc analyses were not preplanned and were performed in an exploratory manner, data are reported descriptively; *p* values are considered nominal and are included for context

1. Kuter DJ, et al. *J Hepatol.* 2023;79:1150-1158. 2. Balwani M, et al. *N Engl J Med.* 2020;382:2289-2301.
AAR, annualized attack rate; AHP, acute hepatic porphyria; EQ-5D, EuroQol-5D; HRQoL, health-related quality of life.

Demographics and Clinical Characteristics

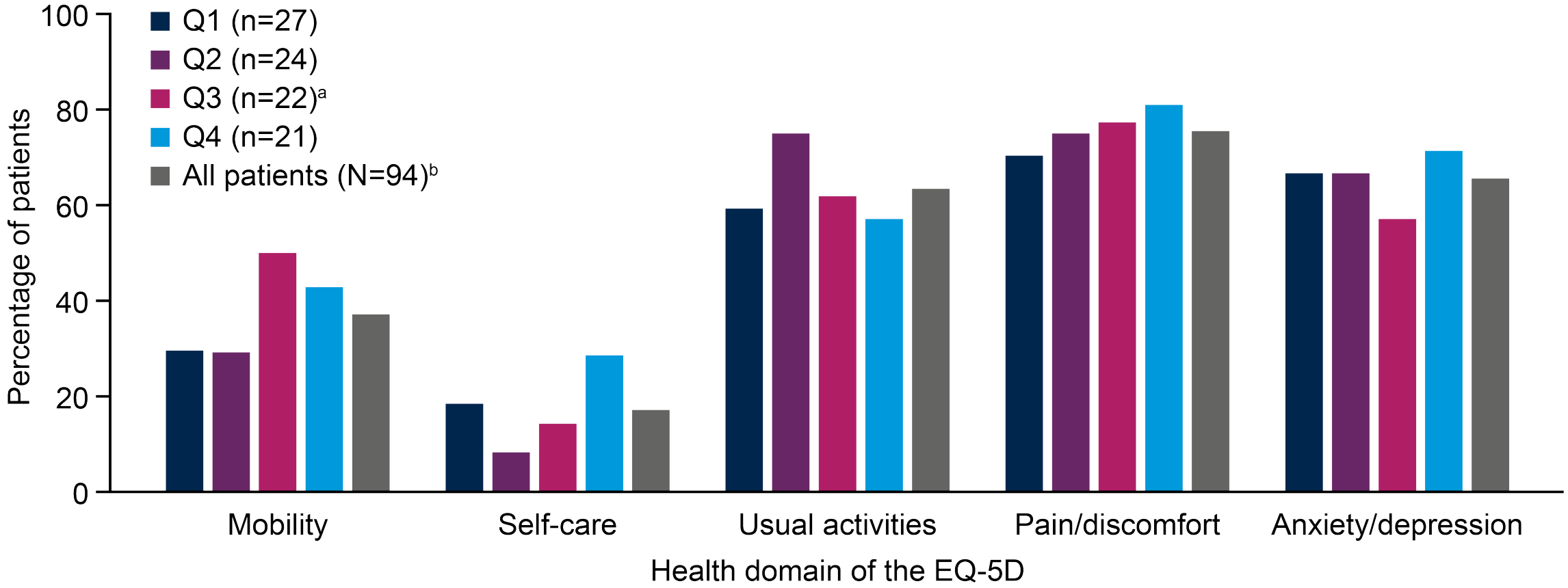
(Stratified by Historical AAR Quartiles)

Characteristic/demographic	Q1 (n=27)	Q2 (n=24)	Q3 (n=22)	Q4 (n=21)	All patients (N=94)
Age at screening, years, mean (SD)	40 (12.0)	37 (8.8)	39 (13.5)	39 (11.2)	39 (11.4)
Female, n (%)	25 (93)	22 (92)	21 (96)	16 (76)	84 (89)
Years since diagnosis, median (range)	4.3 (0.2, 35.3)	4.4 (0.1, 38.5)	8.7 (0.2, 34.2)	9.4 (0.7, 43.3)	6.6 (0.1, 43.3)
Historical AAR,[a] median (range)	4.0 (0.0, 4.0)	6.0 (6.0, 8.0)	12.0 (10.0, 16.0)	24.0 (18.0, 46.0)	8.0 (0.0, 46.0)
History of hemin prophylaxis, n (%)	8 (30)	11 (46)	11 (50)	10 (48)	40 (42.6)
History of symptoms between attacks,[b] n (%)	13 (48)	15 (63)	12 (55)	9 (43)	49 (52)
Urinary ALA,[c,d] mmol/mol					
Mean (SD)	13.6 (9.2)	16.6 (10.7)	22.6 (17.9)	22.7 (16.3)	18.5 (14.1)
Range	0.7, 40.1	2.2, 42.7	2.8, 88.9	6.0, 82.0	0.7, 88.9
Urinary PBG,[c,e] mmol/mol					
Mean (SD)	35.0 (22.4)	44.0 (25.2)	53.5 (34.1)	60.2 (33.4)	47.3 (29.9)
Range	0.4, 80.4	1.5, 103.8	0.4, 150.0	8.9, 147.2	0.4, 150.0

[a]Historical AAR was calculated based on the number of attacks requiring hospitalization, healthcare facility visit, or hemin use at home in the 6 months before randomization. [b]Defined as symptoms of porphyria when not having an attack daily or on most days before the study. [c]Normalized to creatinine. [d]Median ALA in healthy individuals: 0.46 mmol/mol. [e]Median PBG in healthy individuals: 0.02 mmol/mol.
AAR, annualized attack rate; ALA, δ-aminolevulinic acid; PBG, porphobilinogen; Q, quartile; SD, standard deviation.

EQ-5D Dimensions at Baseline

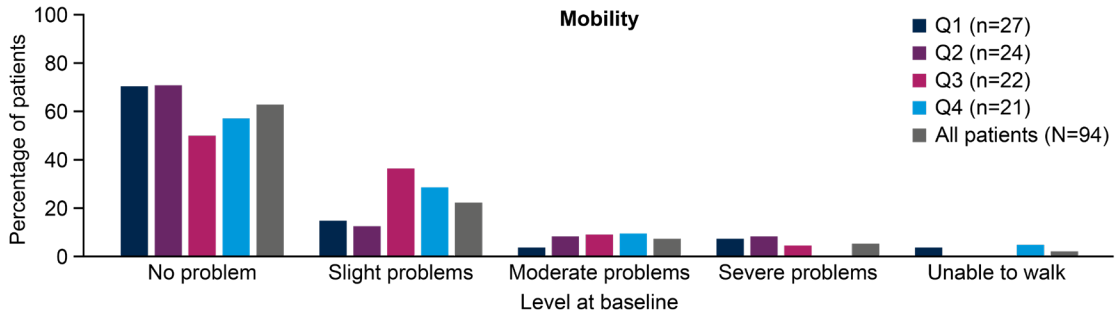
(Stratified by Historical AAR Quartiles)

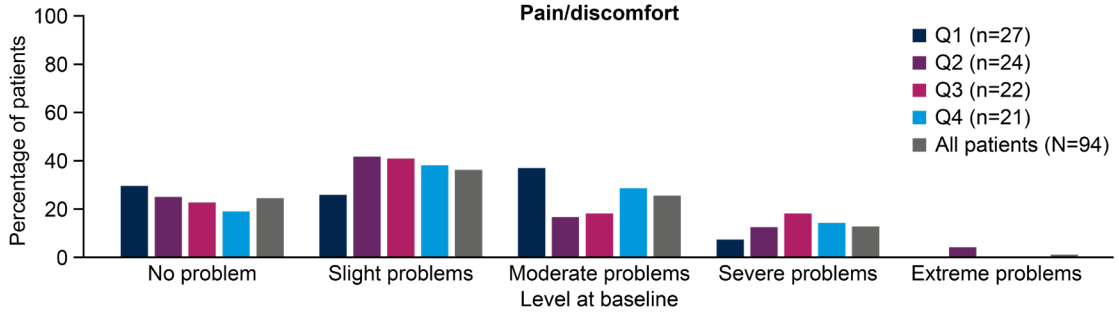


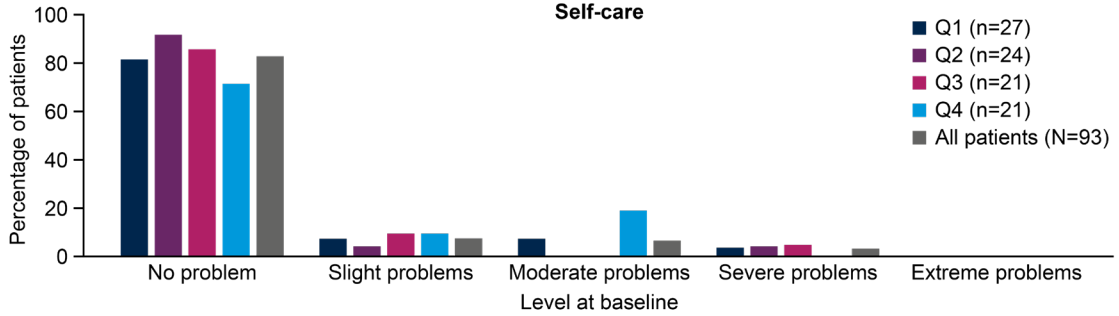
[a]n=21 in Q3 for domains of self-care, usual activities, and anxiety/depression. [b]N=93 in 'all patients' for domains of self-care, usual activities, and anxiety/depression.
AAR, annualized attack rate; EQ-5D, EuroQol-5D; Q, quartile.

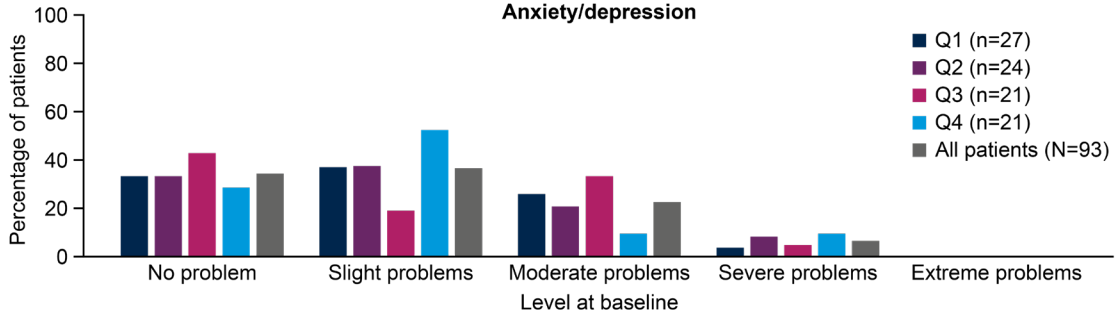
EQ-5D Levels at Baseline

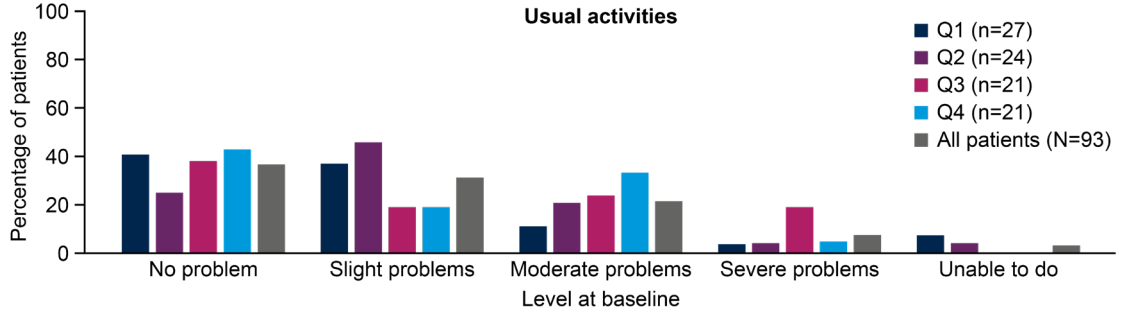
(Stratified by Historical AAR Quartiles)











AAR, annualized attack rate; EQ-5D, EuroQol-5D; Q, quartile.

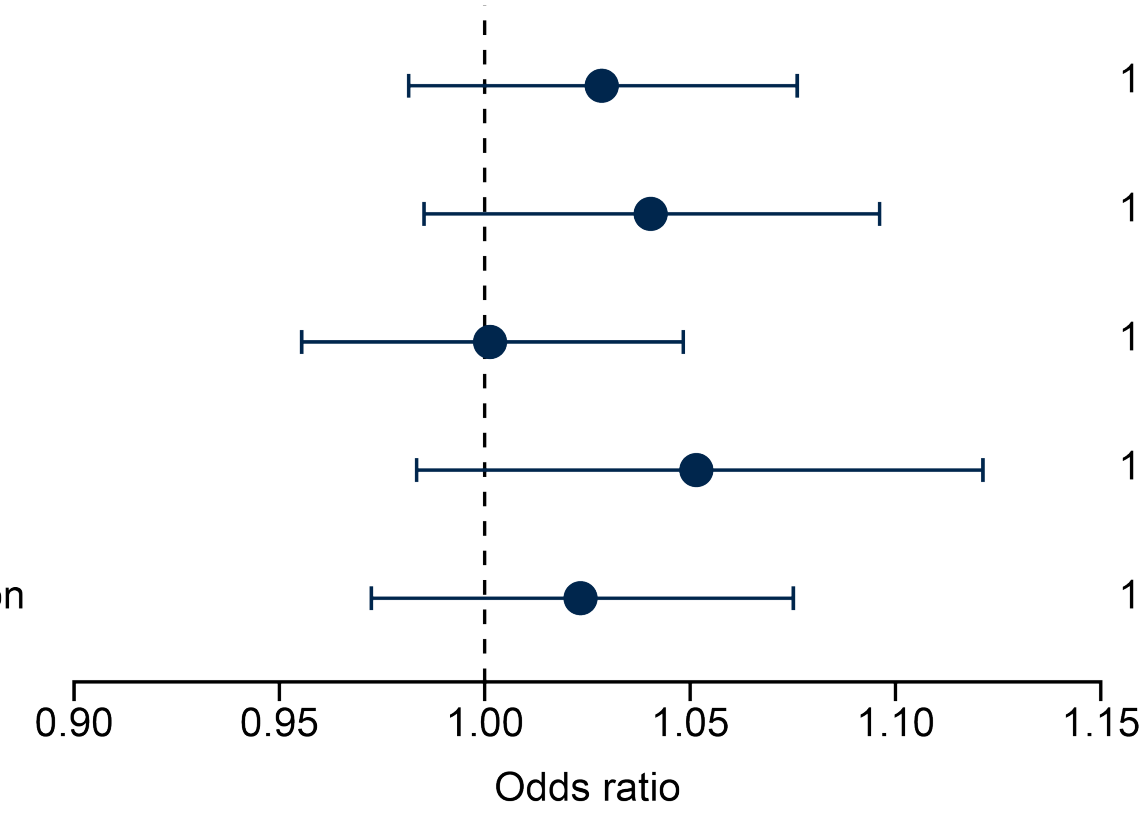
Data Suggest Lack of Correlation Between EQ-5D Levels and Historical AAR

Dimension	Spearman correlation coefficient	Nominal *p* value
Mobility	0.1240	0.2339
Self-care	0.1151	0.2720
Usual activities	0.0478	0.6494
Pain/discomfort	0.0720	0.4906
Anxiety/depression	−0.0073	0.9447

Individual dimension levels were coded as 1 (no problems), 2 (slight problems), 3 (moderate problems), 4 (severe problems), or 5 (extreme problems/unable to carry out task) for the Spearman correlation calculation. Spearman correlation coefficient can range from −1 to +1; values close to 0 indicate no relationship.
AAR, annualized attack rate; EQ-5D, EuroQol-5D.

Data Suggest No Relationship Between EQ-5D Dimensions and Historical AAR[a]

Dimension	Odds ratio (95% CI)	Nominal *p* value
Mobility	1.03 (0.98-1.08)	0.2468
Self-care	1.04 (0.99-1.10)	0.1563
Usual activities	1.00 (0.96-1.05)	0.9849
Pain/discomfort	1.05 (0.98-1.12)	0.1475
Anxiety/depression	1.02 (0.97-1.08)	0.3894



[a]Effect on odds ratios is per 1 unit increase in historical AAR. Odds ratios, 95% CIs, and *p* values were calculated from a logistic regression model predicting individual EQ-5D levels of 2–5 (slight to extreme problems) vs level of 1 (no problems).
AAR, annualized attack rate; CI, confidence interval; EQ-5D, EuroQol-5D.

Conclusions

- These results suggest that patients with AHP experience chronic symptoms, such as pain/discomfort or anxiety/depression, that are not associated with acute AHP attacks or predicted by historical AAR
- This analysis builds on earlier findings,[1-4] and suggests the chronic impact of AHP on HRQoL should be assessed regularly to guide treatment management decisions
- Additional research is needed to characterize disease burden in patients with lower historical AAR who, to date, have not been included in clinical trials

1. Kuter DJ, et al. *J Hepatol.* 2023;79:1150-1158. 2. Balwani M, et al. *N Engl J Med.* 2020;382:2289-2301. 3. Gouya L, et al. *Hepatology.* 2020;71:1546-1558. 4. Cassiman D, et al. *J Inherit Metab Dis.* 2022;45:1163-1174.
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