Understanding the Health-Related Quality of Life Burden in Chronic Hepatitis Delta Infection: A Systematic Literature Review

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Robert J Wong[1], Arman P Sali[2], Pankaj Rai[3], Chong Kim[4], Barinder Singh[3], Marvin Rock[4], Robert G Gish[5]

[1]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Palo Alto, CA, USA; [2]Gilead Sciences, Ltd., Stockley Park, UK; [3]Pharmacoevidence, Mohali, India; [4]Gilead Sciences, Inc., Foster City, CA, USA; [5]Hepatitis B Foundation, Doylestown, PA, USA

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Conclusions

- Patients with chronic hepatitis delta (CHD) experienced consistently poorer health-related quality of life (HRQoL) compared with those with chronic hepatitis B monoinfection, demonstrating lower EuroQol 5 Dimension scores, greater fatigue burden, and broader impairment across physical, emotional, and functional domains
- HRQoL declined substantially with increasing CHD severity from early-stage fibrosis (F0–F3) to decompensated cirrhosis and hepatocellular carcinoma, as consistently demonstrated by multiple validated instruments
- Well-being, daily functioning, emotional health, and fatigue emerged as the most adversely affected domains, alongside a notable rise in caregiver dependence, underscoring the significant unmet needs in this population
- These findings emphasize the critical need for early detection and timely intervention in CHD to slow disease progression, reduce symptom burden, and ultimately preserve and improve patients' HRQoL

Plain Language Summary

- Chronic hepatitis delta is the most severe form of viral hepatitis that can rapidly progress and, if left untreated, may lead to cirrhosis, hepatocellular carcinoma, and death
- This systematic literature review included evidence from multiple countries to understand the impact of chronic hepatitis delta infection on patients' quality of life and overall well-being
- The findings suggested that patients with chronic hepatitis delta infection experience worse quality of life as compared to patients with hepatitis B virus infection alone, across various validated quality of life assessment scales
- The burden on quality of life worsened with increasing disease severity from the early stage to advanced stages, affecting physical, emotional, and functional domains
- Patients with chronic hepatitis delta with more advanced liver disease were much more likely to require caregiver support, while those in earlier stages needed it far less often, adding considerable burden to families and caregivers
- Overall, this review highlights how chronic hepatitis delta significantly deteriorates patients' quality of life and increases dependency on caregiver support as the disease advances
- This reinforces the vital need for early diagnosis and intervention to prevent rapid disease progression, reduce symptom burden, and protect patients' quality of life. Effective and timely management will not only benefits patients clinically but also alleviate the extensive physical, emotional, and social strain experienced by both patients and caregivers

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Correspondence: Barinder Singh, barinder.singh@pharmacoevidence.com

Introduction

- Approximately 10 to 20 million people worldwide are infected with hepatitis delta virus (HDV), and nearly 77% of individuals develop chronic hepatitis delta (CHD) following acute HDV superinfection[1]
- CHD is associated with substantially higher risk of cirrhosis, liver failure, and hepatocellular carcinoma (HCC)[2]
- Given its progressive nature and high morbidity, CHD is expected to substantially impact health-related quality of life (HRQoL), highlighting the need for a systematic evaluation of HRQoL outcomes

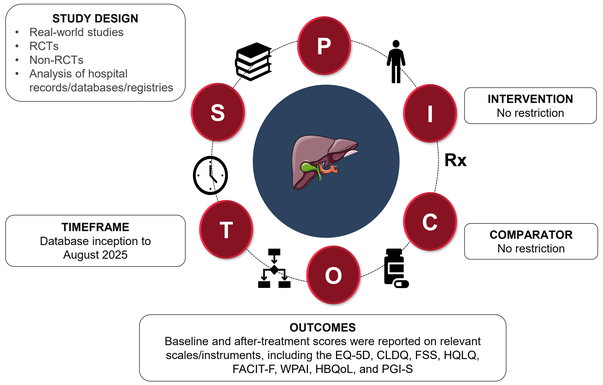
Objective

- This systematic literature review (SLR) aims to identify and summarize the published HRQoL burden in adults with CHD

Methods

- This study adhered to the National Institute for Health and Care Excellence (NICE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[3] guidelines for SLRs, following standard methodology with a transparent, reproducible, and unbiased approach
- Key biomedical databases, including Embase, MEDLINE, and CENTRAL, were searched from database inception to August 2025 to identify relevant studies reporting HRQoL burden in CHD. The prespecified eligibility criteria are presented in **Figure 1**
- Evidence was screened using both, a manual approach (reviewer 1) and an artificial intelligence (AI) tool (reviewer 2), with a quality check (QC) by a subject matter expert (SME) as per NICE UK[4] and Canada's Drug Agency[5] position papers
- To ensure a robust QC, AI-excluded citations were checked at 2 distinct levels: a QC level (disagreement between the human reviewer and the AI tool resolved by an SME) and a quality assurance level (applied when both the human and AI agreed to exclude the citation), ensuring that exclusion decisions were consistently accurate

Figure 1. Eligibility Criteria of the SLR

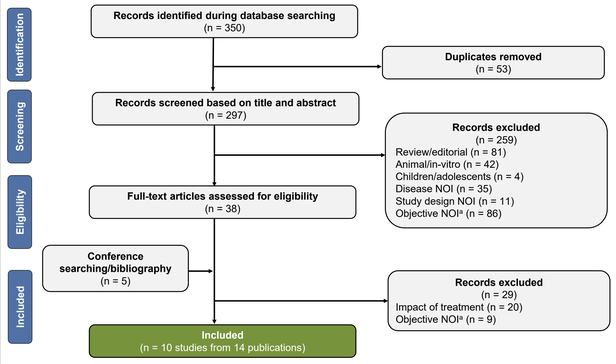


CHD, chronic hepatitis delta; CLDQ, Chronic Liver Disease Questionnaire; EQ-5D, EuroQol 5 Dimension; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FSS, Fatigue Severity Scale; HBQoL, Hepatitis B Quality of Life Questionnaire; HQLQ, Hepatitis Quality of Life Questionnaire; PGI-S, Patient Global Impression of Severity; RCT, randomized controlled trial; SLR, systematic literature review; WPAI, Work Productivity and Activity Impairment Questionnaire.

Results

- Out of 350 publications screened, 10 studies, including 6 journal articles and 4 conference abstracts, were included. **Figure 2** depicts the PRISMA flowchart of the publications identified through the SLR
- Across included studies, CHD sample sizes ranged from 10 to 168 patients, with 35.9%[6] to 74.0%[7] male representation and mean age between 41.2[8] and 52.8[9] years
- In terms of geography, 4 studies were conducted globally, followed by 2 studies in Spain, while 1 study each was conducted in the United State (US), Germany, Romania, and Kazakhstan
- In terms of study design, the majority were cross-sectional and prospective observational (n = 4 each), while 2 studies adopted a retrospective approach

Figure 2. PRISMA Flowchart of Studies Identified Through the SLR



[a]Studies focused on outcomes other than health-related quality of life. NOI, not of interest; SLR, systematic literature review.

- Across the included evidence, various HRQoL instruments were utilized, including the EuroQol 5 Dimension visual analogue scale (EQ-5D VAS, n = 4), EQ-5D Index, Hepatitis Quality of Life Questionnaire (HQLQ; n = 3 each), Fatigue Severity Scale (FSS), Chronic Liver Disease Questionnaire (CLDQ), Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–F), Work Productivity and Activity Impairment Questionnaire (WPAI; n = 2 each), Hepatitis B Quality of Life Questionnaire (HBQoL), and Patient Global Impression of Severity (PGI–S; n = 1 each), where higher scores indicate better HRQoL, except for the FSS, HBQoL and WPAI questionnaire

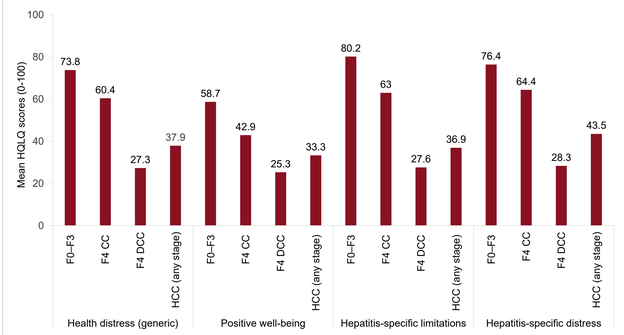
EuroQol 5 Dimension (EQ-5D)

- Patients with CHD showed poorer HRQoL on the EQ-5D scale (VAS: 64.3 and 71.5; Index: 0.8 and 0.6)[8,10] than those with chronic hepatitis B (CHB)(VAS: 79.8; Index: 0.7)[10]
- HRQoL declined further with increasing disease severity; EQ-5D VAS scores dropped substantially from 78.7 in patients with early-stage disease (F0–F3) to 40.2 in those with F4 decompensated cirrhosis (DCC) and 44.9 in individuals with HCC[9]
- A similar deterioration was observed in EQ-5D Index scores, which declined from 0.9 in F0–F3 to 0.4 and 0.5 in F4 DCC and HCC, respectively[9]

Hepatitis Quality of Life Questionnaire (HQLQ)

- HQLQ assessment suggested a similar decline with increasing disease severity across all domains (F0–F3: 58.7-80.2 to F4 DCC: 25.3–28.3), where positive well-being was the most affected domain (**Figure 3**)[9]
- Another study suggested that compared to patients with CHD alone, those with comorbid compensated cirrhosis (CC) reported greater impairment in daily activities (0% vs 39.1%; *P* = 0.153) and more pronounced emotional symptoms on the HQLQ scale. These symptoms included: melancholia (0% vs 54.8%; *P* = 0.046), discouragement (11.2% vs 41.8%; *P* = 0.082), stress (11.1% vs 60.6%; *P* = 0.02), and frustration (0% vs 51.3%; *P* = 0.082) along with reduced energy (49.8% vs 77.8%; *P* = 0.013) and a poorer outlook on life (52.1% vs 88.9%; *P* = 0.103), highlighting substantial physical and psychological burdens[11]

Figure 3. Evaluation of Patient-Reported Outcomes Using the HQLQ Scale



CC, compensated cirrhosis; DCC, decompensated cirrhosis; F0–F3, fibrosis stages 0 to 3; F4, fibrosis stage 4; HCC, hepatocellular carcinoma; HQLQ, Hepatitis Quality of Life Questionnaire.

Fatigue Severity Scale (FSS)

- Fatigue was reported as a highly prevalent symptom in patients with CHD, affecting 82.1% of patients. Nearly half (48.7%) described it as severe, and majority of the patients considered it their most bothersome symptom (63.6%). It occurred daily or weekly for most of the patients with CHD and tended to worsen over time, highlighting its substantial impact on patients' daily functioning and overall well-being[6]
- A separate study observed similar fatigue burden in patients with CHD, with severity rising as disease progressed: 3.9 (F0–F3), 4.7 (F4 CC), and 6.2 (F4 DCC), where scores ≥4 indicate severe fatigue[9]

Chronic Liver Disease Questionnaire (CLDQ)

- Patients with CHD demonstrated numerically lower CLDQ total scores compared with those with CHB (5.8 vs. 6.3; *P* = 0.07), reflecting greater disease burden (**Figure 4A**)[12]
- Abdominal symptoms and worry were among the most significantly impacted CLDQ domains, highlighting the broad impact of CHD on daily functioning (**Figure 4A**)[7,12]

Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–F)

- Compared to patients with CHB, those with CHD experienced worse HRQoL, with lower FACIT–F scores nearly across all domains, and emotional well-being was the most severely affected domain (*P* = 0.042; **Figure 4B**)[7,12]

Work Productivity and Activity Impairment Questionnaire (WPAI)

- Compared to patients with CHB, those with CHD experienced more than 3 times greater work productivity loss and presenteeism, and approximately 10 times greater activity impairment, reflecting substantially heavier functional burden (**Figure 4C**)[12]
- The burden worsened with increasing CHD severity, where the highest impairment was reported in patients with F4 DCC and those with a comorbid diagnosis of HCC compared to early-stage disease (mean activity impairment scores: 24.3, 45.5, 80.0, and 72.9 for F0-F3, F4 CC, F4 DCC, and HCC, respectively)[9]

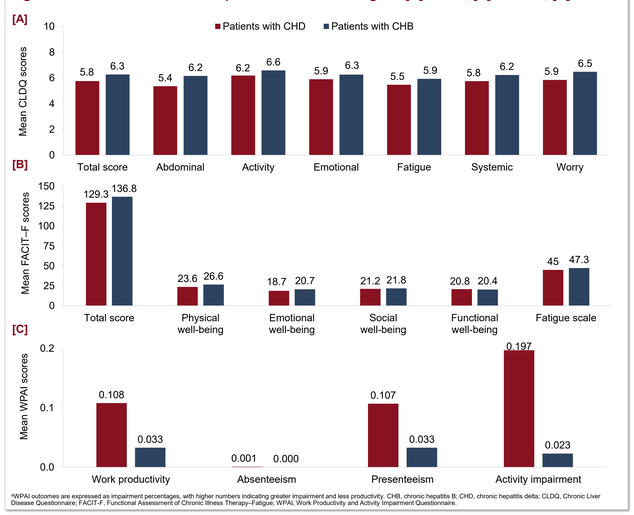
Other Scales (HBQoL, PGI-S)

- Consistent findings were observed across HBQoL and PGI-S scales, demonstrating worse HRQoL with increasing CHD severity, reflected by higher mean HBQoL stigma scores in advanced stages (F4 DCC: 42.8, HCC: 49.5 vs F0–F3: 26.7, F4 CC: 25.7) and severe or very severe symptom burden among most patients with F4 DCC (80.0%) on the PGI-S scale[9]

Caregiver Burden

- A greater proportion of patients with F4 DCC (80.00%) and coexisting HCC (62.50%) reported receiving caregiver support compared to patients with F0–F3 (8.1%) and F4 CC (28.6%)[9]

Figure 4. Evaluation of Patient-Reported Outcomes Using the [A] CLDQ, [B] FACIT-F, [C] WPAI[a]



[a]WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. CHB, chronic hepatitis B; CHD, chronic hepatitis delta; CLDQ, Chronic Liver Disease Questionnaire; FACIT–F, Functional Assessment of Chronic Illness Therapy–Fatigue; WPAI, Work Productivity and Activity Impairment Questionnaire.

Limitations

- The evidence is based on a small number of studies with limited patient populations, which may limit the comparability and generalizability of findings
- Since the included studies were retrospective in nature, they were subject to information bias, with the possibility of incomplete or unclear data