Understanding the Global Economic Burden of Hepatitis Delta Virus: A Systematic Literature Review

EE443

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Conclusion

- Chronic hepatitis delta virus infection is associated with a substantially higher economic burden worldwide compared to hepatitis B virus monoinfection, with inpatient, outpatient, and pharmacy costs as the primary cost drivers
- The economic burden generally increases with disease severity, with a sharp rise in costs at advanced disease stages, particularly among patients with decompensated cirrhosis and liver transplantation
- These findings emphasize the need for improved screening, early detection, and timely treatment to prevent disease progression and reduce long-term costs

Plain Language Summary

- Chronic hepatitis delta is a severe liver infection occurring in people already infected with hepatitis B virus and can rapidly progress to serious liver conditions such as cirrhosis and liver failure
- This review included studies across multiple countries to understand the impact of hepatitis delta virus infection on healthcare systems, particularly in terms of cost and resource use
- Compared to patients who only had hepatitis B virus infection, those with hepatitis delta virus infection reported greater economic burden, including more hospital admissions, emergency department visits, medication use, and long-term monitoring, leading to increased costs
- The economic burden increases with disease progression, with advanced conditions such as cirrhosis, hepatocellular carcinoma, and liver transplantation requiring more healthcare resources and leading to greater financial burden
- Hepatitis delta virus infection also contributes to significant indirect costs, primarily due to premature death, as well as reduced productivity and household productivity losses across all working and non-working groups
- Overall, hepatitis delta virus infection results in a higher economic burden through both direct medical costs and indirect societal losses, underscoring the need for earlier diagnosis, improved management, and better access to effective treatments

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Introduction

- Hepatitis delta virus (HDV) is the most severe form of viral hepatitis, characterized by rapid progression to cirrhosis and liver cancer, affecting 10 to 20 million people worldwide with a 4.6% prevalence in the United States (US) insured population[1-3]
- The real-world healthcare and cost burden of HDV infection is poorly defined, creating a major barrier to assessing the cost-effectiveness of new screening and treatment strategies[4]
- Therefore, it is essential to assess the economic burden of HDV infection, including healthcare resource utilization (HCRU) and associated costs, to better inform policy decisions and support emerging treatment options to mitigate the growing impact of HDV infection

Objective

- This systematic literature review (SLR) aims to synthesize global evidence on the economic burden of patients with HDV infection

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) guidelines for SLRs, following standard methodology with a transparent, reproducible, and unbiased approach
- Key biomedical databases, including EMBASE and MEDLINE were searched for English-language articles from database inception to August 2025. The prespecified eligibility criteria are presented in **Figure 1**
- Citations were screened in parallel by a human (reviewer-1) and an artificial intelligence (AI) based tool (reviewer-2) with any discrepancies resolved by a human subject matter expert (SME, reviewer-3)
- To ensure a robust quality check (QC), AI excluded citations were checked at 2 distinct levels: **QC level** (disagreement between human reviewer and AI tool was resolved by SME) and **quality assurance level** (applied when both the human and AI agreed to exclude the citations) ensuring that exclusion decisions were consistently accurate
- Costs were extracted as reported in the original studies. Inflation or currency adjustment was not performed due to country heterogeneity and limited reporting of cost-years

Figure 1. Eligibility Criteria of the SLR

Study Design

Cost studies/economic burden of illness/studies providing resource use data

Outcomes

Direct and indirect costs associated with disease, resource use data

Population

Adult patients with HDV infection of any race, gender, and ethnicity

Intervention/Comparator

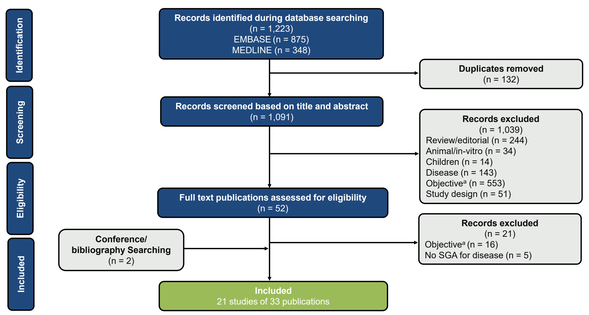
No restriction

HDV, hepatitis delta virus; SLR, systematic literature review.

Results

- Of the 1,223 publications screened, 21 studies (sample size: 117 to 416,390 patients; journal articles: 7; conference abstracts: 14) met the inclusion criteria of the SLR
- The studies were conducted across multiple countries, including the US (n = 8), followed by Italy and Spain (n = 4 each), and 1 study each from China, Israel, South Korea, Germany, and France
- The majority of studies used a retrospective design (n = 16), followed by 4 model-based economic burden studies, while 1 study employed a case-control design
- The PRISMA diagram describing the flow of citations is presented in **Figure 2**

Figure 2. Flow of Studies Identified in the SLR

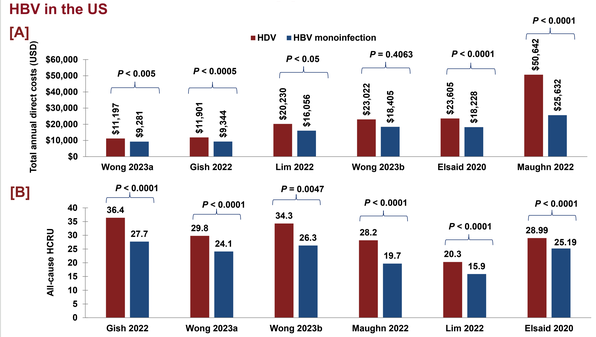


[a]Studies focused on outcomes other than cost and resource use. SGA, subgroup available.

United States[4-9]

- Patients with HDV infection reported significantly higher mean annual healthcare costs ($11,197–$50,642) compared to those with HBV monoinfection ($9,281–$25,632; **Figure 3A**). Similarly, all-cause HCRU was significantly higher among patients with HDV infection (20.3–36.4 visits) than in patients with HBV monoinfection (15.9–27.7 visits; **Figure 3B**)

Figure 3. [A] Annual Healthcare Costs [B] All-cause HCRU of Patients With HDV vs HBV in the US



HBV, hepatitis B virus; HCRU, healthcare resource utilization; HDV, hepatitis delta virus; USD, United States dollars.

- Patients with HDV infection incurred higher costs than those with HBV monoinfection, driven primarily by inpatient admissions ($220–$17,649 vs $290–$7,624), outpatient visits ($2,471–$9,951 vs $1,650–$7,710), and pharmacy expenses ($5,722–$13,310 vs $4,579–$10,766; **Table 1**).The HCRU burden was mainly driven by outpatient visits (8.6–16.8 vs 5.5–14.8), followed by inpatient visits (0.9–8.8 vs 0.7–5.0) and emergency department visits (0.3–1.1 vs 0.4–0.9)

Table 1. Comparison of Major Cost Drivers Between HDV Infection and HBV Monoinfection Across the US Studies

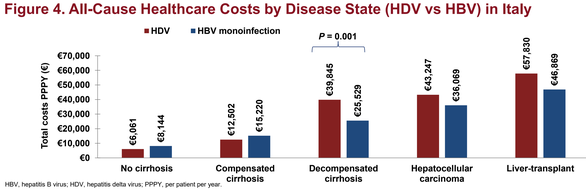
Study name	Inpatient costs ($)			Outpatient costs ($)			Pharmacy costs ($)		
	HDV	HBV	*P*-value	HDV	HBV	*P*-value	HDV	HBV	*P*-value
Gish 2022[5]	507	426	0.50	2,945	1,870	**<0.0001**	5,722	4,579	0.20
Wong 2023a[6]	220	316	0.40	2,471	1,650	0.0001	6,104	4,987	0.20
Wong 2023b[7]	442	290	**<0.0001**	6,213	3,118	**0.0001**	10,616	10,766	**0.0021**
Maughn 2022[8]	17,649	7,624	**<0.0001**	7,570	5,194	**<0.0001**	13,310	8,021	**<0.0001**
Lim 2022[9]	8,748	6,876	**<0.05**	5,272	4,176	**<0.05**	6,210	5,004	**<0.05**
Elsaid 2020[4]	6,418	4,562	**0.01**	9,951	6,488	**<0.0001**	6,504	6,749	**0.04**

HBV, hepatitis B virus, HDV: hepatitis delta virus

Italy

- The total costs per patient per year (PPPY) increased with disease severity and were generally higher with HDV infection than with HBV monoinfection, particularly among patients at advanced disease stages such as decompensated cirrhosis (DC; €39,845.30 vs €25,528.90; *P* = 0.001), hepatocellular carcinoma (HCC; €43,246.70 vs €36,068.60; *P* = 0.182), and liver transplantation (LT; €57,829.50 vs €46, 869; *P* = 0.388; **Figure 4**)[10]

Figure 4. All-Cause Healthcare Costs by Disease State (HDV vs HBV) in Italy



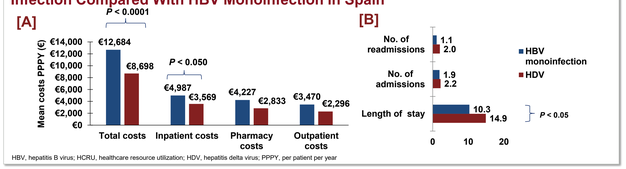
HBV, hepatitis B virus; HDV, hepatitis delta virus; PPPY, per patient per year.

- Similarly, a separate study reported significantly higher annual costs among patients with HDV and comorbid liver conditions (CC, DC, LT) and those with substance dependency (alcohol or drug abuse) compared with HDV infected patients without comorbidities. Total costs were $71,553 (liver comorbidities) and $68,819 (substance dependency) vs $28,258 (no comorbidities), with corresponding inpatient costs of $17,518 and $16,328 vs $4,396, outpatient costs of $11,929 and $12,344 vs $5,853, and pharmacy costs of $14,481 and $13,850 vs $9,780 (all *P* < 0.0001)[11]

Spain

- Mean PPPY all-cause costs were significantly higher among patients with HDV compared to those with HBV monoinfection (*P* < 0.0001), driven largely by the inpatient costs (*P* < 0.05; **Figure 5A**). Similarly, patients with HDV had significantly higher mean PPPY admissions, readmissions, and length of stay (*P* < 0.05; **Figure 5B**)[12]

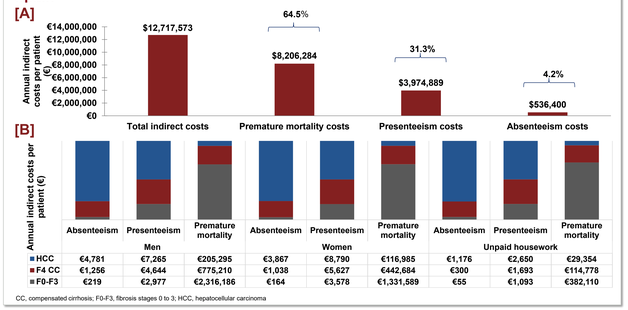
Figure 5. [A] All-cause Healthcare Costs [B] HCRU Among Patients with HDV Infection Compared With HBV Monoinfection in Spain



HBV, hepatitis B virus; HCRU, healthcare resource utilization; HDV, hepatitis delta virus; PPPY, per patient per year

- Consistent with findings from Italy, disease severity in Spain had a marked impact on economic burden, with costs increasing from €882,400 in patients without liver disease to €616,248 (CC), €774,259 (HCC), €2,662,111 (DC), and €12,875,775 (LT); total cost, €16,928,393[13]
- Only one study[14] estimated annual indirect costs of €12,717,573, with premature mortality as the largest contributor (64.5%; **Figure 6A**). Across advanced disease stages, premature mortality costs were highest in the F0 to F3 stages, whereas productivity losses (absenteeism and presenteeism) were greatest in HCC, this pattern was consistent among both working adults and individuals performing unpaid housework (**Figure 6B**)

Figure 6. Annual Indirect Costs Per Patient [A] Overall [B] by Disease Severity in Spain

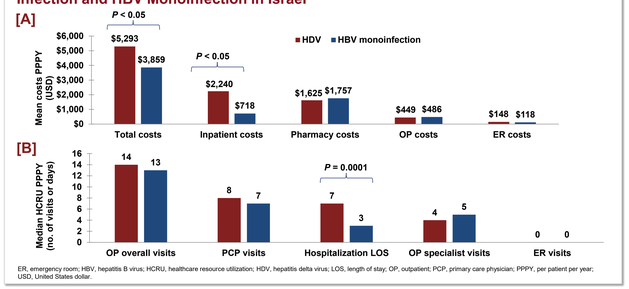


CC, compensated cirrhosis; F0-F3, fibrosis stages 0 to 3; HCC, hepatocellular carcinoma

Israel

- Patients with HDV infection reported significantly higher mean total costs PPPY compared to those with HBV monoinfection ($5,293 vs $3,859; *P* < 0.05), which were primarily driven by inpatient costs ($2,240 vs $718; *P* < 0.05; **Figure 7A**)[15]
- Similarly, HCRU was also greater among patients with HDV, reflected by a significantly longer median length of stay (*P* = 0.0001; **Figure 7B**)[15]

Figure 7: [A] Annual PPPY Mean Costs [B] Annual Median PPPY HCRU of HDV Infection and HBV Monoinfection in Israel



ER, emergency room; HBV, hepatitis B virus; HCRU, healthcare resource utilization; HDV, hepatitis delta virus; LOS, length of stay; OP, outpatient; PCP, primary care physician; PPPY, per patient per year; USD, United States dollar.

Other Countries

- In South Korea, total healthcare costs among patients with HDV infection were $7.43 million (194 cases among HBV population) whereas in China, annual costs associated with chronic HBV/HDV co-infection were $1,783 per patient[16,17]
- A France-based Markov model study estimated an average lifetime cost of €42,318 per patient based on simulated disease progression and treatment outcomes[18]
- In Germany, the mean total annual cost for patients with HBV/HDV coinfection was €3,466; however, it should be noted that 37.5% of patients did not receive treatment[19]

Limitations

- Variation in cost components, currency types, and severity definitions, limited comparability across studies
- Indirect costs were reported in only one study, reducing the robustness of societal-level estimates and likely underestimating the true indirect economic burden of HDV infection