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Association of hepatitis delta virus with liver morbidity and mortality: A systematic literature review and meta-analysis

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Abstract

Background and Aims: Studies have suggested that patients with chronic hepatitis B, either co- or superinfected, have more aggressive liver disease progression than those with the HDV. This systematic literature review and meta-analysis examined whether HDV RNA status is associated with increased risk of advanced liver disease events in patients who are HBsAg and HDV antibody positive.

Approach and Results: A total of 12 publications were included. Relative rates of progression to advanced liver disease event for HDV RNA +/detectable versus HDV RNA−/undetectable were extracted for analysis. Reported OR and HRs with 95% CI were pooled using the Hartung-Knapp-Sidik-Jonkman method for random-effects models. The presence of HDV RNA+ was associated with an increased risk of any advanced liver disease event [random effect (95% CI): risk ratio: 1.48 (0.93, 2.33); HR: 2.62 (1.55, 4.44)]. When compared to the patients with HDV RNA− status, HDV RNA+ was associated with a significantly higher risk of progressing to compensated cirrhosis [risk ratio: 1.74 (1.24, 2.45)] decompensated cirrhosis [HR: 3.82 (1.60, 9.10)], HCC [HR: 2.97 (1.87, 4.70)], liver transplantation [HR: 7.07 (1.61, 30.99)], and liver-related mortality [HR: 3.78 (2.18, 6.56)].

Conclusions: The patients with HDV RNA+ status have a significantly greater risk of liver disease progression than the patients who are HDV RNA−. These findings highlight the need for improved HDV screening and linkage to treatment to reduce the risk of liver-related morbidity and mortality.

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; MA, meta-analysis; NICE, National Institute for Health and Care Excellence; QUIPS, Quality in Prognosis Studies; ROBINS-I, Risk of Bias in Non-randomized Studies of Interventions; RR, risk ratio; SLR, systematic literature review; WHO, World Health Organization.

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INTRODUCTION

The HDV is a defective single-stranded RNA virus that requires a synergistic relationship with the HBV to replicate and invade hepatocytes.[1,2] HDV is spread through parenteral exposure and is characterized as either an acute co-infection or a superinfection.[2] The global prevalence of HDV/HBV infection is poorly understood and often debated. Recent prevalence estimates vary widely from 0.16% to 0.80% in the general population and increase to 1 in 6 when considering people with liver disease.[3–5] Recent estimates provided by the World Health Organization (WHO) found that approximately 1 in 22 (4.5%) of individuals with HBV are HDV antibody–positive with some higher estimates based on geographical location (eg, Mongolia, Pakistan, the Republic of Moldova, and countries in Africa)[5], translating to between 12 and 72 million individuals living with HDV/HBV worldwide.[3–5]

Chronic HBV/HDV infection is recognized as the most aggressive form of viral hepatitis in humans, leading to the rapid progression of liver disease to acute liver failure or cirrhosis. Recent studies suggest that individuals with chronic HDV are at a significantly higher risk of cirrhosis, liver decompensation, HCC, liver transplant, and liver-related mortality.[1,4,6–9] The official status of HDV as an oncogenic virus has yet to be determined, despite the suggested link between HDV infection and the increased risk of HCC versus HBV mono-infection as demonstrated by various studies and 2 recent meta-analyses.[9–14]

Currently, there are no direct-acting antiviral treatments approved for HDV.[1] Notable non-antiviral therapies are currently under development, which include bulevirtide (which recently obtained approval for use by the European Medicines Agency[15]), lonafarnib (farnesyl transferase inhibitor), and pegylated interferon lambda (ie, Lambda, type III interferon lambda receptor inhibitor).[16] The primary treatment strategy involves a 48-week course of pegylated interferon alpha (pegINF-α).[1,17] However, pegINF-α treatment is associated with adverse events and worsened patient quality of life, is not recommended for those who already have decompensated cirrhosis (DCC), and has a high relapse rate in patients who initially respond to treatment (approximately 50%).[18,19] Therefore, timely diagnosis and consistent monitoring of HDV RNA detectability is important for the management of disease progression.

The relationship of virological and other disease biomarkers to HDV/HBV disease progression is not well characterized and the existing studies consist of either small cohort studies or specific high-risk populations (eg, compensated HBV cirrhosis, HIV, immigrants, veterans with HCV infection).[11,20–22] Recent studies have linked HDV RNA detectability to the progression of various advanced liver disease end points.[21,23–25] However, findings differ in the magnitude of the associations reported, which may be a consequence of the heterogeneity observed across the included populations, study designs (eg, retrospective vs. prospective, or multicenter vs. single-center), and follow-up periods. In general, several studies have reported positive correlations of a detectable HDV RNA and the development of either liver-related events (eg, cirrhosis), or HCC, or both.[21,23,24] Conversely, one small cohort (n = 49), single-center study in Germany reported that HDV RNA positivity at baseline did not correlate with any clinical outcomes over a very short follow-up period of 3 years.[25] However, another study highlighted that HDV viremia was less predictive of poor liver outcomes once cirrhosis had developed, indicating that the stratification of results by baseline cirrhosis status is an important factor when calculating risk estimates.[23]

Accurately assessing and understanding the link between HDV RNA viremia as a risk factor for disease progression is vital to the improved management of people living with chronic HDV infection. The relationship between HDV RNA detectability and disease progression has not been systematically assessed to date. The aim of this study was to systematically review the literature regarding the relationship between HDV RNA detectability and disease progression.

METHODS

The systematic literature review (SLR) was conducted as per the guidelines provided by the National Institute for Health and Care Excellence (NICE)[26] and the Cochrane Handbook[27]; results are reported per the preferred reporting items for systematic reviews and meta-analyses guidelines.[28]

Search strategies were executed in Embase (Embase.com), MEDLINE (Embase.com), MEDLINE In-Process (PubMed interface), Cochrane Central Register of Controlled Trials (Cochrane library interface), and the Cochrane Database of Systematic Reviews (Cochrane library interface). The searches were conducted from database inception to March 15, 2023. Restrictions included non-English publications and conference abstracts. Searches were not restricted by geographical location or by date. In addition, manual recursive searching of the reference list was performed for each of the included studies and any relevant previously published reviews. See Supplemental Tables S1–S5, http://links.lww.com/HEP/I48 in the Supplemental Material for the search strategies, http://links.lww.com/HEP/I48.

Screening for both the title/abstracts and full texts was done by 2 independent investigators against the predetermined population, intervention, comparator, outcomes, and study design criteria (details in Supplemental Table S6 in the Supplemental Material, http://links.lww.com/HEP/I48). Any discrepancies were resolved by a third investigator.

Studies meeting the inclusion criteria had their data extracted independently by 2 investigators. Long-term follow-up data from clinical trials were prioritized over primary/interim data analyses for extraction and inclusion in meta-analyses to avoid data duplication of individual studies. Any discrepancies in the extraction were resolved by means of discussion or arbitration by a third investigator. Data were entered directly into report-ready tables. All studies were checked for duplicate reporting of the same or overlapping cohorts for data from the same region during the same time period. In instances where duplicate cohorts were suspected, only the largest of the cohorts was used for a given outcome.

Quality assessment was completed utilizing both the Quality in Prognosis Studies (QUIPS) and the Risk of Bias in Non-randomized Studies tools to assess the overall risk of bias for each included study. Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) is a tool developed for the assessment of the risk of bias in the results of nonrandomized studies that compare the health effects of 2 or more interventions.

For the purposes of this review and meta-analysis, disease progression was defined as the progression of noncirrhotic to compensated cirrhosis (CC), CC to HCC, CC to DCC, liver transplant, and/or death.

Meta-analysis

Quantitative heterogeneity was assessed by evaluating as the proportion of the variance of the pooled estimate due to heterogeneity (Crippa Rb), formal Cochran Q test of homogeneity, and complemented with 95% prediction intervals assuming the t-distribution. While a CI is a measure of the precision of the estimated mean effect size (in 95% of all analyses repeated on different samples, this CI will contain the true mean effect size), the prediction interval is a measure of dispersion indicating where the effect size from a future study is likely to fall. Prediction intervals were calculated for analyses comprising at least 3 primary studies. Random-effect meta-analyses were performed using Hartung-Knapp models with between-study variance (τ) estimated as per Sidik-Jonkman with *ad hoc* correction (R package meta version 6.2-1). Given the large heterogeneity in population characteristics and outcomes, random-effect estimates were used for inference, with common effect estimates provided in the forest plots. Reported inferential statistics (ie, ORs, risk ratios [RRs], and HRs) with associated uncertainty (ie, 95% CI, SEs) were used as the input parameters to meta-analyze the study level data. Further, univariable random-effect meta-regressions were evaluated using gender distribution, follow-up duration, age, and proportion of patients with cirrhosis at baseline as covariates. Studies reporting descriptive statistics (ie, proportional data) or qualitative data only were excluded from the analysis and have not been pooled.

Reconstruction of individual patient data from published Kaplan-Meier survival curves was performed using published algorithms.[29,30] HRs were calculated from digitized individual patient data using the Cox proportional hazards model; the R code is available in the Supplemental Material, http://links.lww.com/HEP/I48. OR to RR conversions were performed using a formula recommended by Zhang and Yu.[31] Subgroup analyses were performed to evaluate the impact of baseline cirrhosis status, the length of the follow-up period, and the study risk of bias on the meta-analysis results. Statistical analyses were performed using R.[32]

RESULTS

Studies and patient characteristics

Database searches were executed on March 15, 2023, and identified a total of 2052 manuscripts (Figure 1). Of those, following the removal of 42 duplicate publications after screening, 2010 citations underwent title/abstract screening and 1845 records were excluded. A total of 165 records were included for full-text screening. In addition to the database searches, a supplementary manual search of relevant bibliographies and keywords in Google Scholar was performed, yielding an additional 8 publications (n = 5 from bibliography review, n = 3 from Google Scholar). Of the 173 full texts, 10 were not available (publication date ranges from 1982 to 1998 and not indexed online). Following the review of the available 163 full texts, 161 were excluded, resulting in 12 publications being included in the meta-analysis.

The 12 included studies assessed either the impact of HDV RNA negativity (or undetectability) or ALT normalization on disease progression in patients from 9 countries (including one international study) and were largely retrospective in nature (Table 1). Overall, studies were heterogenous in nature and most of the studies did not report covariate details. Sample size across studies ranged from 53 to 1349 for a combined total of 4876 patients for the meta-analysis. The majority of the patients were male (range: 53%–77%) with a mean/median age range of 30–52.9 years. Study follow-up varied across studies and ranged from 3 to almost 20 years. An overview of the definition of the comparator and intervention group is provided in Supplemental Table S9, http://links.lww.com/HEP/I48. While Mahale and colleagues reported a significant association of HDV RNA with adverse liver disease events, given that no CIs were reported, their estimates were not included in any quantitative analyses. Table 1 provides a summary of the 12 studies from the SLR included in the meta-analysis.

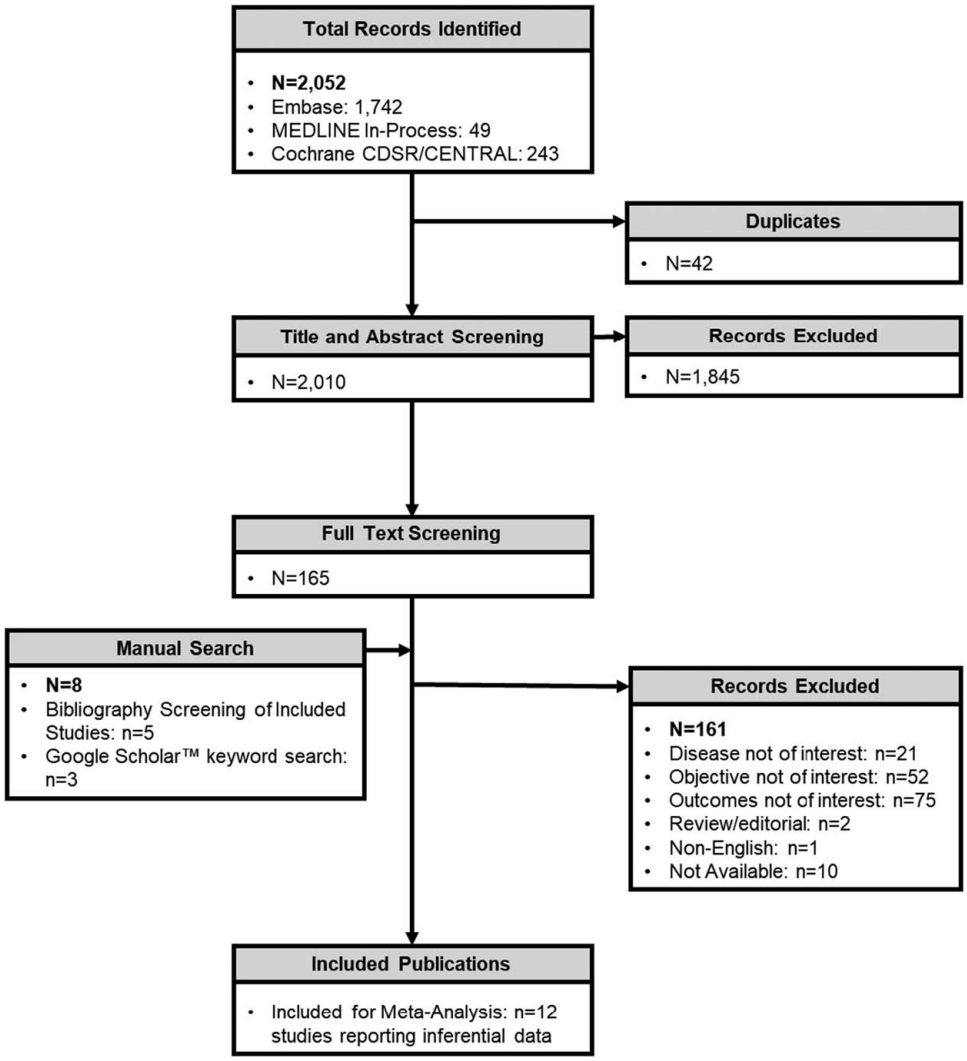

FIGURE 1 PRISMA flow diagram of screened and included studies. Abbreviation: PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Risk of bias assessment

QUIPS for prognostic studies

Of the 12 included studies, 11 exhibited a low risk of bias across all 6 bias domains. All studies were associated with a low risk of bias in terms of study participation, outcome assessment, and statistical analysis and reporting. One study[36] was graded as potentially high risk of bias due to the lack of information regarding the assessment of "Confounding Factors."

Risk of bias in nonrandomized studies

As most of the studies (n = 11) included in the SLR were noninterventional, the ROBINS-I tool was modified to assess the quality of the included noninterventional studies by excluding the 2 domains associated with the intervention and evaluating the 5 remaining domains broadly (rather than using the "Preintervention," "At Intervention," or "Postintervention" categories provided by the tool).

Of the 11 noninterventional studies for which the modified ROBINS-I tool was used to evaluate the risk of bias, 2 were determined to have a "critical" risk of bias, 7 had a "serious" risk of bias, and 2 were determined to have a "moderate" risk of bias. Domains associated with the greatest risk of bias included issues related to confounding, study participant selection, measurement of outcomes, and missing data.

The full ROBINS-I assessment was used to evaluate the risk of bias for the one interventional nonrandomized study,[39] which was determined to have a "serious" risk of bias. The serious risk of bias was due to missing data in the postintervention phase (Supplemental Tables S7, http://links.lww.com/HEP/I48, and S8 in the Supplemental Material for the detailed assessment, http://links.lww.com/HEP/I48).

TABLE 1 Study characteristics of the included studies

References	Study country	Study setting	Study design	Male %	Follow-up (Y)/study period	Sample size	Mean age (y)
Jang et al[33]	Taiwan	Single-center	Retrospective Obs	72.4	5.0	1349	48.0
Scheller et al[34]	Germany	Single-center	Retrospective Obs	60.0	4.6	53	26.0[a]
Wranke et al[35]	Global	Multicenter	RCT	58.3	8.9	60	39.6
Roulot et al[21]	France	Multicenter	Retrospective Obs	68.6	3.0[a]	1112	36.5[a]
Spaan et al[36]	UK	Single-center	Retrospective Obs	53.3	4.4[a]	107	36.0
Palom et al[37]	Spain	Multicenter	Retrospective Obs	58.0	8.0[a]	118	49.0[a]
Kamal et al[24]	Sweden	Multicenter	Retrospective Obs	54.0	6.5	426	38.0
Mahale et al[38]	Gambia	Multicenter	Retrospective Obs	73.0	1997–2001[b]	901	NR
Yurdaydin et al[39]	Turkey	Single-center	Retrospective Obs	70.7	4.6[a]	99	40.0[a]
Wranke et al[40]	Germany	Single-center	Retrospective Obs	67.0	5.2	136	37.6
Romeo et al[23]	Italy	Single-center	Cross-sectional	76.0	9.5[a]	193	40.8
Romeo et al[12]	Italy	Single-center	Retrospective Obs	76.9	19.4[a]	299	30.0

[a]Median values reported.
[b]Study period.
Abbreviations: NR, not reported; Obs, observational study.

Meta-analyses

Association of HDV viremia and any liver-related event

A total of 8 studies reported the association of HDV status with any liver-related event. Among the studies reporting an OR (n = 3), patients with an HDV RNA+ status were found to be at nonsignificantly higher risk for any liver-related event compared to the patients with an HDV RNA− status [Figure 2A RR: 1.48 (95% CI: 0.93, 2.33)]. The variation across the 3 studies due to heterogeneity was not significant (R_b = 19%). All 3 studies included younger populations with a mean age range of 37.6–48.0 years of age, with follow-up periods ranging from 4.6 to 8.9 years.

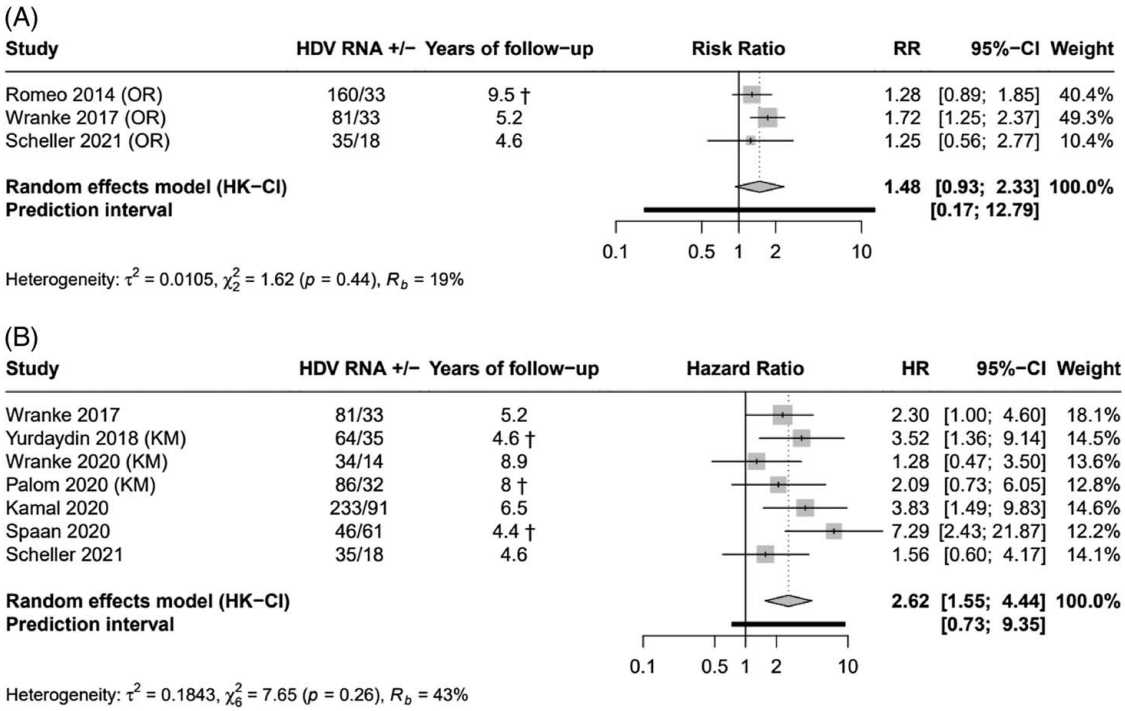

FIGURE 2 Association of HDV RNA status with any liver-related event: RR (A) and HR (B). (OR) indicates that the RR was calculated from the OR. (KM) indicates that the HR was calculated from KM curves. †Median values reported for follow-up. Abbreviations: HK-CI, Hartung-Knapp confidence interval; KM, Kaplan-Meier; RR, risk ratio.

The overall estimate for the studies reporting an HR (n = 7) agreed with the overall RR estimate [Figure 2B; HR: 2.62 (95% CI: 1.55, 4.44)]. The heterogeneity of outcomes among these studies was moderate (R_b = 43%). Factors potentially contributing to the moderate heterogeneity across the 9 studies included sample sizes (range: n = 53–426), population age (mean range: 26.0–49 y), and variations in follow-up periods (mean range: 4.6–8.9 y; median range: 4.4–8.0 y). Three of the 7 studies[34,35,37] reported CIs that crossed the line of null effect, and 2 of these studies had the lowest sample sizes (n = 53 in the study by Scheller and colleagues and 48 in Wranke and colleagues).

In both the above analyses, the 95% prediction intervals crossed the line of null effect (RR analysis: 0.17–12.79; HR analysis: 0.73–9.35). However, the prediction interval provided should be interpreted with caution for the meta-analysis among studies reporting ORs as less than 4 primary studies were included; the prediction interval based on the meta-analysis of studies reporting HRs (n = 7) may be considered more reliable (Figure 2B).

Association of HDV viremia and CC

Two studies reported the association of HDV status with CC. The patients with an HDV RNA+ status were found to be at a significantly higher risk for CC compared to the patients with an HDV RNA− status [RR: 1.74 (95% CI: 1.24, 2.45)] (Figure 3A). The heterogeneity between the 2 studies reporting the OR was minimal with an R_b = 0%. It should be noted that the RR estimate is based on 2 studies, neither of which reported CIs that span the line of null effect. These 2 studies included sample sizes of 299 and 743, with predominantly male populations and similar age ranges (mean range: 30.0–40.8 y).

One study reported the association of HDV status with CC, with an HR of 5.75 (95% CI: 3.67, 9.03) (Figure 3B).

Association of HDV viremia and DCC

While 2 studies reported OR data for the association of HDV RNA detectability status with DCC, only one was included due to cohort overlap (Figure 4A). The estimate suggests that the patients with an HDV RNA+ status were at a significantly higher risk for DCC compared to the patients with an HDV RNA− status [RR: 2.28 (95% CI: 1.40, 3.71)]. This study had a sample size of 299 subjects, with a majority male population, a mean age of 30.0 years, and a relatively long follow-up (median of 19.4 y). A total of 4 identified studies reported an association of HDV RNA detectability status with DCC using HRs (Figure 4B), resulting in an HR of 3.82 (95% CI: 1.60, 9.10). The heterogeneity across the 4 studies presenting HR data was minimal to moderate (R_b = 33%).

Given that the 95% prediction interval for the HR analysis crossed the line of null effect (0.40, 36.54), future evidence may help better understand the varying effectiveness of HDV RNA+ status as a risk factor for DCC across populations.

Association of HDV viremia and HCC

A total of 6 studies reported the association of HDV status with HCC. Of the 2 studies reporting OR data, only one was included due to cohort overlap. As reported in the primary study, the patients with an HDV RNA+ status are at nonsignificantly higher risk for developing HCC compared to the patients with an HDV RNA− status [RR: 1.34 (95% CI: 0.74, 2.43)] (Figure 5A).

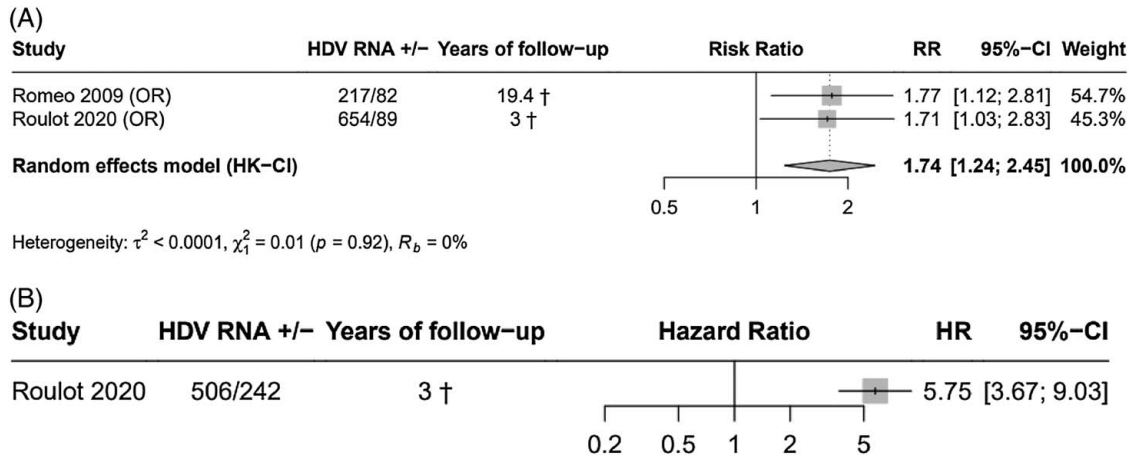

FIGURE 3 Association of HDV RNA status with compensated cirrhosis: RR (A) and HR (B). (OR) indicates that the RR was calculated from the OR. †median values reported for follow-up. Abbreviations: HK-CI, Hartung-Knapp confidence interval; RR, risk ratio.

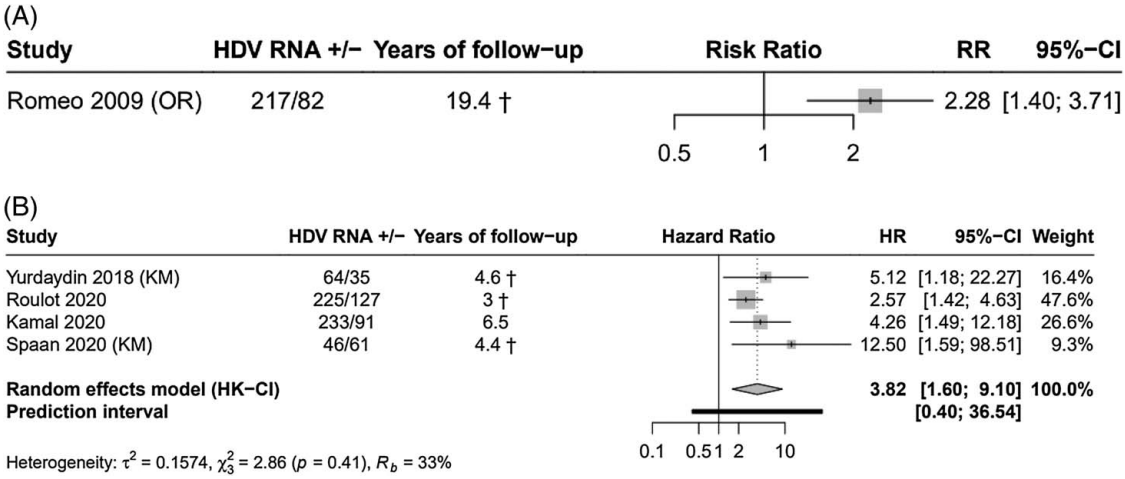

FIGURE 4 Association of HDV RNA status with DCC: RR (A) and HR (B). (OR) indicates that the RR was calculated from OR. (KM) indicates that the HR was calculated from KM curves. †Median values reported for follow-up. Abbreviations: DCC, decompensated cirrhosis; HK-CI, Hartung-Knapp confidence interval; KM, Kaplan-Meier; RR, risk ratio.

The overall HR estimate across 5 studies was 2.97 (95% CI: 1.87, 4.70) with minimal heterogeneity (R_b = 9%) (Figure 5B). The true effect size of a theoretical future study assessing HDV RNA+ status (as indicated by the prediction interval) would fall between 1.21 and 7.28. This 95% prediction interval suggests that an HDV RNA+ status is a risk factor for HCC within comparable populations.

Association of HDV viremia and liver transplant

Two of the identified studies reported the association of HDV status with liver transplant using HRs. The overall estimate of the 2 studies suggests that the patients with an HDV RNA+ status were at a significantly higher risk for having a liver transplant compared to the patients with an HDV RNA− status [HR: 7.07 (95% CI: 1.61, 30.99)] (Figure 6). It should be noted that these results are based on 2 studies, both of which reported wide-ranging CIs that crossed the line of null effect. Further investigations are needed to confirm this relationship. As the minimum number of studies for calculating a 95% predictive interval (n = 3) was not met, a prediction interval was not included in the analysis.

Association of HDV viremia and mortality

A total of 5 studies reported the association of HDV status with mortality. Two studies reported OR data (only 1 was included due to cohort overlap) and 4 studies reported association using HRs. The estimate

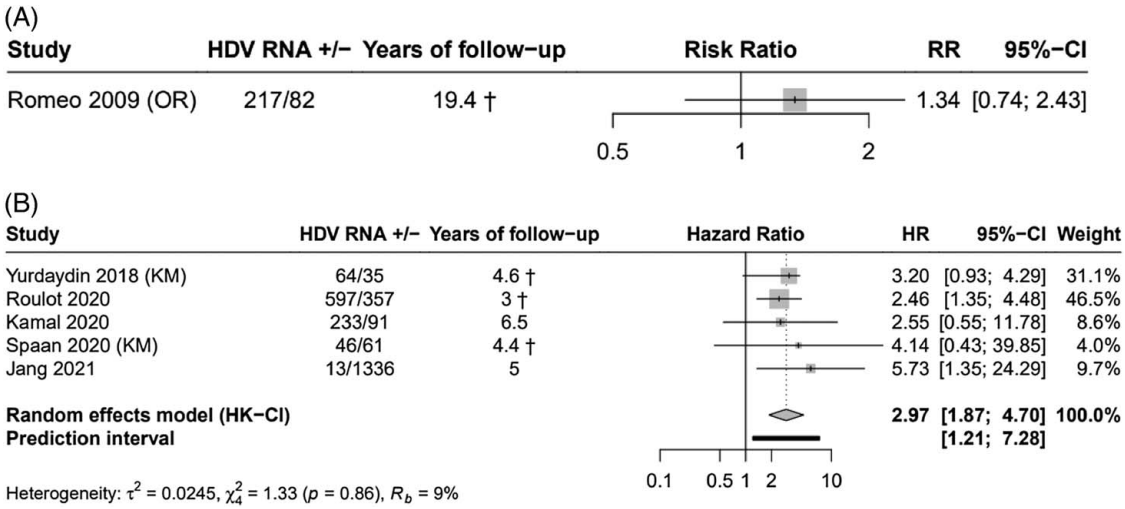

FIGURE 5 Association of HDV RNA status with HCC: RR (A) and HR (B). (OR) indicates RR was calculated from OR. (KM) indicates HR was calculated from KM curves. †Median values reported for follow-up. Abbreviations: HK-CI, Hartung-Knapp confidence interval; KM, Kaplan-Meier; RR, risk ratio.

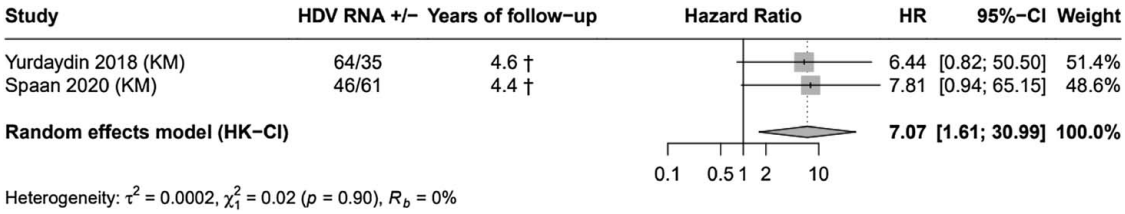

FIGURE 6 Association of HDV RNA status with liver transplant: HRs. (KM) indicates HR was calculated from KM curves. †Median values reported for follow-up. Abbreviations: HK-CI, Hartung-Knapp confidence interval; KM, Kaplan-Meier.

from the primary study for the OR suggests that patients with an HDV RNA+ status were at a significantly higher risk for mortality compared to the patients with an HDV RNA− status [Figure 7A: RR: 3.22 (95% CI: 2.06, 5.04)]. The overall estimate for the HR analysis found similar results [HR: 3.78 (95% CI: 2.18, 6.56)]; the heterogeneity across the 4 HR studies was minimal with an R_b = 13% (Figure 7B). Of note, all 4 studies reported on a younger age range (mean range: 36.5–40.0 y), majority male population, and over follow-up periods ranging from 3.0 to 6.5 years. Of note, Roulot and colleagues had one of the largest sample sizes of n = 1112, contributing 69% to the overall estimate.

The true effect size of a theoretical future study assessing HDV RNA status as a risk factor for mortality would fall between 0.86 and 16.64, suggesting that further evidence is needed to better understand HDV RNA+ status as a risk factor for mortality (Figure 7B).

Base-case and subgroup analyses

Subgroup analyses were performed to estimate the impact of baseline cirrhosis [baseline disease status as either "cirrhosis" (≥50% of the patients with cirrhosis at baseline) or "mixed" (<50% of the patients with cirrhosis at baseline)] and studies marked as "Critical Risk" using the ROBINS-I tool on the base-case results (Supplemental Material Table S10, http://links.lww.com/HEP/I48).

None of the subgroup analyses showed significantly different findings from the base-case analyses. The effect estimates of HDV RNA+ versus RNA− were generally lower among studies including ≥50% of the patients with cirrhosis at baseline compared to mixed populations (<50% of the patients with cirrhosis at baseline). Further, the subgroup analyses excluding studies with critical risk using the ROBINS-I tool found no significant differences. Therefore, studies with a critical risk of bias were not a significant factor in the overall results of the analysis.

Meta-regression

Univariate meta-regression was performed to investigate sources of between-study variability. The parameters selected for meta-regression included gender distribution, follow-up duration, age, and proportion of the patients with cirrhosis at baseline (Supplemental Material Table S11, http://links.lww.com/HEP/I48). None of the coefficients of the covariates evaluated by means of meta-regression were statistically significant at consensual α = 5% in the

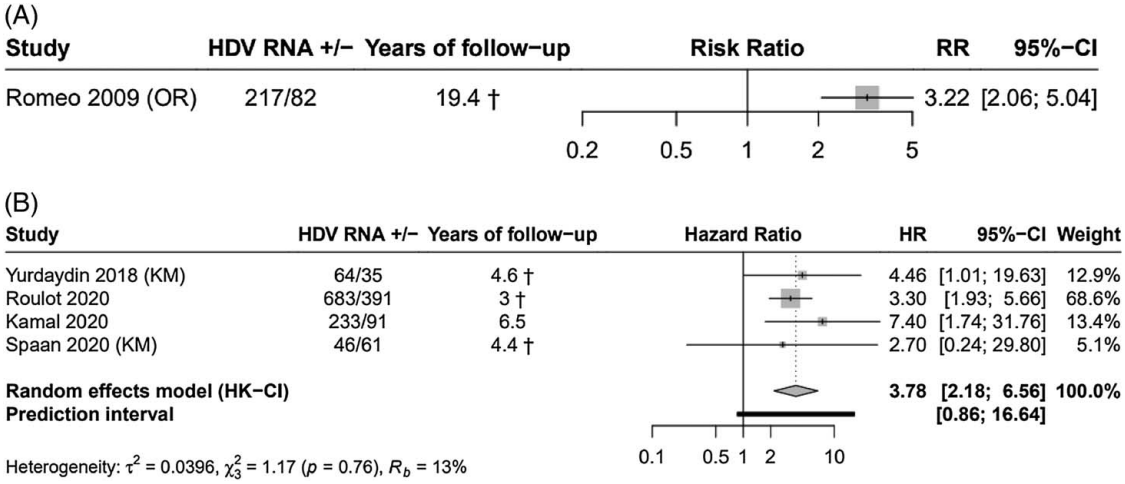

FIGURE 7 Association of HDV RNA status with mortality: RR (A) and HR (B). (OR) indicates RR was calculated from OR. (KM) indicates HR was calculated from KM curves. †Median values reported for follow-up. Abbreviations: HK-CI, Hartung-Knapp confidence interval; KM, Kaplan-Meier; RR, risk ratio.

HR- and RR-based analyses, with the exception of mean age as a predictor for HCC ($p = 0.028$). While gender, follow-up duration, age, and proportion of the patients with cirrhosis at baseline did not independently explain the high variability between study estimates, age does seem to modify the effect of HDV on the development of HCC.

DISCUSSION

This study systematically reviewed and synthesized findings for HDV RNA status and its association with liver-related morbidity and mortality. Following a comprehensive search of the literature, a total of 12 studies were included for analysis. The results of the meta-analyses suggest that the patients with an HDV RNA+ status were at a higher risk of experiencing any liver-related event compared to the patients who were RNA−. Furthermore, patients with HDV RNA+ status were at a higher risk of developing CC, DCC, and HCC compared to those who were HDV RNA−. Analyses showed that the patients who were HDV RNA+ were 7 times more likely to undergo liver transplantation compared to those who were HDV RNA−. Additionally, the patients with an HDV RNA+ status were at a higher risk of mortality compared to those who were HDV RNA−. Each end point analyzed underscores the importance of treatment among patients who were HDV RNA+ to achieve viral suppression or clearance of HDV RNA, significantly reducing morbidity and mortality.

Prediction intervals are generally more conservative than CIs because they do not only take account of the uncertainty associated with estimating the true population parameter but also the variability between studies. Thus, prediction intervals estimating outcomes in future studies demonstrated that HDV RNA is an effective predictive marker for progression to HCC (n = 5 studies). While our findings support previous links between detectable HDV RNA and severe liver outcomes such as cirrhosis and HCC,[12,23,35,39] the results should be interpreted with caution as the low power of the analyses due to the sample number of studies may increase the risk of false-negative results. Despite this, our findings suggest a strong relationship between HDV RNA and liver disease progression, with a similar direct effect across all analyses. This finding supports the evidence base that HDV viremia is associated with severe liver disease outcomes, including mortality. Therefore, there is an urgent need for the timely diagnosis of patients with HDV through effective implementation of screening programs, and treatment that focuses on the reduction of HDV RNA to improve overall patient outcomes.

Recent clinical trials[35,39] are measuring and reporting changes in detectable HDV RNA in response to treatment. Treatment with INF-α and peg-INFα-2a has been shown to reduce detectable HDV RNA to achieve an HDV RNA− status and log reduction in some patients who remain HDV RDV+, thereby reducing the risk of liver-related disease and death in responders.[35,39] However, high rates of nonresponders and relapse following treatment stoppage/discontinuation remain ongoing issues among patients receiving INF-α and peg-INFα therapy. In one study with a 10-year follow-up period, patients continued to report disease relapse 5 years following the termination of peg-INFα treatment, with 1 patient relapsing after 9 years of a "sustained virological response."[35] Recent clinical trials have also reported that the clearance of the HBsAg may be an optimal end point for chronic HDV/HBV infection and that reduced detectability of HDV RNA may be predictive of HBsAg clearance and vice versa.[35,39] Future studies may wish to explore the relationship of the levels of HDV RNA and HBV viremia, particularly the impact of the level of HDV RNA or HBsAg over time to better help understand the impact of treatment.

An inherent limitation of the analyses is the small sample of studies included in the meta-analyses (n = <10), resulting in relatively small pooled sample sizes, with multiple testing due to the range of analyses. While this study aimed to generate hypotheses on the risk factors for HDV RNA positivity, the prediction intervals estimating the likely result of a future study should be interpreted in the context of the number of studies and sample size. Further, there was notable heterogeneity that was observed across several of the end points analyzed. There are differences in several patient characteristics that may be influencing study results in this meta-analysis, which may be impacting the observed heterogeneity. Further, additional studies evaluating the association of HDV RNA status, the impact of persistently negative HDV RNA, and liver-related events would allow for more reliable predictions regarding the effectiveness of HDV RNA as a risk factor within various populations and the modulators related to observed effects. For example, studies with larger proportions of males and/or younger patients were important population characteristics associated with the variability of study outcomes, specifically regarding liver-related mortality in the RR analyses. Our study aimed to include all available peer-reviewed evidence; however, additional evidence may be available beyond the sources included here.

We observed that males were more likely to experience liver-related mortality, while younger patients were less likely to have liver-related mortality. The inclusion of study populations that have larger proportions of males and/or younger patients may have also contributed to the heterogeneity of the results of the meta-analyses presented in this study. Study populations with a larger proportion of males may be an accurate representation of a generalized population with HDV. Further, the populations included in the meta-

analyses in our study were largely of European origin. Given the significant heterogeneity that can exist in populations with HDV across geographies, the results should be interpreted with caution. Future studies evaluating HDV infection and liver mortality should consider these population characteristics carefully when determining inclusion criteria. In addition, it is highly recommended that future studies stratify clinical outcomes by patients' cirrhosis status to improve the accuracy of future risk estimates across broader geographies. More data on viral load reductions, without clearance, would further bolster the concept of a partial response to antiviral therapy and improved outcomes.

An additional limitation of our analysis is that our findings are likely impacted by the variable duration of follow-up across studies. The length of follow-up time is a reasonable source of variability when considering that an appropriate amount of time is required to understand and compare the true incidence of outcomes assessed, particularly liver transplant and liver-related mortality, as 2 studies reported liver-related mortality as a composite with liver transplant.[21,23,24] However, it is important to note that the course of disease is rather heterogenous in different areas of the world, attributable to several factors including population characteristics, treatment availability, and HBV vaccination programs.[4,40] Future studies may wish to examine the impact of maintained viral suppression on long-term disease morbidity and mortality.

Potential ascertainment bias represents a limitation of meta-analyses of point estimates, such as RRs. Information reported in the primary studies was not sufficient to determine whether the analyses appropriately accounted for time dependency, that is, accounted for differential observation time in the 2 compared groups. However, as nearly all included studies report patients' HDV status at baseline, and outcomes are reported for groups that achieved virological clearance; any potential ascertainment bias is likely to be minimal. The single exception among the included studies was the case-control study by Mahale et al,[38] who recruited control subjects with no clinical evidence of liver disease from general medical outpatient clinics and matched to cases only on age and gender; however, as Mahale did not report CIs, their estimates were not included in any meta-analyses.

While our results suggest that patients with HDV RNA+ status were at a higher risk of developing CC, DCC, and HCC compared to those who were HDV RNA−, some of the studies identified in this analysis using the ROBINS-I tool were identified as being at serious or critical risk of bias. Further, given the wide prediction intervals reported in our results, caution should be used when interpreting the results of this analysis.

Lastly, the impact of other disease end points, such as ALT normalization, would be valuable to explore. Data for ALT normalization were sparse across the studies captured in this SLR, thereby limiting analysis. For our meta-analyses, we used adjusted estimates from multivariable regression, wherever available. Further, a pooled analysis of individual patient data would allow for a better assessment of the impact of patient-level covariates, including baseline disease characteristics and treatment, on the risk of progression of disease. Future research should aim to further explore the impact of baseline characteristics and treatment on liver disease in patient-level data sets.

The strengths of this study include a robust systematic review of the literature, which included a thorough search of multiple databases, the criterion-based inclusion of relevant studies by 2 independent reviewers, and quality appraisal of the literature. This approach ensured a consistent and accurate interpretation of the findings. The results of the meta-analyses were robust across sensitivity and meta-regression analyses to identify any covariate effects.

CONCLUSIONS

This comprehensive systematic review and meta-analysis demonstrate that the patients with an HDV RNA+ status have a significantly greater risk of liver disease progression compared to the patients with an HDV RNA− status. These findings highlight the need for improved HDV screening in patients with chronic HBV, leading to early detection of HBV/HDV, linkage to care, and timely initiation of appropriate antiviral therapies to reduce the risk of liver-related morbidity and mortality.

AUTHOR CONTRIBUTIONS

Robert G. Gish, Robert J. Wong, Gian Luca Di Tanna and Patrick T.F. Kennedy: contributed significantly to the conceptualization, investigation and validation of the manuscript. Ankita Kaushik, Chong Kim and Nathaniel J. Smith: contributed to the data curation and formal analysis. Nathaniel J. Smith contributed significantly to the methodology and original draft of the manuscript. All authors participating in the reviewing and editing of the manuscript.

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CONFLICTS OF INTEREST

Robert G. Gish consults, advises, and is on the speakers' bureau for AbbVie, Genentech, Gilead, and Intercept. He consults, advises, and owns stock in Genlantis, HepQuant, and HepaTX. He consults and

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