

HDV RNA level shows a threshold pattern for liver disease progression but has limited prognostic value alone in chronic hepatitis D

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Abstract

Background and Aims:

Persistent HDV RNA replication predicts worse outcomes in chronic hepatitis D (CHD), but the clinical significance of HDV RNA's levels, relative to other predictors of liver-related events (LREs), remains unclear.

Methods:

Adults with CHD attending a Mongol liver center, 2015–2025, without prior LREs or anti-CHD therapy, were eligible. HDV RNA levels were quantified using Bio-Rad kit (lower limit of quantification of 50 IU/mL). Associations of baseline and longitudinal HDV RNA levels with cirrhosis progression, and LREs were assessed using Cox regression models.

Results:

Overall 2,447 patients were included with: median age 40.3 years, 56.1% females, median HDV RNA 5.3 $\log_{10}$ IU/mL, 37.4% HBeAg+, 76.5% with elevated ALT, and 23.6% with cirrhosis at baseline. During a median follow-up of 7.3 years (range 0.6–12.7), 247 of 1,870 patients (13.2%) progressed to cirrhosis, and 287 of 2,447 patients (11.7%) experienced any LREs, with cumulative risks of 6.9%, and 18.0% at 5 and 10 years, respectively. The risk of HCC, and LREs increased from HDV RNA level above 3 $\log_{10}$ IU/mL, without further increase at higher levels (threshold pattern), while cirrhosis risk rose more gradually to 5 $\log_{10}$ IU/mL. HDV RNA level alone showed limited prognostic discrimination (AUROC <0.70), while age, ALT, GGT, platelet count, liver stiffness, and cirrhosis provided additional prognostic information (AUROC $\geq$ 0.83).

Conclusion:

HDV RNA levels showed a threshold, not a dose-response, association with HCC and liver-related events, with limited prognostic accuracy alone. Adding other liver-related parameters improved risk stratification, potentially guiding monitoring, and treatment decisions.

Introduction

Chronic hepatitis D (CHD) is associated with accelerated cirrhosis, and increased risks of liver-related morbidity and mortality [1, 2]. The global prevalence of hepatitis D virus (HDV) infection is around 10–19 million with Central Asia, Sub-Saharan Africa and South America identified as high endemic regions [2]. In Europe, CHD also contributes to the burden of liver disease [2]. Current guidelines recommend HDV RNA testing in anti-HDV-positive individuals to confirm active infection and guide clinical management, as detectable HDV RNA is strongly associated with a worse prognosis [3]. However, HDV RNA detectability as a dichotomic parameter provides only broad prognostic information [1]. The clinical significance of different quantitative HDV RNA levels remains insufficiently defined, and whether this association follows a linear-like, threshold-like, or another pattern, is unclear [4–7]. This is particularly becoming important to identify patients at greatest risk of CHD progression considering the high cost of

bulevirtide and other emerging anti-HBV/HDV therapies [8, 9]. Therefore, this study aimed to characterize the pattern of association between HDV RNA levels, both at baseline and longitudinally, with cirrhosis progression and other LREs in a large, treatment-naïve Asian cohort with CHD. We further assessed to what extent HDV RNA levels added prognostic value beyond established virological, biochemical, and liver disease severity markers.

Patients and methods

Study design and setting

This retrospective observational study included all patients with CHD attending a single secondary-care referral hepatology center, at Ulaanbaatar, Mongolia from January 2015 to June 2025.

Population

Eligibility criteria were age ≥ 18 years at initial HDV RNA test, a confirmed CHD diagnosis with ≥ 2 HDV RNA+ tests ≥ 50 IU/mL obtained at least 3 months apart, with ≥ 6 months follow-up time. We excluded patients with ever exposure to anti-HDV therapy, and those with hepatic decompensation, liver transplantation, or HCC prior to and within 180 days of baseline. (Figure S1 Study flowchart).

Study outcomes

The primary outcome was the incidence of composite LREs, defined as any of decompensation events, HCC, liver transplantation or liver-related death. The secondary outcome was cirrhosis progression among patients without cirrhosis at baseline.

Laboratory and virological tests

HBsAg, anti-HCV, and anti-HIV were qualitatively tested by rapid diagnostic test (CTK Co.Ltd, USA), while anti-HDV were tested using ELISA (Wantai Co.Ltd, PRC). Quantitative HBsAg was estimated by HISCL-5000 fully automated chemiluminescence analyzer (Sysmex Co.Ltd, Japan). HBeAg was measured using a chemiluminescent immunoassay (CLIA, Sysmex, Japan).

HDV RNA was extracted using the BioActGene® Virus Purification Kit (Bioactiva Diagnostics GmbH, Germany) and quantified using a quantitative reverse-transcription PCR assay with the iTaq Universal Probes One-Step Kit (Bio-Rad, USA). The assay was performed on an Mx3005P qPCR system (Agilent Technologies, USA) and had a lower limit of detection of 50 IU/mL. Details on ascertainment of outcome, laboratory, virological variables, and LSM are provided in Supplementary methods.

Statistical analysis

Continuous variables were presented as mean ($\pm$ SD) or median (IQR, interquartile range) and categorical variables were described as frequencies (numbers) and proportions. Student's t-test, Mann-Whitney U, Chi-Square or Fisher's exact tests were used, as appropriate.

Follow-up and cumulative incidence

The baseline date was defined as the first HDV RNA positive (≥ 50 IU/mL). Follow-up was defined from the baseline date to the date of first LRE, last recorded visit, death or end of the study set at 30 June 2025, whichever occurred first. The cumulative incidence of LREs across HDV RNA categories was estimated using the Kaplan-Meier analysis.

Predictors of study outcomes

The association between baseline predictors with the incidence of study outcomes was examined using Cox regression analysis. Significant factors and those of clinical interest in univariable analysis, were introduced in the multivariable analysis.

Dynamic analysis of HDV RNA trajectory

Patients with at least two HDV RNA measurements spaced ≥ 6 months apart were considered for the dynamic analysis. For each eligible patient, three summary measures of HDV RNA values were derived: the first measurement (baseline), the time-weighted mean of all measurements during follow-up, and the relative change between the first and last measurements. The time-weighted mean was calculated by weighing each interval between consecutive measurements by its duration, to account for unequal spacing between visits.

The association between baseline HDV RNA value and time-weighted mean with the incidence of cirrhosis and LREs was examined using restricted cubic splines (RCS) with three knots placed at the 5th, 35th, and 65th percentiles of the predictor distribution, fitted within a cause-specific Cox regression model. The reference value was set at the HDV RNA < 1000 IU/mL. The prognostic utility of a relative change in HDV RNA levels was also evaluated defined as ≥ 1 log decline, ≥ 1 log increase and stable level for those < 1 log change across follow-up.

Sensitivity analyses

As a sensitivity analysis, the cumulative risk of the primary outcome was estimated across HDV RNA categories using the Aalen-Johansen estimator, accounting for competing events. All analyses were performed in R (version 4.2.2). Statistical significance was defined as a two-sided p-value < 0.05 .

Ethical aspects

All data were anonymized, and statistical analyses were conducted at Karolinska Institutet. Ethical approval was granted from the local ethics review boards in Mongolia and Sweden, with waived individual patient consent. The study was funded by ALF grant from Region Stockholm, Sweden, and was conducted in accordance with the Declaration of Helsinki.

Results

Baseline characteristics of study cohort

Overall, 2,447 patients were eligible (Figure S1). As shown in Table 1, the median age was 40.3 years, females constituted 56.1% and 23.6% had cirrhosis. The prevalence of elevated ALT and GGT $\geq$ ULN was 76.5%, and 42.6%, respectively. The median (IQR) HDV RNA level was 5.3 (4.1–6.1) $\log_{10}$ IU/mL, 13.6%, 28.4% and 58.1% had $< 3 \log_{10}$, $3-<5 \log_{10}$, and $\geq 5 \log_{10}$ IU/mL, respectively. No significant difference in HDV RNA levels by cirrhosis, and sex was noted. While younger age (18–29 years) had higher HDV RNA levels. (Figure S2 A-B) The difference between patients with HDV RNA < 5 vs $\geq 5 \log_{10}$ IU/mL (Table 1) is presented in the supplements.

Incidence rate and cumulative risks of liver-related events

During a median follow-up of 7.3 years (min-max 0.6–12.7), corresponding to 17,095.1 person-years, 247 of 1,870 patients without cirrhosis at baseline (13.2%) progressed to cirrhosis. Among 247 patients who progressed to cirrhosis, 92 (37.2%) did so within 2 years and were classified as “fast-progressors”, while 87 (35.2%) and 68 (27.5%) progressed within 5 and 10 years, respectively.

Overall, 287 (11.7%) experienced any LREs, at an annual incidence rate (IR) of 1.74% with 3-, 5- and 10-years cumulative incidence of 4.0%, 6.9%, and 18.0%, respectively. Among 577 patients with baseline cirrhosis, 28.3% experienced any LREs, corresponding to an IR of 4.5% and cumulative risks of 9.9%, 17.6%, and 41.7% at 3, 5, and 10 years, respectively. In patients without cirrhosis, the IR of LREs was 1.0%, with corresponding cumulative incidence of 2.1%, 3.6%, and 11.3%, respectively.

Cirrhosis progression and liver-related events according to baseline HDV RNA levels

The cumulative incidence of cirrhosis, and LREs was significantly lower in patients with HDV RNA levels $< 3 \log_{10}$ IU/mL. Specifically, patients with $< 2 \log_{10}$ had an annual IR of cirrhosis of 0.5%, and patients with $2-<3 \log_{10}$ showed an annual IR of 1.24%. The corresponding 3, 5- and 10-year cumulative risks were 0.0%, 3.3%, and 5.1%, for $< 2 \log_{10}$, 5.0%, and 5.6%, and 11.3% for $2-<3 \log_{10}$ IU/mL, respectively.

The risk of cirrhosis progression increased progressively with HDV RNA levels up to approximately $5 \log_{10}$ IU/mL, more consistent with a graded, dose-dependent relationship than a sharp threshold (Fig. 1A). By contrast, the cumulative risk of HCC increased from HDV RNA level $\geq 3 \log_{10}$ IU/mL, with little additional increase at higher viral loads, showing a clearer threshold effect (Fig. 1B). This distinction

between HDV RNA categories for composite LREs was more pronounced among patients with baseline cirrhosis (Fig. 1D; $p = 0.004$) than among those without (Fig. 1C, $p = 0.37$). None of the patients with HDV RNA $< 2 \log_{10}$ progressed to cirrhosis within 2 years, while only 5 (5.4%) among those “fast-progressors” had HDV RNA $< 3 \log_{10}$ IU/mL at baseline.

Predictors of cirrhosis progression

In Table S2, univariable analysis showed that age, sex, prior NUC, ALT, AST, GGT, albumin, total bilirubin, platelets count, HBsAg, HDV RNA, and LSM were all significant factors. In the adjusted model, independent predictors were older age (aHR = 1.03; 1.01–1.04), elevated ALT $\geq 2 \times \text{ULN}$ (aHR = 1.37; 1.06–1.78), elevated GGT $\geq 2 \times \text{ULN}$ (aHR = 1.32; 1.58 – 2.76), platelets count $< 150,000$ cells/ μL (aHR = 1.29; 1.10–1.63), and higher HDV RNA level (aHR = 1.12; 1.02–1.23), higher LSM (aHR = 1.22; 1.16–1.28). In separate models, patients with HBsAg $\geq 3 \log_{10}$ IU/mL had 1.51-fold higher risk to progress to cirrhosis, those with HDV RNA $\geq 3 \log_{10}$ had 2.20-fold, and those with HDV RNA $\geq 5 \log_{10}$ IU/mL had 1.33-fold the risk compared to peers below these cutoffs, respectively. Those with LSM ≥ 10 kPa had 1.98-fold (1.51–2.60) higher risk.

Notably, elevation of ALT and GGT levels $\geq \text{ULN}$ alone was not independently associated with cirrhosis progression, whereas two-times elevation $\geq \text{ULN}$ was (Table S2).

Predictors of composite liver-related events

In Table 2, independent factors associated with composite LREs were older age (aHR = 1.05; 1.04–1.06), smoking (aHR = 1.75; 1.22–2.49), elevated GGT (aHR = 2.09; 1.58–2.76), albumin < 35 g/L (aHR = 1.80, 1.22–2.65), low platelets (aHR = 2.02; 1.58–2.59), HBeAg+ (aHR = 1.29; 1.10–1.63), lower HBV DNA level (aHR = 0.88; 0.82–0.97), higher HDV RNA level (aHR = 1.14; 1.06–1.26), LSM ≥ 10 kPa (aHR = 2.20; 1.69–2.87) and baseline cirrhosis (aHR = 2.60; 2.02–3.35). In a separate categorical model, HDV RNA $\geq 3 \log_{10}$ IU/mL was associated with a 2.40-fold higher risk of composite LREs compared with HDV RNA $< 3 \log_{10}$ IU/mL. Using < 2 – $< 3 \log$ as reference, HDV RNA 3 – $< 4 \log_{10}$, HDV RNA 4 – $< 5 \log_{10}$ and $\geq 5 \log_{10}$ IU/mL showed significantly increased risk of LREs (aHR 1.46, $p = 0.007$, aHR = 2.09, $p = 0.002$ and aHR 1.61, $p = 0.01$, respectively).

Association of summary HDV RNA measures with risk of composite outcome

Overall, 1,615 patients (66.0%) had ≥ 2 measurements ≥ 6 months (median 3 measurements per patient). Consistent with the primary analysis, the risk of cirrhosis, HCC, and composite LREs increased from $3 \log_{10}$ IU/mL when using time-weighted mean HDV RNA level, with a consistent inflection point around this level across all three outcomes on restricted cubic spline analysis, though the shape of the association above this level again differed; a more gradual, continued rise for cirrhosis versus a peak around 4 – $5 \log_{10}$ IU/mL followed by a modest decline for HCC and composite LREs. (Fig. 2A-F)

Dynamic analysis of HDV RNA trajectory

During a median of 4.2 years (IQR 2.1–8.5) between first and last HDV RNA measurements, HDV RNA remained stable (< 1 log change) in 69.6% of patients, increased ≥ 1 log in 12.2%, declined ≥ 1 log in 12.6%, and became undetectable in 5.6%. (Table S3) Patterns were broadly similar across subgroups by baseline cirrhosis, HBeAg status, and sex.

The cumulative incidence of composite LREs by HDV RNA trajectory was comparable during the first 5 years of follow-up ($p = 0.49$), thereafter patients with undetectable HDV RNA showed lower cumulative rates than the other trajectory groups. (Fig. 3) Compared to patients with declining HDV RNA levels (≥ 1 log decline), patients with undetectable HDV RNA showed significant lower risk of composite events (HR = 0.31; 0.07–0.83), whereas those with increasing HDV RNA showed a trend of increased risk (HR = 1.33; 0.85–2.37).

Validation of HDV RNA level to predict liver disease progression

Although a consistent positive association was demonstrated between HDV RNA levels and the risk of composite LREs, the predictive accuracy of HDV RNA as a standalone parameter was suboptimal and declined further at prolonged time horizons as demonstrated by time-dependent area-under the curve (AUROC): 61.2% at 3-years using an optimal baseline cutoff of 5.24 $\log_{10}$ IU/mL (sensitivity 59.6%, specificity 50.2%, PPV 13.7%, NPV 90.3%), 57.8% at 5-years using a cutoff of 4.03 $\log_{10}$ IU/mL (sensitivity 85.4%, specificity 25.4%, PPV 13.2%, NPV 92.9%), and only 53.0% at 10-years using a cutoff of 3.39 $\log_{10}$ IU/mL (sensitivity 92.7%, specificity 17.4%, PPV 13.0%, NPV 94.7%). (Figure S3A) The progressively lower optimal cutoff and declining AUROC at longer time-horizons suggest that a single baseline HDV RNA measurement becomes less informative over time, consistent with the added value of longitudinal monitoring described above.

The addition of age, ALT, GGT, platelets count, and cirrhosis to HDV RNA summary measures significantly improved prediction of liver outcomes, yielding AUROC ≥ 0.83 at all-time horizons. (Figure S3B)

Sensitivity analysis

The *competing risk analysis of composite liver-related events* showed consistent results with the primary analysis. (Figure S4)

Discussion

In ~ 2500 treatment-naïve patients with chronic hepatitis D, HDV RNA $> 1,000$ IU/mL was associated with a more than two-fold increased-risk of liver-related events, with a threshold rather than a linear dose-response effect. The risk of liver-events rose when HDV RNA exceeded ~ 1,000 IU/mL, with little additional increase in the risk at higher levels. Older age, HBeAg positivity, elevated GGT, and cirrhosis were independent determinants of worse outcomes. Although 93% of those who developed a major liver

outcome had HDV RNA level above 1,000 IU/mL, HDV RNA level alone showed a limited prognostic accuracy and combining it with other clinical markers substantially improved risk discrimination.

These findings extend on previous literature, which has largely characterized HDV RNA detectability as a binary predictor of disease progression without addressing whether viral load level, shape, or trajectory carries additional prognostic information [1, 10–12]. Earlier studies have been limited by small sample size and heterogeneous, often treatment-experienced populations. By leveraging a large cohort from a highly-endemic country, we were able to characterize the shape of the HDV RNA–disease progression relationship more precisely.

In our study, patients with HDV RNA < 100 and < 1000 IU/mL showed a lower incidence of cirrhosis than HDV RNA+ patients in several European studies, but still higher than that reported for patients with undetectable or resolved HDV RNA [1, 13, 14]. Notably, 70% of patients with cirrhosis remained free of liver-related events during follow-up; challenging the severe course often ascribed to cirrhotic CHD. For instance, compared with the multicenter D-SOLVE, and DELTAVIR studies [7, 10], our cohort was younger, had fewer HCV/HIV co-infections, fewer baseline cirrhosis, but higher HBeAg + and HDV RNA levels. The more advanced fibrosis and lower viremia typical of non-endemic cohorts likely reflect their tertiary-care, treatment-experienced populations [7]. Despite these compositional differences, all cohorts agreed on the deleterious impact of persistent HDV RNA viremia on disease progression [1, 10–12].

Restricted cubic spline analyses of both baseline and time-weighted mean HDV RNA levels showed a consistent inflection point around 3 log₁₀ IU/mL (1,000 IU/mL) across liver-events, with the hazard ratio crossing one relative to lower reference. Above this threshold, however, the shape of the association differed by outcome: the risk of cirrhosis rose progressively with HDV RNA level up to approximately 5 log₁₀ IU/mL; a graded, dose-dependent pattern also reflected in the ordinal categorical model; whereas HCC and composite LREs risk peaked around 4–5 log₁₀ IU/mL and declined modestly at higher levels. Our findings agree with emerging data suggesting that a pragmatic threshold of HDV RNA < 1,000 IU/mL is linked to better liver outcomes, particularly in non-cirrhotic CHD [7], a threshold which was also associated with a higher likelihood of spontaneous HDV RNA resolution [15]. Our findings contrast, however, reports of an attenuated HDV RNA effect after cirrhosis develops, possibly reflecting the small number of low-replication patients in those studies [4, 6].

Only 13.6% of patients had HDV RNA < 1,000 IU/mL at diagnosis, indicating that most patients with CHD remain at increased risk of liver-related complications, including HCC, and will likely need antiviral therapy at some point. Despite the recognized role of HDV viremia, HDV RNA level alone showed limited and time-dependent prognostic accuracy for liver-related outcomes, with discrimination worsening at longer time-horizons — from an AUROC of 61.2% at 3-years to 53.0%, approaching chance, at 10-years. Adding age, ALT, GGT, platelet count, and cirrhosis to HDV RNA substantially improved discrimination, yielding AUROC ≥ 0.83 at all-time horizons. In the multivariable Cox model, additional independent predictors of composite LREs included smoking, albumin < 35 g/L, and HBeAg positivity, while ALT

approached but did not reach conventional significance ($p = 0.06$). These factors should be considered into risk stratification models and patient counselling.

Longitudinal HDV RNA data remain scarce in the literature, yet dynamic changes may carry prognostic information beyond a single baseline measurement. Among the 1,615 patients with ≥ 2 HDV RNA measurements at least 6 months apart, HDV RNA remained stable (< 1 log change) in 69.6%, increased ≥ 1 log in 12.2%, declined ≥ 1 log in 12.6%, and became undetectable in 5.6% by the end of follow-up. The cumulative incidence of composite LREs by HDV RNA trajectory was comparable during the first 5 years but diverged thereafter, with undetectable HDV RNA associated with consistently lower cumulative rates. These findings, together with the progressively declining accuracy of a single baseline HDV RNA measurement noted above, suggest that repeated testing – particularly to confirm viral suppression or resolution – could better capture the ongoing, fluctuating risk of CHD than a one-time baseline value.

Two phenotypes emerged from our data. Patients with HBeAg positivity had higher HDV RNA, HBV DNA, and HBsAg levels than HBeAg-negative patients, consistent with prior observations [16], this high-replication phenotype could be prioritized for anti-CHD therapy. Conversely, the combination of low HDV RNA, low HBsAg, and HBeAg-negative status identified non-cirrhotic patients at negligible risk of disease progression over a 5-year horizon, a group in whom watchful monitoring rather than immediate treatment intensification may be reasonable.

Our study has limitations. The retrospective design, and the lack of histological fibrosis staging could introduce ascertainment bias, however we adopted biopsy-proven cutoffs for liver stiffness and platelets count with high sensitivity for cirrhosis [17]. Other limitations include the non-standardized timing of virological testing, and possible immortal time bias for those with repeated tests. We accounted for these limitations by time-weighted analyses with consistent findings. We acknowledge that robust data on comorbidities, therapies and behavioral factors were lacking. HDV RNA quantitative assays showed intraassay variability (> 1 log), and absolute HDV RNA values might not be directly interchangeable across studies [18, 19]. The present study involved a single ethnic group, mostly attributed to HDV genotype 1 and HBV genotype D to the contrast of more prevalent HBV genotypes B and C in Asia [2]. Although current management of CHD is similar for all genotypes, evidence is lacking to mandate HDV genotyping outside clinical trials, which might not be possible also in low-viremic patients. Nevertheless, our findings warrant validation in other populations and genotypes.

In conclusion, HDV RNA levels showed a threshold, not a dose-response, association with liver disease progression in this large treatment-naïve cohort, with limited prognostic accuracy when used alone. A multi-marker approach incorporating age, ALT, GGT, HBeAg, platelet count, and cirrhosis diagnosis, together with longitudinal HDV RNA trajectory, may improve risk stratification and potentially guide monitoring and treatment decisions.

Statements and Declarations

Funding: The study was funded by ALF grant from Region Stockholm, Sweden to the principal investigator Soo Aleman.

Competing Interests: HK has no conflict of interest. SA has received honoraria for lectures/educational events from Gilead, has participated in advisory board for Gilead and Ribocure, and reports grants from Gilead. ED received research grants from Gilead and honoraria for lectures from Gilead and IPSEN, has participated in advisory board for Gilead, Mirum and Roche,

Authors Contribution:

Habiba Kamal, Soo Aleman, Naranjargal B Dashdorj contributed to the study conception and design. Material preparation, data collection were performed by Ganbolor Jargalsaikhan and Sanjaasuren Enkhtaivan. Data analysis was performed by Habiba Kamal. The first draft of the manuscript was written by Habiba Kamal and Soo Aleman, all authors read and approved the final manuscript.

References

1. Kamal H, Westman G, Falconer K, Duberg A, Weiland O, Haverinen S, et al. Long-term study of hepatitis D infection at secondary care centers: the impact of viremia on liver-related outcomes. *Hepatology*. 2020;:hep.31214.
2. Stockdale AJ, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, et al. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. *J Hepatol*. 2020;0.
3. Association for the Study of the Liver E, Rossana Brunetto M, Ricco G, Negro F, Wedemeyer H, Yurdaydin C, et al. EASL Clinical Practice Guidelines on hepatitis delta virus. *J Hepatol*. 2023;0.
4. Palom A, Degasperi E, Coco B, Loglio A, Ciano A, Niro GA, et al. Baseline HDV-RNA Levels Could Stratify Clinical Risk Before, But Not After, Cirrhosis in Chronic Hepatitis D: A Multicentre European Study. *Aliment Pharmacol Ther*. 2026.
5. Mangia A, Squillante MM, Fraticelli F, Cavorsi MC, Paroni G, Zaffarano L, et al. HDV RNA Levels and Progression of Hepatitis Delta Infection: A 14 Year Follow Up Experience in Italy. *Cells*. 2023;12:1413.
6. Romeo R, Foglieni B, Casazza G, Spreafico M, Colombo M, Prati D. High serum levels of HDV RNA are predictors of cirrhosis and liver cancer in patients with chronic hepatitis delta. *PLoS One*. 2014;9:e92062.
7. Kamal H, Degasperi E, Radu M, Sambarino D, Wranke A, Carey I, et al. Course and clinical outcomes of chronic hepatitis delta: a longitudinal analysis of 565 patients from the D-SOLVE and HDV-1000 consortia. *Gut*. 2026.
8. Asselah T, Chulanov V, Lampertico P, Wedemeyer H, Streinu-Cercel A, Pântea V, et al. Bulevirtide Combined with Pegylated Interferon for Chronic Hepatitis D. *New England Journal of Medicine*. 2024.

9. Degasperi E, Anolli MP, Uceda Renteria SC, Sambarino D, Borghi M, Perbellini R, et al. Bulevirtide monotherapy for 48 weeks in patients with HDV-related compensated cirrhosis and clinically significant portal hypertension. *J Hepatol.* 2022;77:1525–31.
10. Roulot D, Brichler S, Layese R, BenAbdesselam Z, Zoulim F, Thibault V, et al. Origin, HDV genotype and persistent viremia determine outcome and treatment response in patients with chronic hepatitis delta. *J Hepatol.* 2020;73:1046–62.
11. Palom A, Rodriguez-Tajes S, Navascues CA, Garcia-Samaniego J, Riveiro-Barciela M, Lens S, et al. Long-term clinical outcomes in patients with chronic hepatitis delta: the role of persistent viraemia. *Aliment Pharmacol Ther.* 2020;51:158–66.
12. Wranke A, Lobato C, Ceausu E, Dalekos GN, Rizzetto M, Turcanu A, et al. Long-term outcome of hepatitis delta in different regions world-wide: Results of the Hepatitis Delta International Network. *Liver International.* 2024;44:2442–57.
13. Furquim d’Almeida A, Ho E, Govaerts L, Michielsen P, Sersté T, Bourgeois S, et al. Severe Liver-Related Outcomes in Patients With Hepatitis Delta: Results From a Multi-Ethnic Multicenter Long-Term Follow-Up Study. *J Viral Hepat.* 2025;32:1–15.
14. Bockmann JH, Grube M, Hamed V, von Felden J, Landahl J, Wehmeyer M, et al. High rates of cirrhosis and severe clinical events in patients with HBV/HDV co-infection: longitudinal analysis of a German cohort. *BMC Gastroenterol.* 2020;20:24.
15. Kamal H, Jargalsaikhan G, Enkhtaivan S, Lindahl K, Dashtseren B, Lkhagva-Ochir O, et al. Diabetes, male sex, low levels of HBsAg, HDV RNA and ALT predict spontaneous HDV suppression in chronic hepatitis D. *Hepatology.* 2026.
16. Heidrich B, C. Serrano B, Idilman R, Kabaçam G, Bremer B, Raupach R, et al. HBeAg-positive hepatitis delta: virological patterns and clinical long-term outcome. *Liver International.* 2012;32:1415–25.
17. Sandmann L, Degasperi E, Port K, Aleman S, Wallin JJ, Manuilov D, et al. Liver stiffness measurement as a noninvasive method for the diagnosis of liver cirrhosis in patients with chronic hepatitis D virus infection. *Aliment Pharmacol Ther.* 2024;00:1–10.
18. Anolli MP, Uceda Renteria S, Degasperi E, Facchetti F, Sambarino D, Borghi M, et al. Comparing methods for plasma HDV RNA quantification in bulevirtide-treated and untreated patients with HDV. *JHEP Reports.* 2025;7:101299.
19. Wedemeyer H, Leus M, Battersby TR, Glenn J, Gordien E, Kamili S, et al. HDV RNA assays: Performance characteristics, clinical utility, and challenges. *Hepatology.* 2023.

Tables

Tables 1 and 2 are available in the supplementary files section

Figures

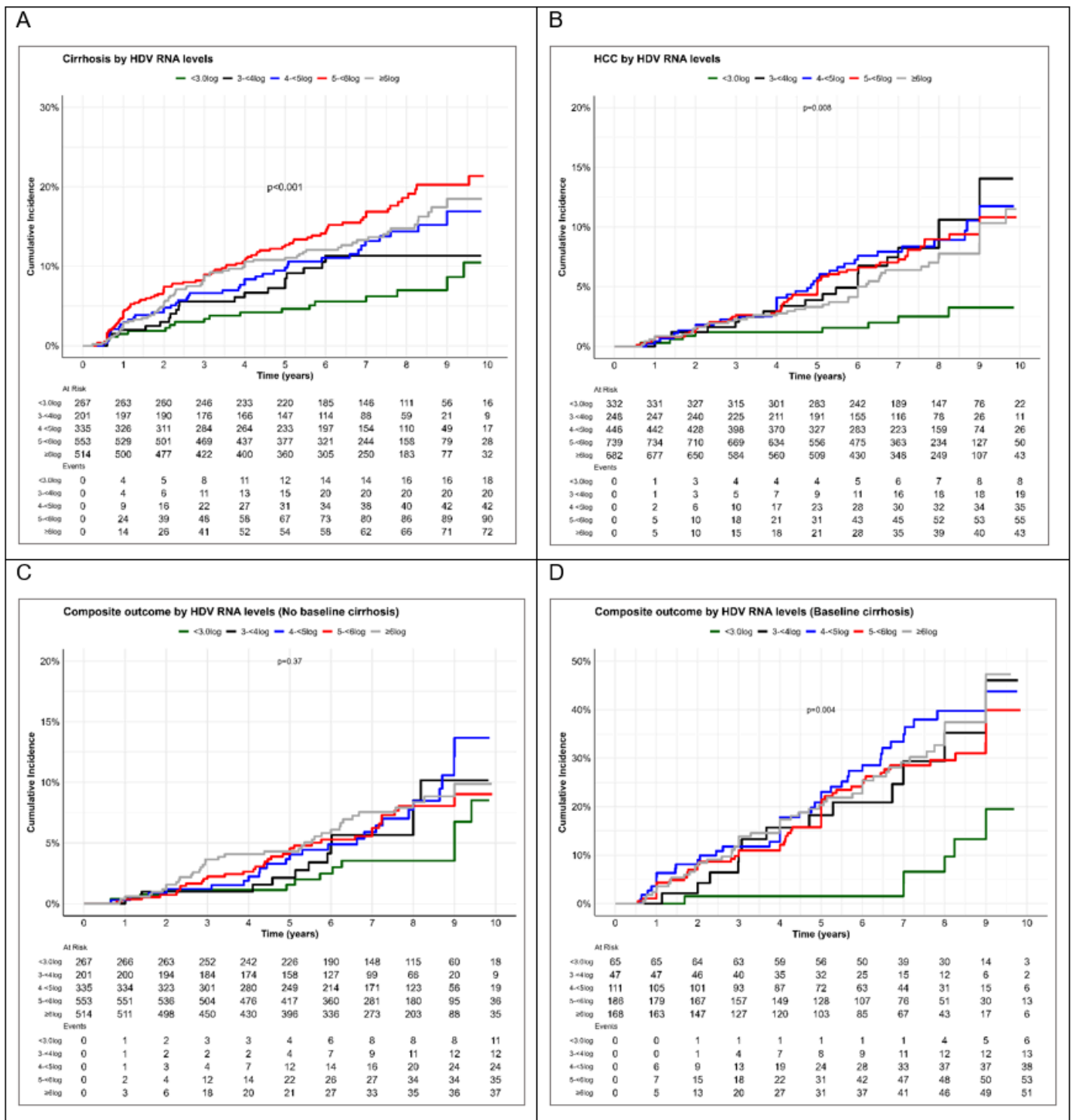


Figure 1

The cumulative incidence of cirrhosis, hepatocellular carcinoma and composite liver-related events by baseline cirrhosis subgrouped by HDV RNA levels. Significance was tested by log-rank test.

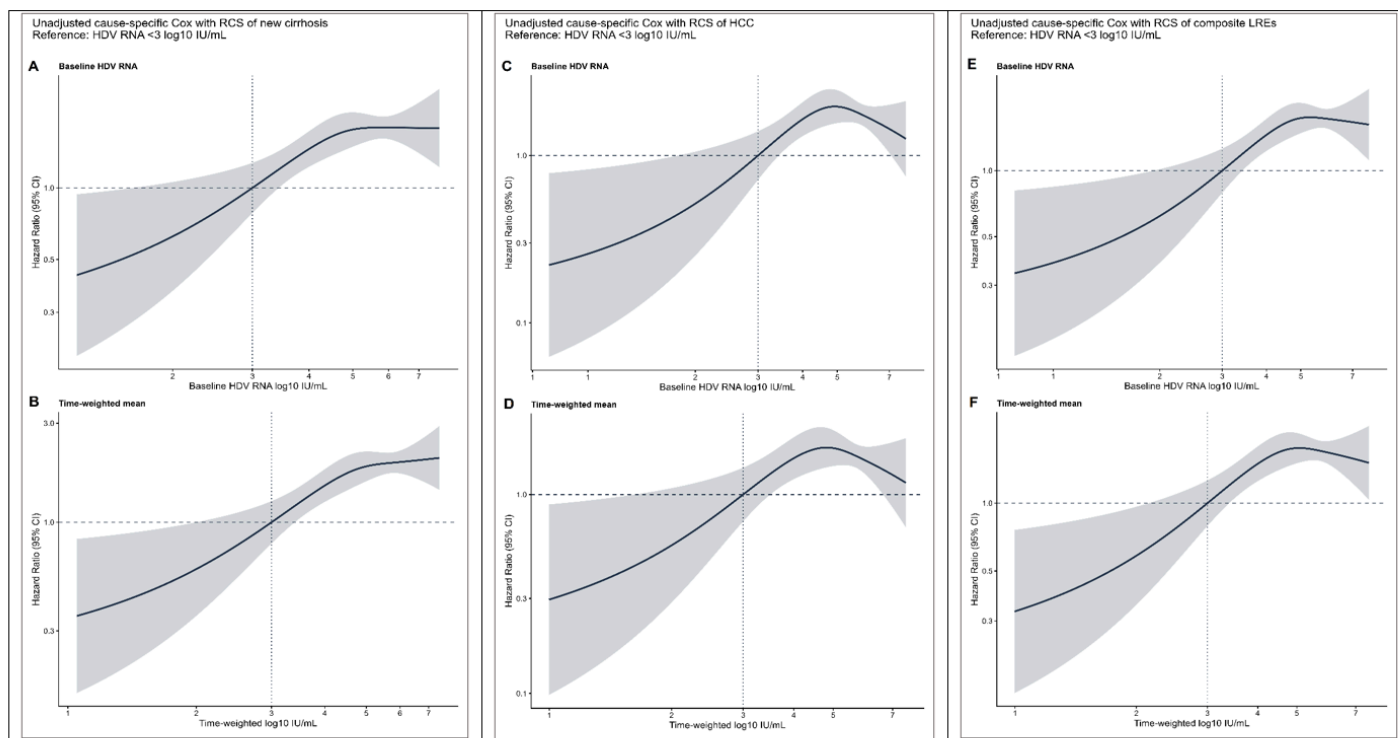


Figure 2

The association between HDV RNA summary measures during study period with the hazard to develop cirrhosis (A, B), hepatocellular carcinoma (C, D) and composite liver-related events (E, F).

Time weighted mean adjusted for duration between, and the number of visits. Analysis of only patients with ≥ 2 HDV RNA measurements spaced ≥ 6 months for a median of 4.6 (1.2-8.1) years. The total number of HDV RNA measurements 4,749 tests at median 3 measurements per patient. Abbreviations: HCC=hepatocellular carcinoma; LREs= liver-related events

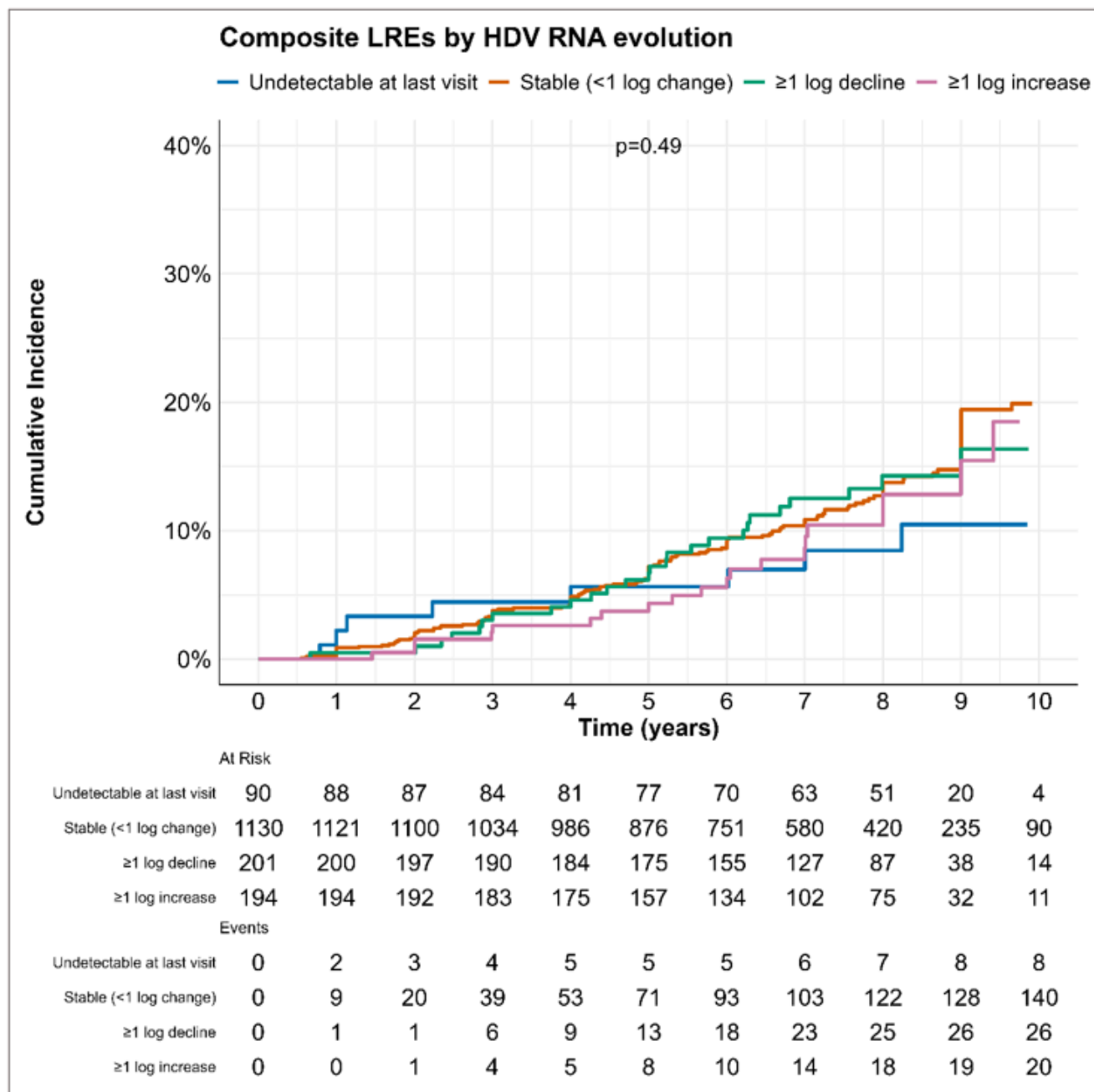


Figure 3

The cumulative incidence of composite liver-related events by HDV RNA evolution during a median follow-up time of 7.3 (0.6-12.7) years.

Supplementary Files

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- [naturalhistmong.supplementsHepInter260910.docx](#)