

Progression to cirrhosis in chronic hepatitis D with mild-to-moderate fibrosis: Insights from a multicenter European cohort

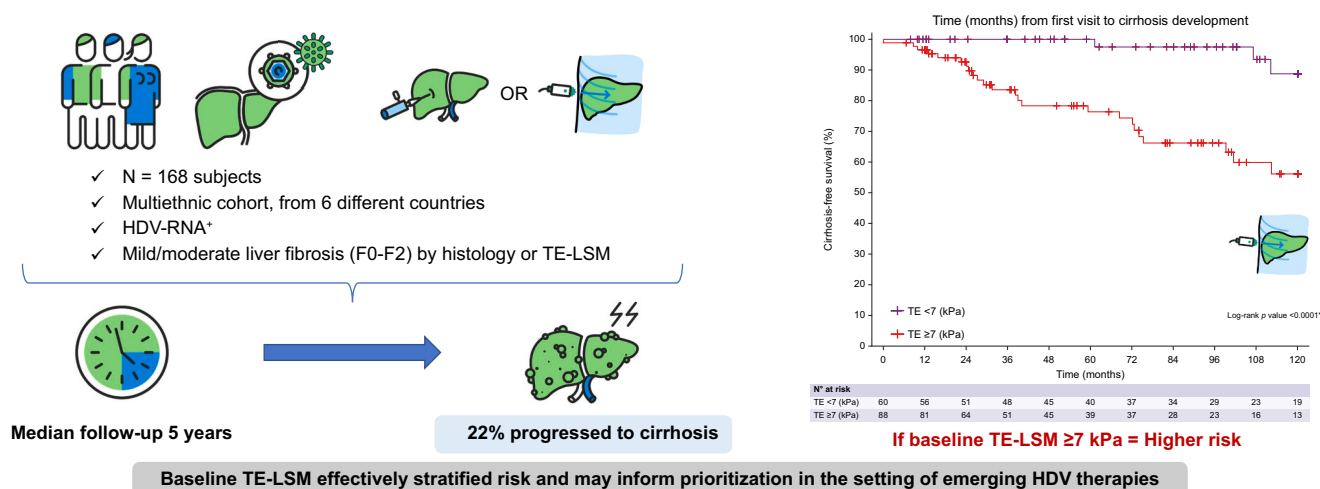
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Graphical abstract



Highlights:

- Over 20% of patients with HDV and mild-to-moderate fibrosis progressed to cirrhosis.
- Baseline liver stiffness was the strongest predictor of progression, with a LSM ≥ 7 kPa defining a high-risk group.
- FIB-4 proved to be a useful marker in the absence of LSM.
- ALT and HDV RNA levels (baseline/longitudinal) did not predict fibrosis progression.
- Early risk stratification based on LSM or FIB-4 can be used to guide treatment decisions.

Impact and implications:

Patients with HDV and mild-to-moderate fibrosis remain at substantial risk of progression, with more than 20% developing cirrhosis during a median follow-up of 5 years. Liver stiffness measured by transient elastography (TE-LSM) was the strongest predictor of progression. FIB-4 may have a prognostic value when TE-LSM is not available, whereas ALT levels and HDV-RNA, both at baseline and during follow-up, did not influence fibrosis outcomes. These findings support improved early risk stratification and may help clinicians identify which patients with apparently early-stage disease warrant closer monitoring or timely treatment intervention.

Progression to cirrhosis in chronic hepatitis D with mild-to-moderate fibrosis: Insights from a multicenter European cohort

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Background & Aims: Hepatitis delta virus (HDV) is the most aggressive form of chronic viral hepatitis. As new therapies emerge, a clearer understanding of its natural history – particularly in early disease stages – is needed. We assessed real-world outcomes of HDV-infected patients with mild-to-moderate fibrosis and identified predictors of progression to cirrhosis.

Methods: We performed a multicenter, international, retrospective study including adult patients with active HDV infection (HDV-RNA positive) and no advanced fibrosis at baseline, confirmed by histology or liver stiffness measurement (TE-LSM) within the first year of diagnosis. Demographic, clinical, biochemical, and virological variables were collected at baseline and annually thereafter. The primary outcome was development of cirrhosis; secondary outcomes included liver-related events and longitudinal changes in fibrosis markers.

Results: The cohort included 168 patients (median age 37.5 [31–45] years; 53% male; 56% Caucasian). Fewer than 15% had HIV/HCV coinfection or metabolic/alcohol-related risk factors. At baseline, 36% had ALT $\geq 2 \times$ the upper limit of normal and median TE-LSM was 7.6 (6–9) kPa. Over a median follow-up of 62 (40–94) months, 37 patients (22%) developed cirrhosis. Two developed ascites (one required liver transplantation), and one developed hepatocellular carcinoma and died. HDV clearance occurred in 32 patients (19%), either spontaneously ($n = 14$) or after antiviral therapy ($n = 18$). In the multivariate analysis, only TE-LSM ≥ 7 kPa independently predicted progression (HR 6.02 [1.76–20.6]; $p = 0.004$). FIB-4 ≥ 1.45 also identified higher-risk patients when TE-LSM was unavailable (HR 3.51 [1.68–7.34]; $p < 0.01$). Neither antiviral therapy nor changes on HDV RNA or ALT overtime remained as independent predictors.

Conclusions: Despite mild-to-moderate baseline fibrosis, over 20% of patients progressed to cirrhosis within 5 years. Baseline non-invasive markers effectively stratify risk and may inform prioritization of emerging HDV therapies.

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Introduction

Hepatitis delta virus (HDV) infection represents the most aggressive form of chronic viral hepatitis, resulting in the highest rates of progression to cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) among all hepatitis viruses.¹ HDV is a defective RNA virus that depends on the hepatitis B surface antigen for virion assembly, yet it is the main driver of the severe liver injury observed in coinfecting patients. Global estimates suggest that at least 12 million individuals are living with HDV, although true prevalence is likely underreported due to limited screening and diagnostic inconsistencies.^{2,3} Longitudinal data from international cohorts have revealed that up to 80% of patients with HDV develop

cirrhosis over time.⁴ Even more striking, a recent analysis of the SAVE-D cohort reported that up to one-third of patients develop liver-related events – including decompensation or HCC – within 10 years of diagnosis, confirming HDV's severe natural course despite suppression of HBV replication.⁵ Nonetheless, a subset of patients remains stable for prolonged periods, particularly those with mild liver injury or fibrosis at baseline, leading to uncertainty regarding prognosis and management.^{1,5} Until recently, treatment options were limited to pegylated interferon-alpha (PegIFN α), which provides sustained virological response in fewer than 25% of cases.⁶ The therapeutic landscape for chronic hepatitis delta (CHD) changed when the European Medicines Agency approved

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bulevirtide (BLV) for the treatment of patients with CHD and compensated liver disease.⁷ However, BLV treatment remains costly, access is restricted in some regions, and criteria for initiation often rely on the presence of advanced fibrosis or elevated alanine aminotransferase (ALT) levels – markers that do not fully predict disease progression. Besides BLV, other new drugs aimed at suppressing or curing CHD are in phase III trials.⁸ As current guidelines do not offer precise tools for identifying patients with early-stage HDV infection who are at the highest risk of liver disease progression, this has important implications for access to antiviral treatment, as many individuals with mild-to-moderate fibrosis are not prioritized for therapy or clinical trial inclusion despite a potentially unfavorable trajectory. Our study aimed to fill this gap by assessing the real-world clinical course of HDV-infected patients with mild-to-moderate fibrosis, with the objective of identifying baseline predictors of fibrosis progression. Using a large multinational cohort, we aimed to refine risk stratification in this understudied subgroup, thereby supporting timely treatment decisions and informing long-term monitoring strategies.

Patients and methods

We conducted a multicenter, international, retrospective cohort study involving adult patients (≥ 18 years old) with confirmed chronic HDV infection and no evidence of advanced fibrosis at baseline. Participants were recruited from 20 tertiary liver centers across six different countries in Europe. Eligible patients for entry into the study had detectable HDV-RNA, determined by commercial or in house HDV-RNA test assays, and either a liver biopsy showing fibrosis stage METAVIR F0–F2 or, when histological assessment was unavailable, a liver stiffness measurement by transient elastography (TE-LSM) < 10 kPa⁹ performed within 12 months prior to inclusion. Patients with advanced liver fibrosis or signs of cirrhosis at baseline – either histologically, by TE-LSM ≥ 10 kPa, or by clinical or endoscopic signs of portal hypertension or past liver decompensation – were excluded. Individuals with prior HCC, liver transplantation, or undetectable HDV-RNA were also excluded. Data were collected retrospectively from medical records and included demographic characteristics, comorbidities (diabetes, hypertension, obesity), excessive alcohol use, coinfection with HIV and/or HCV, laboratory parameters (ALT, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase [GGT], albumin, platelets, international normalized ratio, total bilirubin), and serological and virological markers (hepatitis B surface antigen, hepatitis B e antigen, HBV-DNA, HDV-RNA). Treatment with PegIFN α and/or bulevirtide was also recorded.

Liver stiffness values and non-invasive fibrosis scores (Fibrosis-4 [FIB-4], aspartate aminotransferase-to-platelet ratio index [APRI], Delta-4 fibrosis score [D4FS]) were collected or calculated at baseline and at annual follow-up time points. Liver stiffness measurements were performed using the FibroScan® (Echosens SA) with the M or XL probe as appropriate and always in accordance with the manufacturer's instructions. Examinations were carried out under standard fasting conditions by experienced operators, applying the recommended quality criteria: at least 10 validated readings, an overall success rate $\geq 60\%$, and an interquartile range $< 30\%$ of the median value. LSM devices at all participating sites were inspected and calibrated according to the manufacturer's

recommendations, and examinations not meeting these criteria were excluded. Annual TE-LSM increase ≥ 2 kPa or annual HDV-RNA drop > 1 log were defined as the difference between consecutive yearly measurements.

The primary endpoint was progression to cirrhosis, defined with ultrasound (nodular liver surface, coarse hepatic echotexture, or blunt hepatic edges), evidence of portal hypertension (spleen > 12 cm, portal vein dilation, or presence of portosystemic collaterals), or TE-LSM ≥ 12.5 kPa, as previously reported.⁹ No individual parameter was used as a standalone criterion for the diagnosis of cirrhosis. Instead, each case was reviewed by the index center and interpreted in the context of the overall clinical picture, including laboratory and imaging findings.

Secondary endpoints included the occurrence of liver-related events (hepatic decompensation, HCC, and liver transplantation), changes in non-invasive fibrosis markers (NITs) over time, and the impact of sustained HDV-RNA clearance (> 12 months) on clinical outcomes.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Hospital Clinic (2023-0500). Written informed consent was not collected due to the retrospective nature of the study.

Statistical analysis

Continuous variables were expressed as median and IQR, while categorical variables were reported as absolute numbers and percentages. Group comparisons were performed using Fisher's exact test for categorical variables and Student's *t* test or Mann–Whitney *U* test for continuous variables, as appropriate. Univariate and multivariate Cox regression analyses were performed to identify baseline and follow-up factors associated with the development of cirrhosis. To assess the impact of longitudinal changes in covariates on study outcomes, we applied time-varying Cox univariate and multivariate models. Missing data were handled using a variable exclusion approach without imputation. Multivariable Cox models included variables with $p < 0.05$ in univariate analysis and/or variables considered clinically relevant, while avoiding collinearity. In time-dependent models, covariates were updated at each visit (~ 1 -year intervals) and annual changes were calculated from differences between consecutive measurements until the last visit before the event (e.g. cirrhosis) or the last follow-up in patients without events. From these differences, dichotomous variables were created using the pre-defined cut-offs and were included in the univariate model.

Kaplan–Meier curves and Log-rank tests were used to assess the development of cirrhosis and liver-related events across the different categories of patients. Repeated measures were used to capture longitudinal changes in key variables over the study period. A p value < 0.05 was considered statistically significant. All analyses were performed using SAS, version 9.4.

Results

Baseline characteristics

A total of 168 patients with viremic HDV infection and baseline evidence of mild-to-moderate fibrosis were included in the analysis (see flowchart in Fig. S1).

The median age was 37.5 years [IQR 31–45.5], and 53% were male. The cohort was ethnically diverse: 56% were Caucasian, 21% Asian and 18.5% Sub-Saharan. A minority (<15%) of patients were co-infected with HIV or HCV or had other risk factors associated with liver disease progression such as metabolic factors (type 2 diabetes, obesity) or excessive alcohol use (Table 1).

At baseline assessment, the median ALT was 67 IU/L (IQR 42–112), with 36% of patients displaying ALT ≥ 2 x the upper limit of normal (ULN). Median platelet count was 192 (IQR 151–233) $\times 10^9/L$ and median albumin was 4.1 (IQR 3.9–4.3) g/dl; 14% of patients were hepatitis B e antigen positive, and

21% had HBV-DNA $\geq 2,000$ IU/ml (40% were virally suppressed under nucleos(t)ide analogue therapy). Median HDV-RNA level was 5.8 (IQR 4.2–7.1) $\log_{10}$ IU/ml. Liver fibrosis was primarily assessed by histology in 72 patients (42.8%) with available data; in the absence of histology, fibrosis staging was based on TE-LSM. In the whole cohort, TE-LSM was available in 148 patients (88%) and the median value was 7.6 kPa (IQR 5.9–9.3). Regarding other non-invasive markers of fibrosis, most had FIB-4 <1.45 (59%), and 27% had APRI <0.5. D4FS was low (0.16; IQR 0.10–0.26), with no patient exceeding the previously defined cut-off for cirrhosis.¹⁰

Table 1. Baseline characteristics of patients included in the analysis and according to the development of cirrhosis during follow-up.

Variables	Total (N = 168)	No cirrhosis at follow-up (n = 131)	Cirrhosis at follow-up (n = 37)	p value
Sex				0.264
Female	80 (47.6)	59 (45.0)	21 (56.8)	
Male	88 (52.4)	72 (55.0)	16 (43.2)	
Age (years)	37.5 (31–45.5)	38 (30–45)	37 (35–46)	0.289
Ethnicity				0.027
Caucasian	94 (56.0)	68 (51.9)	26 (70.3)	
Asian	35 (20.8)	25 (19.1)	10 (27)	
Latin	4 (2.4)	4 (3.1)	0	
Sub-Saharan African	31 (18.5)	30 (22.9)	1 (2.7)	
Other	4 (2.4)	4 (3.1)	0	
Caucasian vs. others	94 (56.0)	68 (51.9)	26 (70.3)	0.060
BMI (n = 113)	24.7 (22.3–26.8)	24.7 (22.9–26.5)	24.8 (21.6–28.4)	0.890
HIV coinfection	7 (4.6)	6 (5.2)	1 (2.7)	1.000
HCV coinfection	17 (11.0)	15 (12.7)	2 (5.4)	0.363
Diabetes mellitus	6 (4.5)	4 (4.0)	2 (5.4)	0.636
Arterial hypertension	11 (8.2)	10 (9.9)	1 (2.7)	0.292
Excessive alcohol use	18 (10.7)	15 (11.4)	3 (8.1)	0.826
Follow-up, years	6.44 (2.35–9.82)	5.21 (2.9–9.09)	8.15 (4.27–10.91)	0.010
Fibrosis staging and blood tests				
Liver biopsy: Yes	72 (42.9)	56 (42.7)	16 (43.2)	0.357
Staging (METAVIR):				
F0-1	38 (52.8)	32 (57.1)	6 (37.5)	0.256
F2	34 (47.2)	24 (42.9)	10 (62.5)	
TE-LSM value (kPa) (n = 148)	7.6 (5.9–9.3)	7.2 (5.8–8.7)	9.0 (7.4–10.1)	0.004
TE-LSM <7 kPa	60 (40.5)	54 (47.0)	6 (18.2)	0.003
TE-LSM ≥ 7 kPa	88 (59.5)	61 (46.6)	27 (72.9)	
FIB-4 score (n = 154)	1.35 (0.90–1.86)	1.27 (0.87–1.85)	1.52 (1.05–1.94)	0.082
FIB-4 <1.45	91 (59.1)	74 (62.2)	17 (48.6)	0.133
FIB-4 1.45–3.25	58 (37.7)	42 (35.3)	16 (45.7)	
FIB-4 ≥ 3.25	5 (3.2)	3 (2.5)	2 (5.7)	
APRI score (n = 154)	0.68 (0.47–0.99)	0.68 (0.45–1.04)	0.67 (0.54–0.85)	0.653
APRI <0.5	42 (27.3)	35 (29.4)	7 (20)	0.456
APRI 0.5–1.5	89 (57.8)	66 (55.5)	23 (65.7)	
APRI ≥ 1.5	23 (14.9)	18 (15.1)	5 (14.3)	
D4FS (n = 126)	0.16 (0.10–0.26)	0.15 (0.08–0.22)	0.31 (0.15–0.31)	0.001
AST (IU/L)	50.0 (36–70)	49.5 (35–75)	50.9 (39–58)	0.890
ALT (IU/L)	67 (42–112)	69.7 (42.1–116)	55.2 (41–82)	0.312
ALT ≥ 2 xULN	59 (36.0)	50 (39.1)	9 (24.3)	0.444
ALP (IU/L)	76 (60–93)	72 (59–91)	83 (66–97)	0.085
GGT (IU/L)	33 (23–59)	32 (22–54)	35 (29–64)	0.231
Total bilirubin (mg/dl)	0.59 (0.41–0.86)	0.59 (0.41–0.82)	0.56 (0.40–0.87)	0.991
Albumin (g/dl)	4.1 (3.9–4.3)	4.2 (3.9–4.35)	4.0 (3.8–4.3)	0.169
Platelets ($\times 10^9/L$)	192 (151–233)	197.5 (154–236)	180 (135–214)	0.057
INR	1.08 (1.00–1.10)	1.07 (1.00–1.10)	1.10 (1.00–1.10)	0.655
Viral markers				
HBeAg positive (n = 139)	19 (13.7)	17 (15.8)	2 (6.9)	0.233
qHBsAg (IU/ml) (n = 62)	10,854 (4,092–17,398)	10,125 (2,947–15,795)	15,838 (7,861–25,831)	0.025
HBV-DNA $\geq 2,000$ IU/ml	25 (20.7)	21 (22.8)	4 (13.8)	0.295
HDV-RNA ($\log_{10}$) (n = 113)	5.8 (4.2–7.1)	5.9 (4.2–7.1)	5.3 (3.9–6.8)	0.370

p values <0.05 are in bold. Qualitative variables are expressed as n (%) and quantitative variables as median (IQR). p values reflect Fisher's exact test (qualitative), Mann-Whitney U or Student's t test (quantitative) when appropriate. ALP, alkaline phosphatase; D4FS, Delta-4 fibrosis score; INR, international normalized ratio; qHBsAg, quantitative hepatitis B surface antigen levels; TE-LSM, transient elastography–liver stiffness measurement.

Concordance between liver fibrosis assessment tools at baseline

In our cohort of HDV-infected patients with no advanced fibrosis undergoing either TE-LSM or liver biopsy, a comparative analysis of NITs revealed several key insights (Table 2). Patients with TE-LSM ≥ 7 kPa had significantly higher fibrosis stage (F2) on liver biopsy compared to those with TE-LSM < 7 kPa (58.5% vs. 22.7%, $p = 0.008$), indicating an association between higher TE-LSM and histological fibrosis. Additionally, lower FIB-4 and APRI scores were more common in patients with TE-LSM < 7 kPa although their performance was low as many patients fell within the intermediate category. When stratifying patients by histological fibrosis, those with higher METAVIR stage (F2) were significantly more likely to have LSM ≥ 7 kPa than < 7 kPa (82.8% vs. 17.2%, $p = 0.008$). In contrast, patients with METAVIR F0–F1 on liver histology showed greater variability, with 50% falling below and 50% above the 7 kPa LSM threshold. ALT levels did not significantly differ between TE-LSM or METAVIR stage groups, suggesting limited utility of ALT as a standalone marker in this context.

We paid particular attention to the five patients who exhibited a marked discrepancy between histological findings and TE-LSM: all had METAVIR stage F0–1 but TE-LSM values ranging from 10 to 15 kPa, measured within 1 year of liver biopsy. At baseline, four out of the five patients had FIB-4 scores below 1.45, and three had APRI scores under 0.5, suggesting an absence of advanced fibrosis. HDV-RNA levels were high ($> 6 \log_{10}$ IU/ml) in all but one patient ($3 \log_{10}$ IU/ml). Despite the elevated viral loads, ALT levels remained below $2 \times$ ULN in all cases except one (ALT = 101 IU/L). Therefore, neither active hepatic inflammation (as reflected by ALT) nor biochemical markers of cholestasis (data not shown) could account for the discordance between histological staging and TE-LSM values. This is in line with previous findings suggesting that some patients may have discordant results between histology and NITs.¹¹

Incidence of cirrhosis and associated factors

During a median follow-up of 62 months (IQR 40–94), 37 patients (22%) progressed to cirrhosis. Although follow-up duration was longer in patients who developed cirrhosis, progression occurred progressively over time, as illustrated by Kaplan–Meier estimates (Fig. 1), suggesting that the observed differences were not solely driven by longer follow-up. The cumulative incidence of cirrhosis at 3, 5 and 10 years of follow-up was 9.2%, 12.6% and 30.7%, respectively (Fig. 1). Of these, two patients developed ascites (one of them needing liver transplantation) and another patient was diagnosed with HCC and died during follow-up.

The incidence rate of cirrhosis was notably higher among patients with higher baseline TE-LSM, specifically among those with TE-LSM ≥ 7 kPa compared to those < 7 kPa (30% vs. 10%, $p < 0.01$) (Table 1). Fig. 2A shows the Kaplan–Meier curve for cirrhosis development stratified by a TE-LSM cut-off of 7 kPa ($p < 0.001$). The cumulative incidence of cirrhosis at 3, 5 and 10 years was very low among patients with TE-LSM < 7 kPa (0%, 0% and 6.5%; respectively) but increased to 14.8%, 21.7% and 43.8% if the initial TE-LSM was ≥ 7 kPa. On the other hand, progression to cirrhosis was not statistically different when stratifying patients according to histologic liver fibrosis assessment (Fig. 2B).

Patients with baseline FIB-4 > 1.45 progressed to cirrhosis more frequently than those with baseline FIB-4 < 1.45 (28.6% vs. 18.6%, $p = 0.005$) while the discriminative ability of the APRI score was lower (Table 1). Additionally, patients who did not progress to cirrhosis had significantly lower baseline D4FS values ($p < 0.01$) than those who did, but the previously defined cut-off was not useful as no patient had values ≥ 7.8 .¹⁰ Patients progressing to cirrhosis also had a trend towards lower baseline platelet counts but baseline ALT, albumin and HDV-RNA levels did not differ significantly between patients with or without cirrhosis progression (Table 1).

In univariate Cox regression analysis (Table 3), when censoring patients at the time of fulfilling criteria for cirrhosis or

Table 2. Comparative analysis of ALT levels and fibrosis staging categories (METAVIR, APRI, FIB-4, TE-LSM) according to baseline TE-LSM (< 7 vs. ≥ 7 kPa) and histology (METAVIR 0–1 vs. ≥ 2) at baseline.

Variables (at baseline)	TE-LSM < 7 kPa (n = 60)	TE-LSM ≥ 7 kPa (n = 88)	p value	METAVIR 0–1 (n = 38)	METAVIR 2 (n = 34)	p value
Liver biopsy	22 (36.6)	41 (46.5)	0.242			
Staging METAVIR			0.008			
F0–1	17 (77.3)	17 (41.5)				
F2	5 (22.7)	24 (58.5)				
ALT categories			0.086			
<ULN	19 (31.6)	11 (12.5)		7 (18.4)	5 (13.5)	
1–2xULN	22 (36.6)	44 (50.0)		16 (42.1)	15 (45.9)	0.718
≥ 2 xULN	19 (31.6)	33 (37.5)		15 (38.9)	14 (40.5)	
FIB-4	n = 53	n = 86	0.035	n = 35	n = 32	
<1.45	38 (71.7)	47 (54.7)		20 (57.1)	18 (56.3)	
1.45–3.25	15 (28.3)	35 (40.7)		12 (34.3)	13 (40.6)	0.909
≥ 3.25	0 (0.0)	4 (4.7)		3 (8.6)	1 (3.1)	
APRI	n = 53	n = 86	0.009	n = 35	n = 32	
<0.5	22 (41.5)	17 (19.8)		10 (28.6)	7 (21.9)	
0.5–1.5	26 (49.1)	55 (64.0)		19 (54.3)	20 (62.5)	0.729
≥ 1.5	5 (9.4)	14 (16.3)		6 (17.1)	5 (15.6)	
TE-LSM				n = 34	n = 29	
<7 kPa				17 (50)	5 (17.2)	0.008
≥ 7 kPa				17 (50)	24 (82.8)	

p values < 0.05 are in bold. Qualitative variables are expressed as n (%). p values reflect Fisher's exact test (qualitative). ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, Fibrosis-4 score; TE-LSM, transient elastography-derived liver stiffness measurement; ULN, upper limit of normal.

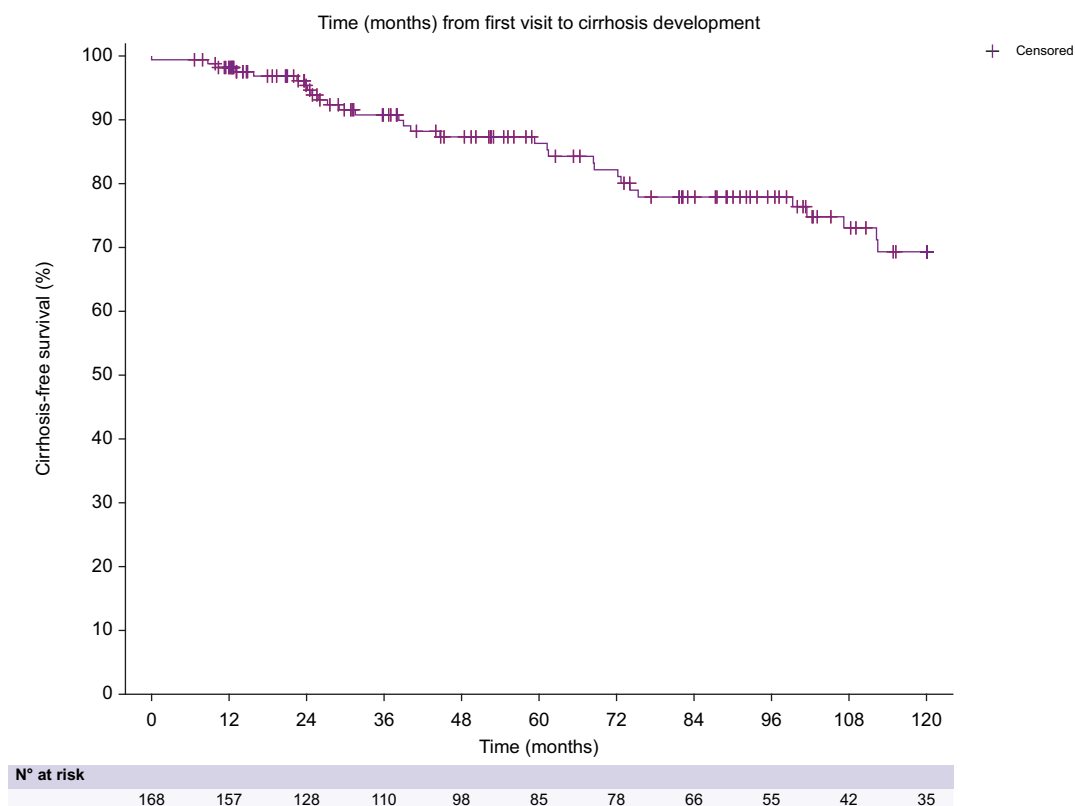


Fig. 1. Cirrhosis-free survival in patients with chronic HDV and baseline mild-to-moderate fibrosis (Kaplan-Meier analysis).

last follow-up, the following baseline variables were associated with a higher risk of cirrhosis development over time: TE-LSM ≥ 7 kPa (HR 7.7; 95% CI 2.3-25.6; $p < 0.001$), FIB-4 ≥ 1.45 (HR 2.82; 95% CI 1.36-5.84; $p < 0.01$), higher D4FS (HR 1.83; 95% CI 1.03-3.22; $p = 0.037$), antiviral treatment (HR 3.07; 95% CI 1.31-7.20; $p = 0.01$), and platelet count $< 200 \times 10^9/L$ (HR 0.41; 95% CI 0.19-0.89; $p = 0.026$). In contrast, baseline APRI, ALT, albumin or HDV-RNA level (influenced or not by previous antiviral treatment), sex, age, and ethnicity, were not associated with cirrhosis progression.

In multivariate analysis, only baseline TE-LSM ≥ 7 kPa remained independently associated with progression to cirrhosis (HR 6.02; 95% CI 1.76-20.56; $p = 0.004$), supporting the superior prognostic value of TE-LSM compared to other NITs for early identification of at-risk individuals. However, when TE-LSM is not available, FIB-4 ≥ 1.45 also identified patients at higher risk of cirrhosis progression (HR 3.51; 95% CI 1.68-7.34; $p < 0.01$) (Table S2).

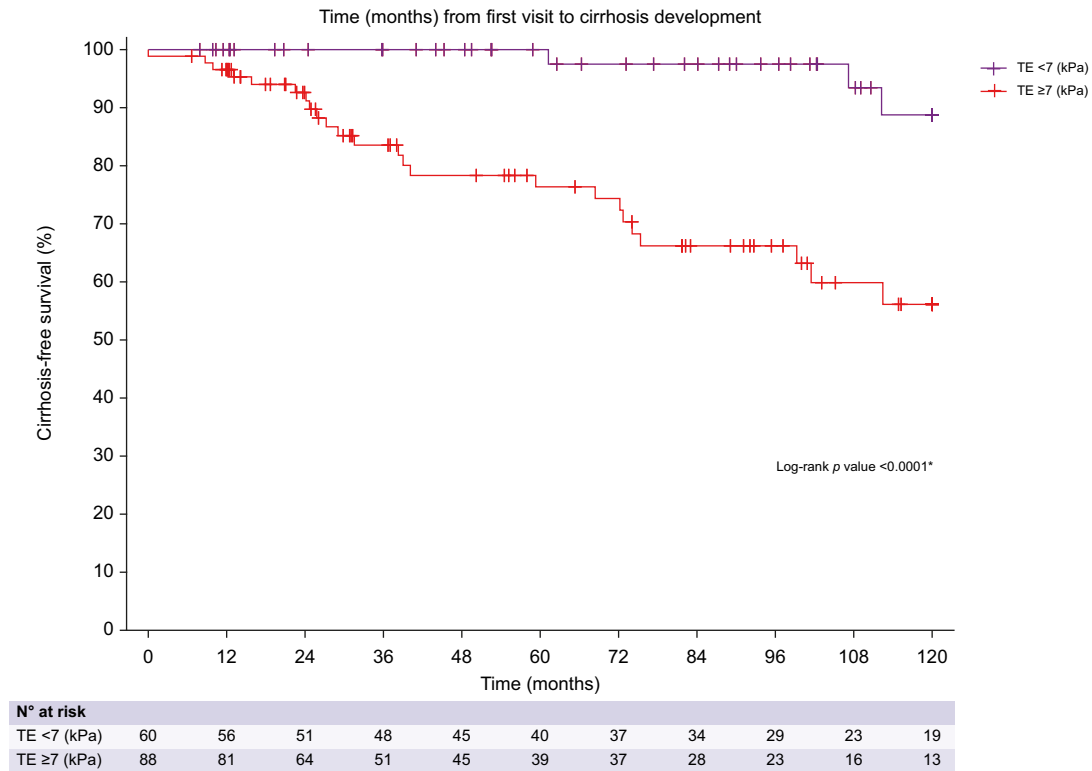
Non-invasive marker dynamics and longitudinal predictors of cirrhosis

As expected, serial measurements demonstrated significant changes in non-invasive markers over time among patients who progressed to cirrhosis. Overall, median TE-LSM increased; however, this change was primarily driven by patients who progressed to cirrhosis, in whom TE-LSM rose from 9.0 to 14.25 kPa; median increase +5.3 kPa (IQR +2.9 to +11.2; $p < 0.0001$). In contrast, no significant change in TE-LSM was

observed among patients with TE-LSM < 7 kPa (Table S3; Fig. 3). Other fibrosis scores also increased significantly from baseline to the last visit in patients who developed cirrhosis and were higher than in those who did not meet cirrhosis criteria: FIB-4 (2.65 vs. 1.40), APRI (1.33 vs. 0.52), and D4FS (0.74 vs. 0.14); all $p < 0.0001$ (Table S3).

Taking advantage of the longitudinal information (annual visits), we examined the impact of episodic increases in liver enzymes, HDV-RNA decline, and changes in liver stiffness in predicting cirrhosis development. During follow-up, 92 (55.1%) patients experienced ALT elevation $\geq 2 \times$ ULN, 15 (9.3%) a GGT ≥ 150 IU/L and 33 (28%) an annual increase in TE-LSM of ≥ 2 kPa. On the other hand, 59 (56.2%) patients experienced an annual decline in HDV-RNA levels of ≥ 1 log. Experiencing ALT $\geq 2 \times$ ULN, GGT ≥ 150 IU/L, or an annual HDV-RNA decline of $\geq 1 \log_{10}$ were not modifiers of the risk of cirrhosis. In contrast, at least one annual increase in TE-LSM ≥ 2 kPa was strongly associated with subsequent cirrhosis development: 80% of patients who progressed to cirrhosis had experienced at least one annual increase in TE-LSM ≥ 2 kPa, compared with 17.3% of those who did not progress to cirrhosis ($p < 0.001$) (Table 3). This association remained consistent across the two baseline TE-LSM categories. Among patients who developed cirrhosis, 100% of those with baseline TE-LSM < 7 kPa and 73.3% of those with baseline TE-LSM ≥ 7 kPa had experienced at least one annual increase of TE-LSM ≥ 2 kPa, compared with 20.5% and 15.7% of those who did not progress, respectively ($p = 0.001$ and $p < 0.001$).

A



B

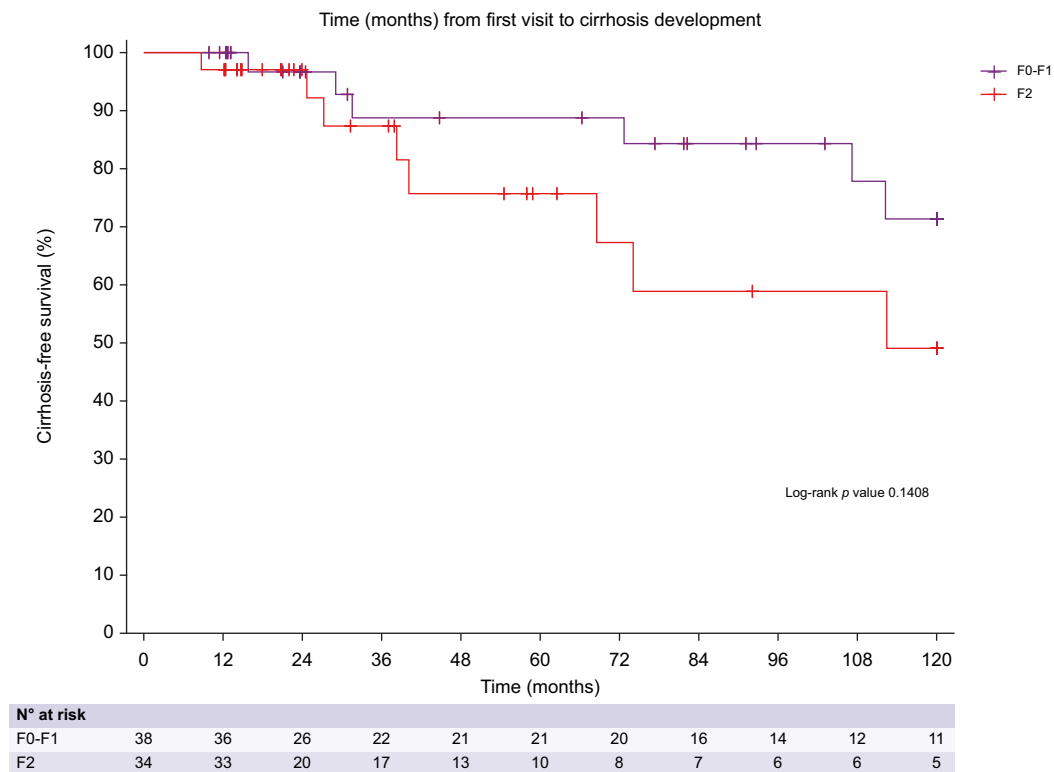


Fig. 2. Cirrhosis-free survival in patients with chronic HDV and baseline mild-to-moderate fibrosis (Kaplan-Meier analysis). (A) according to baseline TE-LSM (TE-LSM <7 vs. ≥7 kPa) ($n = 148$). (B) According to histologic assessment at baseline (F0-F1 vs. F2) ($n = 72$) (KM analysis, Log rank p value <0.0001 and 0.1408; respectively).

Table 3. Cox regression analysis for predicting cirrhosis development during follow-up.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Sex (male vs. female)	0.799	0.393–1.621	0.534			
Age (years)	1.021	0.988–1.055	0.207			
Race (Caucasian vs. others)	1.717	0.808–3.648	0.159			
ALT ($\geq 2\times$ ULN vs. $< 2\times$ ULN)	0.584	0.251–1.363	0.214			
TE-LSM (kPa)	1.486	1.285–1.719	<0.001			
TE-LSM (≥ 7 kPa vs. < 7 kPa)	7.701	2.313–25.645	<0.001	6.021	1.763–20.561	0.004
FIB-4	1.630	1.231–2.158	<0.001			
FIB-4 (≥ 1.45 vs. < 1.45)	2.817	1.360–5.836	0.005	2.105	0.957–4.629	0.064
APRI	1.144	0.822–1.591	0.425			
Platelets (≥ 200 or $< 200 \times 10^9/L$)	0.410	0.190–0.890	0.026			
Albumin (g/dl)	0.554	0.252–1.220	0.142			
HDV-RNA ($\log_{10}$ IU/ml)	0.854	0.693–1.051	0.137			
D4FS	1.838	1.037–3.221	0.037			
Antiviral treatment	3.072	1.311–7.197	0.010	2.057	0.818–5.174	0.125
Episodic increase in ALT $\geq 2\times$ ULN	0.696	0.352–1.375	0.297			
Episodic increase in GGT > 150 IU/L	1.077	0.270–3.134	0.892			
Episodic annual HDV RNA drop > 1 log	0.590	0.227–1.534	0.279			
Episodic annual rise in TE-LSM ≥ 2 kPa	7.957	2.628–24.093	<0.001			

p values < 0.05 are in bold. Cox regression analysis.

ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; D4FS, Delta-4 fibrosis score; FIB-4, Fibrosis-4 score; HR, hazard ratio; TE-LSM, transient elastography-derived liver stiffness measurement; ULN, upper limit of normal.

We then applied a Cox proportional hazards model with time-varying covariates to evaluate the effect of sustained changes during follow-up visits. Prolonged exposure to ALT $\geq 2\times$ ULN, TE-LSM ≥ 7 kPa, FIB-4 ≥ 1.45 , APRI ≥ 1 , platelet count $< 200 \times 10^9/L$, low albumin, low D4FS, and an annual TE-LSM increase of ≥ 2 kPa were all associated with higher cirrhosis risk, whereas prolonged exposure to GGT ≥ 150 U/L, annual HDV-RNA decline $\geq 1 \log_{10}$, or lower absolute HDV-RNA levels were not associated. In multivariable analysis, prolonged values of TE-LSM ≥ 7 kPa and FIB-4 ≥ 1.45 remained independently associated with cirrhosis development (Table 4).

Impact of antiviral therapy and HDV-RNA clearance

IFN-based therapy was administered to 33.9% of patients during follow-up, while BLV +/- PegIFN α was initiated in 16.7% of cases. Baseline characteristics of treated and untreated patients are depicted in Table S1. A total of 32 patients (19%) achieved sustained HDV-RNA clearance, defined as undetectable levels for more than 12 months. However, this occurred spontaneously in 14/32 patients (43.7%), whereas it was induced by antiviral treatment in the remaining 18/32 (56.2%). Of the patients achieving HDV clearance at any visit, 29/32 (90.6%) maintained suppression for over a year. Among patients who achieved HDV-RNA clearance, only 1/32 (3.1%) progressed to cirrhosis and only 2/26 (7.7%) progressed to TE-LSM ≥ 10 kPa, compared with 36/136 (26.5%) and 35/110 (31.8%) among those with persistent viremia ($p = 0.0035$ and $p = 0.012$, respectively). Notably, in the few patients who achieved viral clearance but developed cirrhosis or TE-LSM ≥ 10 kPa, disease progression had occurred prior to HDV-RNA clearance in both cases.

Discussion

In this large, multinational cohort of patients with chronic HDV infection and mild-to-moderate fibrosis at baseline, we found that over 20% of patients progressed to cirrhosis, used as a surrogate endpoint of disease progression, during a median follow-up of 5 years. Importantly, baseline TE-LSM, FIB-4,

D4FS, antiviral treatment, and platelet count were associated with cirrhosis progression, whereas other markers like ALT, HDV-RNA levels, and APRI score were not. These results support the use of baseline TE-LSM in guiding risk stratification and therapeutic decision-making in patients with HDV, even in the early stages of disease, and are consistent with recent evidence validating non-invasive algorithms as robust predictors of disease progression.¹²

Our data reinforce prior findings that TE-LSM is a robust non-invasive marker for assessing liver fibrosis in HDV. Sandmann *et al.* recently demonstrated that TE-LSM significantly outperforms other NITs such as FIB-4 and APRI in diagnosing liver cirrhosis in HDV-infected individuals, with an AUROC of 0.89 and a proposed optimal cut-off of 15.2 kPa to detect cirrhosis.¹¹ In our population of earlier disease stage, we identified a lower TE-LSM cut-off (7 kPa) as predictive of fibrosis progression. Indeed, patients with baseline TE-LSM < 7 kPa had a very low cumulative risk of cirrhosis over 10 years (6.5%), whereas those with values ≥ 7 kPa experienced a substantially higher risk (43.8%). Interestingly, even among patients considered at low risk of disease progression (baseline TE-LSM < 7 kPa), an annual increase of ≥ 2 kPa in TE-LSM was strongly associated with cirrhosis development. These results underscore the prognostic significance of even modest elevations in TE-LSM and support its utility as a stratification tool, particularly in patients not yet prioritized for therapy under current reimbursement constraints.

ALT levels have historically been used to trigger therapeutic intervention in HDV, yet our findings challenge this paradigm. In fact, ALT did not correlate with fibrosis stage (assessed by LSM and histology) or prognosis. Additionally, we observed no significant association between baseline ALT levels or episodic elevations in ALT $\geq 2\times$ ULN and cirrhosis development. These observations may reflect the dissociation between necro-inflammatory activity and fibrogenesis in HDV, the intermittent nature of ALT flares, and suggest that reliance on ALT alone may delay treatment in patients with progressive disease.¹¹

We also evaluated additional non-invasive fibrosis markers. Notably, baseline TE-LSM and FIB-4 outperformed both APRI

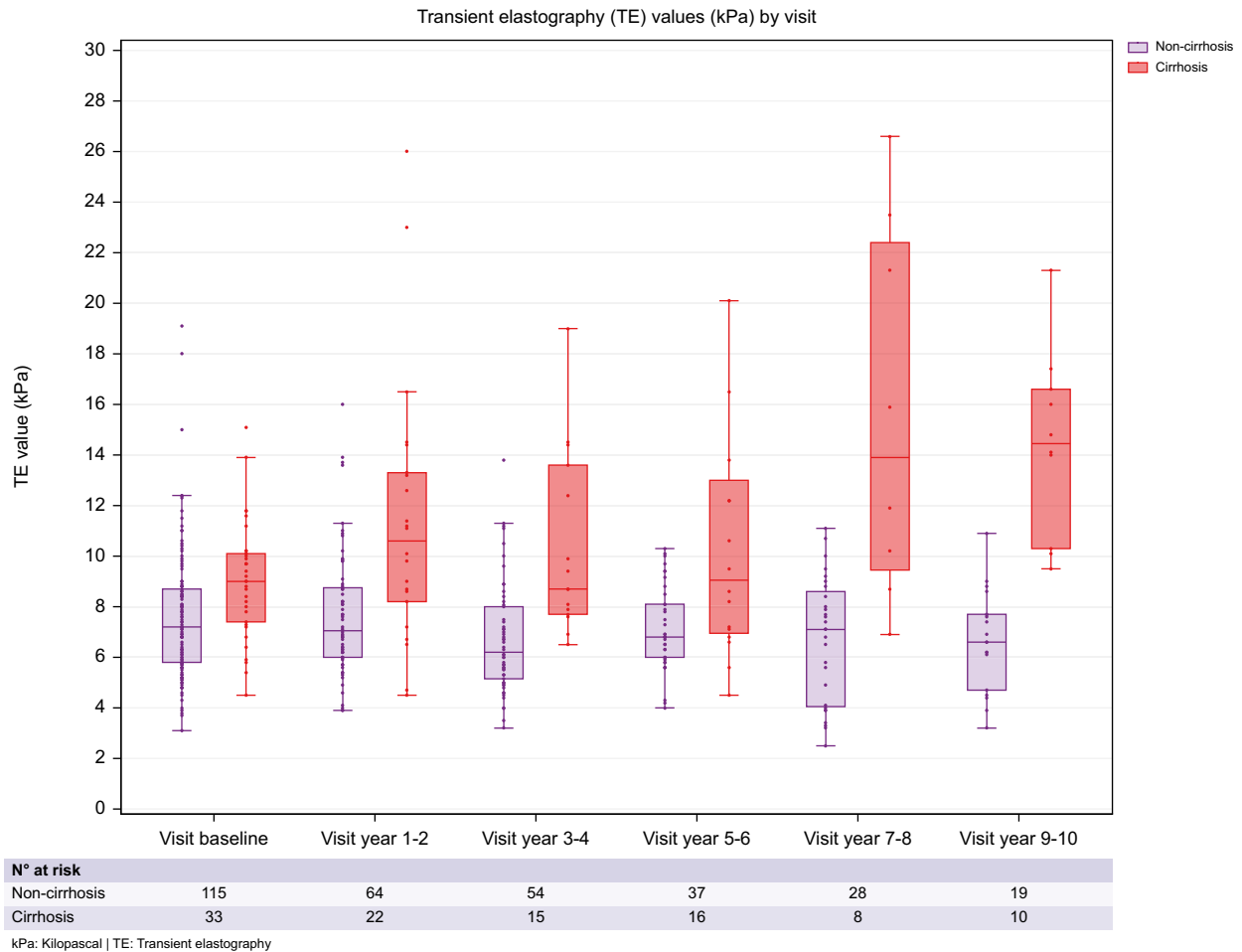


Fig. 3. Longitudinal evolution of TE-LSM during follow-up in patients with and without cirrhosis development during follow-up. Decreasing sample size over time reflects loss to follow-up and event occurrence.

Table 4. Time-dependent Cox regression analysis for progression to cirrhosis during follow-up (number of visits accomplishing these criteria is considered).

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
ALT $\geq 2 \times \text{ULN}$	2.008	1.015–3.970	0.045			
GGT $> 150 \text{ IU/L}$	2.827	0.848–9.424	0.091			
Annual HDV RNA drop $> 1 \text{ log}$	0.520	0.148–1.834	0.310			
Annual rise in TE-LSM $\geq 2 \text{ kPa}$	15.786	5.081–49.041	<0.001			
TE-LSM $\geq 7 \text{ kPa}$	10.783	2.517–46.192	0.001	7.093	1.614–31.168	0.009
HDV RNA	1.016	0.842–1.225	0.871			
PLT $< 200 \times 10^9/\text{L}$	2.849	1.331–6.098	0.007			
FIB-4 > 1.45	4.469	2.075–9.623	<0.001	3.156	1.209–8.240	0.019
APRI > 1	3.006	1.505–6.005	0.002			
Albumin	0.336	0.155–0.725	0.006			
D4FS	2.148	1.388–3.325	<0.001			

p values < 0.05 are in bold. Time-dependent Cox-regression analysis.

ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; D4FS, Delta-4 fibrosis score; FIB-4, Fibrosis-4 score; HR, hazard ratio; PLT, platelet count; TE-LSM, transient elastography-derived liver stiffness measurement.

and even histological staging (F0–1 vs. $\geq \text{F2}$) in stratifying patients according to their risk of fibrosis progression. While APRI has limited reliability in patients with mild-to-moderate fibrosis, and histology offers only a static, sample-dependent snapshot, TE-LSM, FIB-4, and D4FS capture broader and more dynamic disease signals, making them more accurate for predicting fibrosis. The D4FS, which incorporates ALT, GGT, platelet count, and

LSM, has previously demonstrated good diagnostic performance for cirrhosis in HDV,¹⁰ and in our cohort, it appeared to predict fibrosis progression as well – although TE-LSM alone exhibited comparable or superior discriminatory capacity. While not the primary focus of this analysis, these findings support the need for prospective validation of D4FS in early-stage HDV to define its utility across the disease continuum.

Our data also offer insights into the potential impact of HDV clearance. A substantial proportion of patients (19%) achieved HDV-RNA clearance, either spontaneously¹³ or following treatment. Among these, cirrhosis developed in only one patient, suggesting that viral clearance is associated with stabilization or regression of fibrosis.¹⁴

In our cohort, only sustained HDV-RNA clearance was associated with a lower risk of fibrosis progression and cirrhosis. However, the absence of an association between HDV-RNA decline and improved outcomes in our dataset should not be interpreted as evidence against the clinical relevance of viral load reduction. Data from BLV-treated cohorts and clinical trials indicate that even partial or transient virological suppression can translate into biochemical and histological improvement, particularly when initiated early.^{7,15–19} Our findings likely reflect the small number of BLV-treated patients, the variability of single HDV-RNA measurements and the limited duration of viral decline rather than the lack of a biological effect.

This study has several strengths. First, it represents one of the largest international real-world cohorts of patients with HDV and early-stage disease, with long-term follow-up, capturing clinically meaningful outcomes in a previously understudied population. Second, fibrosis assessment was based on histology and validated non-invasive tools, enhancing reliability. Third, the multicenter nature of the study and the variability in patient characteristics support the generalizability of our findings. Nonetheless, several limitations must be acknowledged. First, the retrospective design may have introduced selection bias and residual confounding. To mitigate this limitation, we performed longitudinal assessments at annual intervals to capture the kinetics of NITs and to promptly detect fibrosis progression or any liver-related event. Second, histological assessment was not uniformly available at baseline, and TE-LSM measurements were not always

contemporaneous with liver biopsy; however, we considered values obtained within 12 months before or after biopsy to increase the robustness of our findings and the stability of TE-LSM <7 kPa over time in our cohort supports the reliability of baseline TE fibrosis stratification. Moreover, while TE-LSM and biochemical scores were useful for ruling out cirrhosis, their sensitivity in mild-to-moderate fibrosis stages remains sub-optimal, as highlighted in prior validation studies.¹² Also, there is no clear consensus regarding the optimal TE-LSM threshold for defining cirrhosis in patients with HDV. In our study, a TE-LSM cut-off ≥ 12.5 kPa was used to increase sensitivity for identifying cirrhosis, and all cases classified as cirrhotic were subsequently reviewed to confirm the diagnosis. Lastly, anti-viral therapy was heterogeneous but the proportion of patients achieving HDV-RNA clearance induced by treatment was low. Only a minority of patients received the newer, more effective treatments, and most of those who did initiated therapy shortly before the end of follow-up.

In summary, our study highlights that one-quarter of HDV-infected patients with mild-to-moderate fibrosis at baseline are at risk of progressing to cirrhosis, used as a surrogate endpoint of disease progression. Liver stiffness, both at baseline and through, even modest, longitudinal increases, represents the strongest and most reliable predictor of cirrhosis progression, while HDV-RNA and ALT appear to have limited prognostic value. In the absence of TE-LSM, FIB ≥ 1.45 remains a useful tool for identifying those patients at risk of progression.

These findings support the broader use of non-invasive fibrosis assessment for risk stratification and timely treatment initiation, independent of transaminase and HDV-RNA levels. Given the increasing availability of effective antiviral agents such as BLV, the results of our study may help refine eligibility criteria and optimize outcomes in patients with CHD.

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Abbreviations

ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; BLV, bulevirtide; CHD, chronic hepatitis delta; D4FS, Delta-4 fibrosis score; FIB-4, Fibrosis-4 score; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; HR, hazard ratio; NITs, non-invasive tests; PegIFN α , pegylated interferon-alpha; TE-LSM, transient elastography-derived liver stiffness measurement; ULN, upper limit of normal.

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Conflicts of interest

S.Lens has received advisory/speaker fees from Gilead, Abbvie, Roche and GSK. S.Lens, J.L.Calleja and D.Roulot have received grants from Gilead. C.Moreno has received consulting fee from Gilead, Roche, Astra, Ipsen and Echosens. AGG has received grant support and consulting fees from Gilead; speaking honoraria from W. L. Gore & Associates, Gilead, AbbVie, MSD and Intercept; and travel support from AbbVie, Gilead, Eisai, Cook, W. L. Gore & Associates and Bayer. M.Buti has received honoraria for lectures and/or AB from Gilead, GSK, Abbvie Janssen, and grants from Gilead and AbbVie. George Papatheodoridis has served as advisor for Abbvie, Astra Zeneca, Genesis, Gilead, GlaxoSmithKline, Janssen, Ipsen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Takeda and Vir, as lecturer for Abbvie, Astra Zeneca, Gilead, GlaxoSmithKline, Janssen, Ipsen, Merck Sharp & Dohme, Novartis, Novo

Nordisk and Roche and has received research grants from Abbvie, Gilead, Takeda, Vianex. TV has received grants from Gilead Sciences and equipment from Fujirebio, TV is a consultant for Janssen Pharmaceuticals, Gilead Sciences, Abbvie, MSD, Roche and Ipsen, and a sponsored lecturer for Abbvie, Gilead Sciences, Roche, GlaxoSmithKline. S.Aleman has received honoraria for lectures/educational events from Gilead, MSD and Biogen, has participated in advisory boards for Gilead and Ribocure, and reports grants from Gilead and AbbVie. The remaining authors have nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

JLC, VL, SA, TV and SL contributed to concept and design. All authors collected data. SL and SB: statistical data analysis and draft of the manuscript. All authors contributed to the content and approved final version.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to ethical and institutional restrictions but may be available upon reasonable request.

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Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2026.101898>.

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Author names in bold designate shared co-first authorship

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