Diagnostic Performance of Noninvasive Tests for Hepatic Fibrosis in Patients With Chronic Hepatitis Delta Receiving Bulevirtide

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Conclusions

- In patients with chronic hepatitis delta, liver stiffness measurement (LSM) identified advanced fibrosis and cirrhosis with good diagnostic specificity
- An LSM cutoff of <10.2 kPa to exclude advanced fibrosis after bulevirtide treatment had similar specificity to that seen at baseline, despite a reduction in necroinflammation

Plain Language Summary

- Hepatitis delta virus causes the most severe form of viral hepatitis and increases the risk of severe liver disease
- Diagnosis of severe liver disease requires an invasive liver biopsy, which may not always be accurate
- Liver stiffness measurement using ultrasound is a less invasive way of diagnosing the severity of liver disease
- This study showed that liver stiffness measurement was able to identify advanced liver disease in patients with chronic hepatitis delta

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Introduction

- Hepatitis delta virus (HDV) causes the most severe form of chronic viral hepatitis and is estimated to affect approximately 12 million people worldwide[1,2]
- Infection with HDV is associated with more rapid progression to liver necrosis, fibrosis, and cirrhosis compared with hepatitis B alone[1,3,4]
- Bulevirtide (BLV) is a first-in-class HDV entry inhibitor and is approved in the United States, the European Economic Area, and several other countries for use in patients with chronic hepatitis delta (CHD) with compensated liver disease[5-9]
- BLV treatment was evaluated in patients with CHD with or without compensated cirrhosis in the MYR202 (NCT03546621), MYR203 (NCT02888106), MYR204 (NCT03852433), and MYR301 (NCT03852719) clinical trials
- Although liver biopsy is the gold standard for diagnosing fibrosis, less invasive tests can be used to minimize sampling errors and patient harm[4]
- Liver stiffness measurement (LSM) by transient elastography has shown good diagnostic performance as an indirect noninvasive test (NIT) for hepatic fibrosis, but limited data are available in patients with CHD, particularly in those receiving BLV[4]

Objective

- To evaluate the relationship of LSM and other NITs with necroinflammation and fibrosis as observed by biopsy in clinical trials of patients with CHD

Methods

- Patients with CHD from the MYR202, MYR203, MYR204, and MYR301 clinical trials with available baseline liver biopsy data were included in the study
- Biopsy data were analyzed at baseline, weeks 24 and 48, and week 24 after treatment ("On/After BLV Treatment" cohort) from a pooled cohort of patients receiving BLV 2 mg, 10 mg (approved as 8.5 mg delivered dose in the United States)[9], or 10 mg delayed treatment with or without pegylated interferon alfa-2a (Peg-IFNα-2a)
  - For patients with biopsies during treatment and after treatment, only during-treatment biopsies (1 per patient) were selected
- Biopsy specimens were scored following Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) guidelines for the following:
  - Fibrosis stage (F0–F4)
  - Necroinflammation grade (Histological Activity Index [HAI]: A0–A3)
- The following NITs were assessed within 3 months of biopsy:
  - LSM (FibroScan®)
  - Aspartate aminotransferase to platelet ratio index (APRI)[10]
  - Fibrosis-4 Index (FIB-4)[11]
- NIT cutoffs were evaluated for excluding advanced fibrosis (<F3) and detecting cirrhosis (F4) using sensitivity, specificity, positive predictive value, negative predictive value, and percentage correctly classified
  - The cutoff for cirrhosis (F4) was not evaluated in the On/After BLV Treatment cohort due to the limited number of patients
- The diagnostic accuracy of NITs for advanced fibrosis (≥F3) and cirrhosis (F4) was assessed using area under the receiver operating characteristic (AUROC) curves

Results

Table 1. Baseline Demographics and Characteristics

	Overall N = 308
Age, years, mean (SD)	40 (8.7)
Sex, male, n (%)	205 (67)
Race, n (%)	
Asian	31 (10)
Black	6 (2)
White	270 (88)
Body mass index, kg/m², mean (SD)	25.4 (3.82)
Cirrhosis present, n (%)	73 (24)
HDV RNA, log_{10} IU/mL, mean (SD)	5.25 (1.317)
HDV genotype 1, n (%)	288 (94)
HBsAg, log_{10} IU/mL, mean (SD)	3.78 (0.647)
ALT, U/L, median (Q1, Q3)	85 (61, 129)
ALT category, n (%)	
≤ULN	17 (6)
>ULN to ≤1.5 × ULN	58 (19)
>1.5 × ULN	233 (76)
Concomitant HBV therapy, n (%)	161 (52)
Prior IFN therapy, n (%)	132 (43)

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; Q, quartile; ULN, upper limit of normal.

- Overall, patients had a mean (SD) age of 40 (8.7) years, and 67% were male (**Table 1**)
- Of the 308 patients with baseline biopsies, 263 (85%) patients had available LSM, 279 (91%) had FIB-4 scores, and 279 (91%) had APRI scores

Results

Table 2. Liver Fibrosis Stages and HAI Scores at Baseline

	Baseline
Liver fibrosis (N = 308), n (%)	
F0 (absence of fibrosis)	32 (10)
F1 (portal fibrosis with no septa)	100 (33)
F2 (portal fibrosis with infrequent septa)	106 (34)
F3 (numerous septa but no cirrhosis)	52 (17)
F4 (compensated or decompensated cirrhosis)	18 (6)
HAI (n = 307), n (%)	
A0 (no activity)	23 (7)
A1 (minimal activity)	115 (37)
A2 (moderate activity)	92 (30)
A3 (severe activity)	77 (25)

HAI, Histological Activity Index.

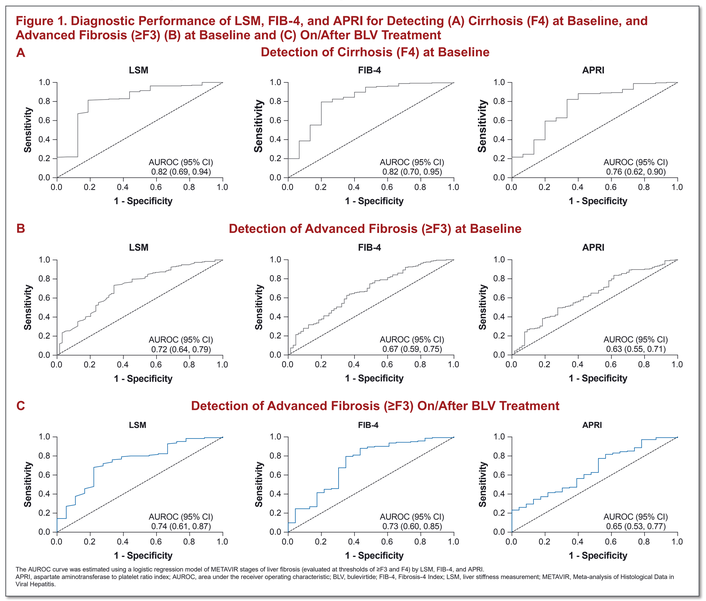
Table 3. Liver Fibrosis Stages and HAI Scores On/After BLV Treatment

	On/After BLV Treatment
Liver fibrosis (n = 166), n (%)	
F0 (absence of fibrosis)	25 (15)
F1 (portal fibrosis with no septa)	61 (37)
F2 (portal fibrosis with infrequent septa)	57 (34)
F3 (numerous septa but no cirrhosis)	21 (13)
F4 (compensated or decompensated cirrhosis)	2 (1)
HAI (n = 167), n (%)	
A0 (no activity)	39 (23)
A1 (minimal activity)	76 (46)
A2 (moderate activity)	35 (21)
A3 (severe activity)	17 (10)

BLV, bulevirtide; HAI, Histological Activity Index.

- At baseline, 238/308 (77%) patients were classified as having fibrosis stage <F3, 52/308 (17%) had F3, and 18/308 (6%) had F4 (**Table 2**)
  - On/After BLV treatment, 143/166 (86%) patients were classified as having fibrosis stage <F3, 21/166 (13%) had F3, and 2/166 (1%) had F4 (**Table 3**)
- At baseline, 230/307 (75%) patients were classified as having HAI category ≤A2, and 77/307 (25%) had A3 (**Table 2**)
  - On/After BLV treatment, 150/167 (90%) had ≤A2, and 17/167 (10%) had A3 (**Table 3**)
- Of the 73 patients classified by the investigator as having cirrhosis at baseline, 10/73 (14%) had stage F4 (cirrhosis) on baseline biopsy, while an additional 19/73 (26%) had stage F3 (advanced fibrosis)
  - Of the 205 classified as not having cirrhosis at baseline, 6/205 (3%) had stage F4 (cirrhosis) on baseline biopsy and 30/205 (15%) had stage F3 (advanced fibrosis)

Figure 1. Diagnostic Performance of LSM, FIB-4, and APRI for Detecting (A) Cirrhosis (F4) at Baseline, and Advanced Fibrosis (≥F3) (B) at Baseline and (C) On/After BLV Treatment



The AUROC curve was estimated using a logistic regression model of METAVIR stages of liver fibrosis (evaluated at thresholds of ≥F3 and F4) by LSM, FIB-4, and APRI.
APRI, aspartate aminotransferase to platelet ratio index; AUROC, area under the receiver operating characteristic; BLV, bulevirtide; FIB-4, Fibrosis-4 Index; LSM, liver stiffness measurement; METAVIR, Meta-analysis of Histological Data in Viral Hepatitis.

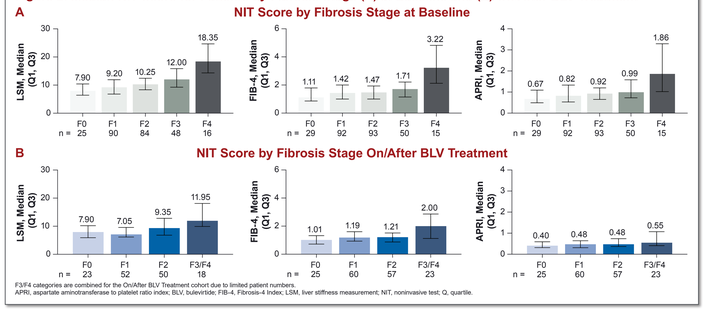
Table 4. Performance of LSM, FIB-4, and APRI Cutoffs for Excluding Advanced Fibrosis (<F3) and Detecting Cirrhosis (F4)

NIT	LSM			FIB-4			APRI		
Fibrosis stage	<F3 (Excluding Advanced Fibrosis)		F4 (Cirrhosis)	<F3 (Excluding Advanced Fibrosis)		F4 (Cirrhosis)	<F3 (Excluding Advanced Fibrosis)		F4 (Cirrhosis)
Biopsy classification, n/N (%)	**Baseline 199/263 (76)**	**On/After BLV 125/143 (87)**	**Baseline 16/263 (6)**	**Baseline 214/279 (77)**	**On/After BLV 142/165 (86)**	**Baseline 15/279 (5)**	**Baseline 214/279 (77)**	**On/After BLV 142/165 (86)**	**Baseline 15/279 (5)**
Cutoff value[a]	<10.2 kPa	<10.2 kPa	≥15.2 kPa	<1.30	<1.30	≥2.67	<1	<1	≥2
Sensitivity, %	57	72	56	46	59	53	59	87	33
Specificity, %	72	72	84	74	70	90	57	26	91
PPV, %	86	95	18	85	92	23	82	88	17
NPV, %	35	27	97	29	22	97	30	24	96
Correctly classified, n/N (%)	159/263 (60)	103/143 (72)	216/263 (82)	147/279 (53)	100/165 (61)	245/279 (88)	164/279 (59)	129/165 (78)	244/279 (88)

Patients with LSM/laboratory data and biopsy dates more than 90 days apart were excluded from analysis. The cutoff for cirrhosis was not evaluated in the On/After BLV Treatment cohort due to the limited number of patients.
[a]LSM cutoff values were based on a study of LSM for the diagnosis of liver cirrhosis in patients with chronic hepatitis delta virus infection.[12]
APRI, aspartate aminotransferase to platelet ratio index; BLV, bulevirtide; FIB-4, Fibrosis-4 Index; LSM, liver stiffness measurement; NIT, noninvasive test; NPV, negative predictive value; PPV, positive predictive value.

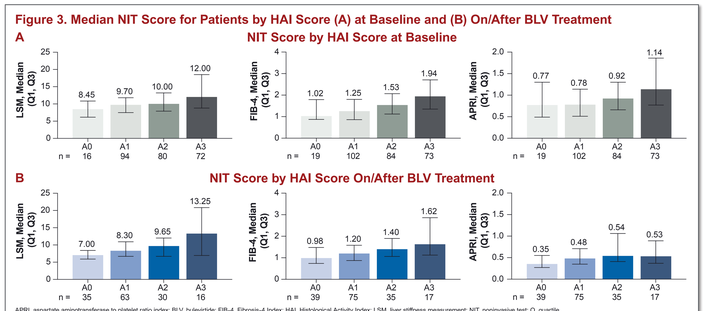
- At baseline, LSM had good diagnostic accuracy for detecting cirrhosis (F4; AUROC: 0.82 [95% CI: 0.69, 0.94]), which was numerically similar to that of FIB-4 (AUROC: 0.82 [95% CI: 0.70, 0.95]) and higher than that of APRI (AUROC: 0.76 [95% CI: 0.62, 0.90]; **Figure 1A**)
  - For diagnosing cirrhosis at baseline, an LSM cutoff of ≥15.2 kPa[12] had 56% sensitivity and 84% specificity (**Table 4**)
- At baseline for advanced fibrosis (≥F3), LSM, FIB-4, and APRI AUROCs (95% CIs) were 0.72 (0.64, 0.79), 0.67 (0.59, 0.75), and 0.63 (0.55, 0.71), respectively (**Figure 1B**)
  - For excluding advanced fibrosis at baseline in patients, a <10.2 kPa LSM cutoff[12] had 57% sensitivity and 72% specificity (**Table 4**)
- In the On/After BLV Treatment cohort, the LSM AUROC for advanced fibrosis was 0.74 (95% CI: 0.61, 0.87; **Figure 1C**)
  - A <10.2 kPa LSM cutoff had similar specificity to baseline for excluding advanced fibrosis (**Table 4**)

Figure 2. Median NIT Score for Patients by Fibrosis Stage (A) at Baseline and (B) On/After BLV Treatment



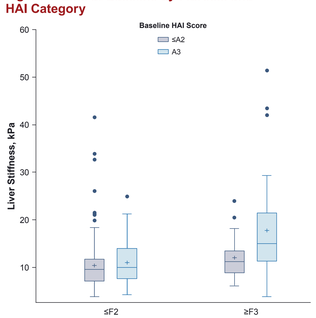
F3/F4 categories are combined for the On/After BLV Treatment cohort due to limited patient numbers.
APRI, aspartate aminotransferase to platelet ratio index; BLV, bulevirtide; FIB-4, Fibrosis-4 Index; LSM, liver stiffness measurement; NIT, noninvasive test; Q, quartile.

Figure 3. Median NIT Score for Patients by HAI Score (A) at Baseline and (B) On/After BLV Treatment



APRI, aspartate aminotransferase to platelet ratio index; BLV, bulevirtide; FIB-4, Fibrosis-4 Index; HAI, Histological Activity Index; LSM, liver stiffness measurement; NIT, noninvasive test; Q, quartile.

Figure 4. LSM at Baseline by Fibrosis and HAI Category



Boxes represent the first and third quartiles (Q1 and Q3); horizontal lines within the boxes represent the median; + represents the mean; whiskers extend to the most extreme values within 1.5 × IQR of Q1 and Q3; points beyond the whiskers represent outliers.
HAI, Histological Activity Index; LSM, liver stiffness measurement; Q, quartile.

- At baseline, increases in the stage of liver fibrosis were accompanied by increases in LSM, FIB-4, and APRI scores (**Figure 2A**)
  - Similar results were observed in the On/After BLV Treatment cohort, but to a lesser extent for the APRI score (**Figure 2B**)
- At baseline and On/After BLV treatment, median LSM, FIB-4, and APRI scores generally increased with HAI score (**Figure 3A/B**)
- When stratified by fibrosis and HAI categories, LSM was numerically highest in patients with both fibrosis stage ≥F3 and HAI category A3 (**Figure 4**)

Limitations

- Data from a pooled cohort of patients treated with BLV (with or without Peg-IFNα-2a), both on and after treatment, were used for the BLV treatment group analysis
- In comparison with prior analyses,[4] which had real-world cohorts with a higher burden of advanced fibrosis, this clinical trial cohort had relatively few patients with advanced fibrosis, which likely limited test performance and precluded evaluation of cirrhosis (F4) detection in the On/After BLV Treatment cohort