

Noninvasive Tests For Detection Of Biopsy-proven Cirrhosis In Chronic Hepatitis D Infected Patients Are Suboptimal

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Introduction

- Hepatitis D virus (HDV) infection is the most severe form of chronic liver disease^{1,2}.
- Non-invasive tests for assessment of liver fibrosis have largely replaced liver biopsy for disease staging in several chronic liver diseases.
- However, the utility of these tests in chronic HDV infection, has not yet been established.

Aim

The aim of the present analysis was to evaluate and compare the diagnostic accuracy of liver stiffness and serum-based markers for diagnosis of biopsy proven cirrhosis in HDV.

Methods

- D-LIVR (NCT03719313) is an ongoing, multicenter Phase 3 clinical trial, evaluating the efficacy of lonafarnib with or without peginterferon alfa compared to placebo, for treatment of HDV.
- We prospectively evaluated the first 100 patients who enrolled in the D-LIVR study.
- At baseline, liver stiffness measurement (LSM) and/or FibroTest[®] were performed.
- ALT, AST and platelet count were obtained and used for calculation of AST to ALT ratio (AAR), AST to platelet ratio index (APRI) and Fibrosis-4 index (FIB-4).
- Percutaneous liver biopsy was performed in all patients.
- Sensitivity, specificity, positive and negative predictive values for detection of cirrhosis were calculated based on cut-offs predefined in the literature.
- Receiver operator curve (ROC) analysis was employed for evaluation of the discriminant capacity of the different tests for diagnosis of cirrhosis.

Results

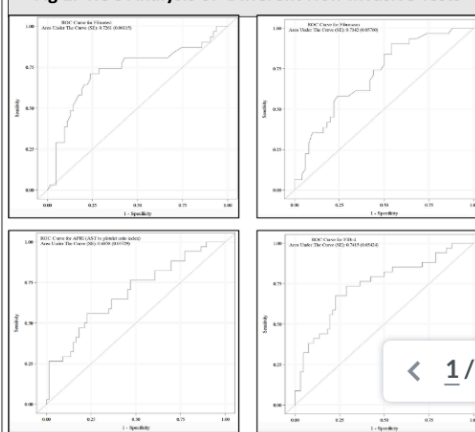
Table 1. Cohort Description

	All Subjects (N=100)
Demographics	
Age, mean (range)	45.6 (19 - 69)
Sex	
Female, n (%)	34 (34.0)
Male, n (%)	66 (66.0)
Ethnicity	
Hispanic or Latino, n (%)	4 (4.0)
Not Hispanic or Latino, n (%)	94 (94.0)
Not Reported, n (%)	2 (2.0)
Race	
Asian, n (%)	14 (14.0)
Black or African American, n (%)	3 (3.0)
Native Hawaiian/Other Pacific Islanders, n (%)	4 (4.0)
White, n (%)	79 (79.0)
BMI, mean (range)	26.7 (17.7 - 40.3)
Disease characteristics	
Cirrhotic per liver biopsy, n (%)	34 (34.0)
HDV-RNA, Log ₁₀ IU/mL, mean (range)	5.3 (3.1 - 7.7)
ALT, U/mL, mean (range)	113 (0.027 - 500)
AST, U/mL, mean (range)	79 (0.020 - 0.429)
Total Bilirubin, mg/dL, mean (range)	0.66 (0.1 - 3.7)
Albumin, g/dL, mean (range)	4.36 (3.0 - 5.3)
INR, mean (range)	1.13 (0.81 - 2.24)
Platelets, x10 ⁹ /L, mean (range)	175 (79 - 493)

Table 2. Diagnostic Accuracy of Non-Invasive Tests for Prediction of Cirrhosis

Non-invasive Test	Cutoffs for Cirrhosis	Subjects with Cirrhosis n (%)	Subjects without Cirrhosis n (%)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Correctly Classified n (%)
Fibrotest	> 0.74	15/31 (48.4)	8/63 (12.7)	48.4 (30.2 - 66.9)	87.3 (76.5 - 94.4)	65.22 (42.73, 83.62)	77.46 (66.00, 86.54)	70/94 (74.5)
	≤ 0.74	16/31 (51.6)	55/63 (87.3)					
Fibroscan	>13 kPa	14/31 (45.2)	10/50 (20.0)	45.2 (27.3 - 64.0)	80.0 (66.3 - 90.0)	58.33 (36.64, 77.89)	70.18 (56.60, 81.57)	54/81 (66.7)
	≤ 13 kPa	17/31 (54.8)	40/50 (80.0)					
APRI (AST to platelet ratio index)	> 1	26/34 (76.5)	34/66 (51.5)	76.5 (58.8 - 89.3)	48.5 (36.0 - 61.1)	43.33 (30.59, 56.76)	80.00 (64.35, 90.95)	58/100 (58.0)
	≤ 1	8/34 (23.5)	32/66 (48.5)					
FIB-4	> 3.25	13/34 (38.2)	7/66 (10.6)	38.2 (22.2 - 56.4)	89.4 (79.4 - 95.6)	65.00 (40.78, 84.61)	73.75 (62.71, 82.96)	72/100 (72.0)
	≤ 3.25	21/34 (61.8)	59/66 (89.4)					
AAR (AST to ALT ratio)	> 1	4/34 (11.8)	3/66 (4.5)	11.8 (3.3 - 27.5)	95.5 (87.3 - 99.1)	57.14 (18.41, 90.10)	67.74 (57.25, 77.07)	67/100 (67.0)
	≤ 1	30/34 (88.2)	63/66 (95.5)					

Fig 1. ROC Analysis of Different Non-Invasive Tests



Discussion

- Similar to other interventional trials conducted in this population, a relatively high proportion of cirrhotic patients at baseline was noted in this cohort.
- At best, non-invasive tests correctly classified cirrhotics vs non-cirrhotics in approximately 75% of cases.
- None of the different tests showed advantage over others for prediction of biopsy-proven cirrhosis.

Table 3. Comparison of ROC for Different Non-Invasive Tests [p-value]

	Fibrotest	Fibroscan	APRI	FIB-4	AAR
Fibrotest		0.89	0.63	0.84	0.48
Fibroscan	0.89		0.73	0.72	0.56
APRI	0.63	0.73		0.48	0.81
FIB-4	0.84	0.72	0.48		0.34
AAR	0.48	0.56	0.81	0.34	

References

- Yurdaydin C, Idilman R, Bozkaya H et al. Natural history and treatment of chronic delta hepatitis: Chronic delta hepatitis. *J Viral Hepat.* 2010;17(11):749-756.
- Fattovich G. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. *Gut.* 2000;46(3):420-426.

Conclusions

- Accuracy of non-invasive tests for predicting cirrhosis in chronic HDV infection is suboptimal.
- Consequently, interpretation of non-invasive test in chronic HDV should be done with caution.
- Liver biopsy is currently the most reliable method for detection of cirrhosis in HDV patients.