PREDICTIVE VALUE OF NON-INVASIVE METHODS LIVERFASt™, ACOUSTIC RADIATION FORCE IMPULSE (ARFI), FIB-4 AND APRI TO IDENTIFY THE NATURAL PHASES OF CHRONIC HEPATITIS B (CHB) INFECTION FROM THE NATIONAL UNIVERSITY HOSPITAL (NUH) CHB STUDY COHORT OF SINGAPORE

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ABSTRACT

Background. In order to determine the outcomes and progression to significant liver fibrosis (SLF) as per ARFI, we set up a prospective NUH HBV cohort with chronic HBV infection (Ch.In f) expected to have no/minimal liver disease vs moderate/severe in chronic hepatitis (Ch.Hep) patients (pts).(JHepatol2017) LIVERFAStTM (LF, Fibronostics, Orlando,US), is a patented technology to assess liver fibrosis (LF-F) and activity (LF-A).

Aim. To estimate the negative predictive value (NPV) and the discriminating value between Ch.In f and Ch.Hep with non-invasive tests LF-F, LF-A, ARFI, FIB-4 and APRI, in CHB pts from the NUH Singapore HBV cohort.

Methods. Prospective naïve CHB pts aged >2Iyrs, w ith ARFI<1.54m /s, were included. HBV phases were defined on HBeAg presence, HBVDNA (VL, IU /m L) and ALT (IU/L): Ch.In f.HBe+ [V L>107, ALT<40]; Ch.Hep.HBe+ [104–107, ALT>40]; Ch.In f.HBe- [V L<2,000,ALT<40]; Ch.Hep.HBe-[V L>2,000, ALT>40]; indeterminate (not all criteria) and resolved HBV [HBsAg(-), VL<10, ALT<40, anti-HBc+].

Results. 724 pts were included, [26 excluded (6 missing data; 7 ARFI>1.54m /s; 13 LF not applicable)] w with the main characteristics [mean(se)] age 50(0.4) yrs, 51.7% males, 89.9% HBeAg(-), ALT 31 (1) IU /L VL 2,4x107(4643) IU /m L qHBsAg 5428 (758), ARFI 1.06 (0.01). Prevalence of CHB profiles were: 60 (8.3%) Ch.Hep.HBe-; 195 (26.9%) Ch.In f.HBe-; 33(4.6%) Ch.Hep.HBe+; 24(3.3%) Ch.In f.HBe+; 32(4.4%) HBsAg not Reactive (nonReact) and 380 (52.5%) indeterminate (50.3%HBe-). Spearman correlations of LF Fib/LF-Act w ith ARFI, FIB-4 and APRI were 0.18/0.21, 0.47/0.11 and 0.23/0.69, respectively (all p<0.01). In HBeAg(-) pts, Ch.In fHBe- phase was discriminated from Ch.HepHBe- as per liver disease estimators LF-F ib (0.23 vs 0.28, p<0.05), LF-Act (0.07 vs 0.23, p<0.001) and APRI (0.28 vs 0.44, p<0.001), respectively. In HBeAg(+) pts, Ch.In f HBe+ phase was discriminated from Ch.HepHBe+ as per LIVERFASt-F ibrosis (0.10 vs 0.19, p<0.001), LIVERFASt-Activity (0.09 vs 0.31, p<0.001), and APRI (0.32 vs 0.46, p<0.001). ARFI and FIB-4 did not discriminate Ch.In f from Ch.Hep in both HBeAg(+) and HBeAg(-)(p=NS).

NPV for LIVERFASt-Fibrosis / LIVERFASt-Activity / APRI were fo r HBeAg(-) 77% / 82% / 27% and HBe(+) 89% / 62% / 12%, respectively. Resolved HBV had significantly lower activity than Ch.HepHBe- as per LIVERFASt-Activity (0.11 vs 0.23, p<0.001). Among 6 pts (0.8%) that scored F4 stage as per LIVERFASt-Fibrosis and F0 as per ARFI, 3 had suspicion of false positive LIVERFASt-Fibrosis.

Conclusion. LIVERFASt-Fibrosis and LIVERFASt-Activity are reliable tools for screening HBV infected patients and fo r detecting phase-related liver disease, with better NPV than APRI or FIB-4. Management of HBV patients could be improved by LIVERFASt tests .

BACKGROUND

In order to determine the outcomes and progression to significant liver fibrosis (SLF) as per ARFI, we set up a prospective NUH HBV cohort with chronic HBV infection (Ch.Inf), selected according to liver ARFI measurements <1.54m/s. These patients are expected to have no/minimal liver disease compared to chronic hepatitis (Ch.Hep) patients expected to have moderate to severe fibrosis. (1,2,3) LIVERFASt™ (LF) is a serum-based proprietary panel for assessing fibrosis (LF-Fibrosis), activity (LF-Activity) and steatosis (LF-Steatosis) in chronic viral hepatitis B and C and in NAFLD patients. (4,5,6) LIVERFASt systemutilizes the AI machine learning technology and clinical scoring algorithms for all stages of liver diseases. The derived score is translated to a stage, based on histological scoring system using predetermined cutoffs, to correspond to the level of histological stage or grade in that liver tests.

AIMS

The study aimed to estimate the negative predictive value (NPV) and the discriminating value between chronic infection profile (Ch.Inf) and chronic hepatitis (Ch.Hep) of several non-invasive tests LIVERASt-Fibrosis, LIVERFASt-Activity, ARFI, FIB-4 and APRI, in naïve chronic hepatitis B (CHB) patients from the NUH Singapore HBV prospective cohort.

PATIENTS & METHODS

Patients : N=750 naïve of treatment chronic hepatitis B (CHB) patients prospectively collected

Statistics: T-test of Student, p value significance <0.05.

Definitions of Chronic Infection and Chronic Hepatitis

Definition used were based on viral markers, viral load and ALT as described in the CPG (1,2,3)

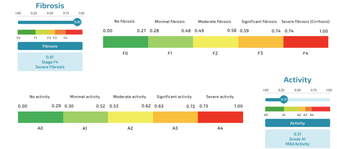
Noninvasive tests (NITs)

Liver fibrosis was evaluated using LIVERFASt-Fibrosis and transaminase-based free NITs FIB-4 and APRI and using ARFI. APRI is combining AST and platelets. FIB-4 is combining age with ALT, AST and platelets.

Necro-inflammatory activity (NIA) was evaluated using LIVERFASt-Activity.

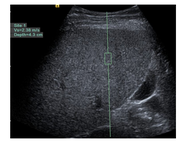
LIVERFASt™ (Orlando, Florida USA)

Blood-based diagnostic tests that combines age, gender with liver specific biomarkers (apolipoprotein A1, alpha2-macroglobulin, haptoglobin), liver function tests (total bilirubin, GGT) to determine the severity of liver fibrosis and cirrhosis and with ALT to determine the severity of necroinflammatory activity.



Acoustic radiation force impulse elastography (ARFI, Siemens Healthineers, PA, USA)

- ARFI-based shear wave velocity quantification is an US-based method for the assessment of liver fibrosis.
- Validated cut-off 1.54 m/s for to confirm detection of fibrosis >=F2 in chronic viral hepatitis.



RESULTS

Prevalences of natural phases of chronic hepatitis B in prospective cohort with ARFI measurements <1.54m/s

Characteristics [Prevalences, median (SE)]	HBeAg(-) Chronic Hepatitis	HBeAg(-) Chronic Infection	P value	HBeAg(+) Chronic Hepatitis	HBeAg(+) Chronic Infection	P value	Resolved CHB HBsAg Non Reactive	P value vs HBeAg(-) Chronic Hepatitis	Indeterminate HbeAg(+)	Indeterminate HbeAg(-)	P value
Definition of phases of CHB profiles *VL= HBV DNA (IU/mL) ALT, IU/L*	HBeAg no-React *HbeAb React* *VL >2000 ALT> 40*	HBeAg no-React *HbeAb React* *VL <2000 ALT< 40*		HBeAg React *HbeAb no-React* *VL 10^4 - 10^7 ALT>40*	HBeAg React *HbeAb no-React* *VL>10^7 ALT< 40*		*HBsAg non-React* *VL undetectable ALT<40*		HBeAg(+) *VL, ALT different from defined categories*	HBeAg(-) *VL, ALT different from defined categories*	
Number	**60 (8.3%)**	**195 (26.9%)**		**33 (4.6%)**	**24 (3.3%)**		**32 (4.4%)**		**16 (2.2%)**	**264 (36.5%)**	
Male Gender	46.7%	57.9%	ns	54.5%	25%	<0.05	65.6%	ns	50%	49.5%	ns
Age, years	47 (1.3)	53 (0.8)	<0.01	44 (1.9)	40 (2.4)	ns	61.8 (1.5)	<0.0001	38 (3.0)	50 (0.7)	<0.01
BMI, Kg/m2	24.0 (0.5)	23.5 (0.3)	ns	24.2 (0.7)	22.1 (0.7)	<0.05	23.9 (0.6)	ns	23.3 (0.9)	23.7 (0.2)	ns
LIVERFASt Fibrosis score	**0.28 (0.02)**	**0.23 (0.01)**	**<0.05**	**0.19 (0.02)**	**0.10 (0.01)**	**<0.001**	0.385 (0.03)	ns	0.22 (0.04)	0.23 (0.01)	ns
LIVERFASt Activity score	**0.23 (0.19)**	**0.07 (0.05)**	**<0.0001**	**0.31 (0.03)**	**0.09 (0.01)**	**<0.0001**	0.11 (0.01)	<0.0001	0.12 (0.03)	0.10 (0.06)	ns
ARFI, m/s	1.03 (0.02)	1.03 (0.01)	ns	1.07 (0.03)	1.04 (0.02)	ns	1.10 (0.02)	ns	1.10 (0.03)	1.05 (0.01)	ns
FIB4	1.04 (0.44)	1.00 (0.55)	ns	0.80 (0.12)	0.79 (0.09)	ns	1.45 (0.08)	<0.01	0.79 (0.08)	0.91 (0.03)	ns
APRI	**0.43 (0.05)**	**0.28 (0.01)**	**<0.0001**	**0.46 (0.06)**	**0.32 (0.03)**	**P<0.01**	0.31 (0.02)	<0.01	0.34 (0.02)	0.30 (0.01)	ns
Quantitative HBsAg	2308 (496)	18 (15)	<0.0001	11971 (6402)	39817 (13026)	<0.05	0.05 (0.01)	<0.0001	2167 (3617)	1021 (3141)	ns
HBV DNA	72053 (692 *10^3)	200 (34)	<0.0001	6985 (5287)*10^4	28429(6319) *10^4	<0.01	0 (18)	<0.0001	8907 (1063*10^3)	3855 (210*10^3)	ns
ALT, IU/L	43 (10.2)	19 (0.4)	<0.0001	52 (6)	26 (1.7)	<0.0001	22 (1.9)	<0.0001	26 (8.3)	24 (17.6)	ns

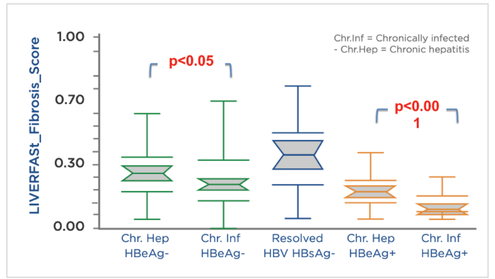
N= 750 patients pre-included with LIVERFASt™ From the CHB Study Cohort included in the in the National University Hospital (NUH) of Singapore

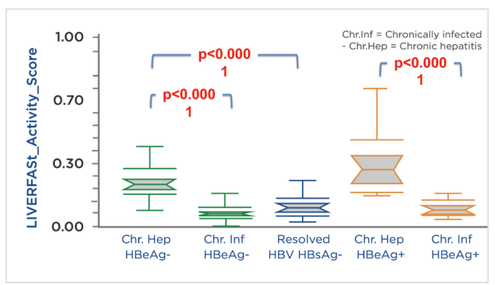
Excluded patients
N=26
6 missing data
7 ARFI>1.54m/s
13 LF not applicable

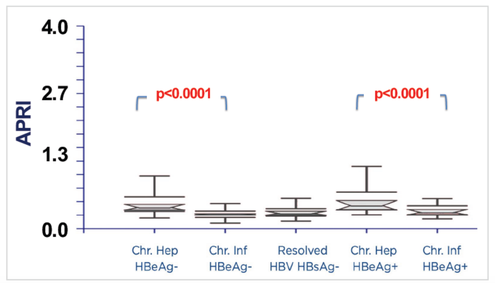
N=726 CHB included with concomitant ARFI measurement, LIVERFASt, APRI, FIB-4

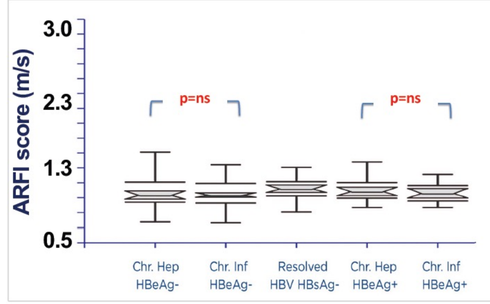
LIVERFASt correlations with ARFI, FIB-4 and APRI			
Spearman correlation coefficient	ARFI	FIB-4	APRI
LIVERFASt Fibrosis score	0.18	0.47	0.23
LIVERFASt Activity score	0.21	0.11	0.69
All p<0.001			

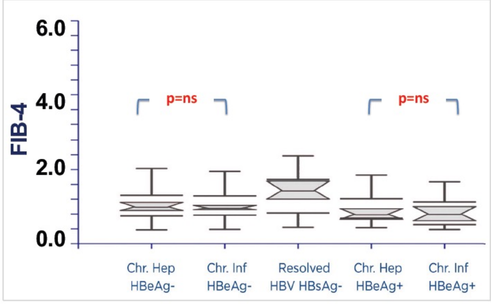
Negative Predictive Values (NPV)			
Spearman correlation coefficient	LIVERFASt Fibrosis score	LIVERFASt Activity score	APRI
HBeAg(-)	77%	82%	27%
HBeAg(+)	89%	62%	12%











CONCLUSION

LIVERFASt tests are reliable non-invasive tools for screening HBV infected patients.

LIVERFASt is detecting and discriminating different phases of liver disease, with better performances than APRI or FIB-4.

Monitoring of HBV infected patients could be improved by LIVERFASt.

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Disclosures

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