FibroTest/FibroMax Scientific Publications

Abstracts & Posters for EASL 2019

EASL 2019

External validation of an algorithm combining multi-analyte blood tests (FibroTest-LCR1-LCR2) for identifying subjects at risk of hepatocellular carcinoma among patients with chronic liver disease

V Peta, M Ziol, F Imbert-Bismut, A Sutton, M Munteanu, F Charlotte, O Lucidarme, T Pham, O Scatton, Y Ngo, A Ngo, O Deckmyn, D Thabut, V Ratziu2, C Housset, T Poynard, P Nahon.

The early non-invasive detection and prediction of hepatocellular carcinoma (HCC) in patients with chronic liver disease, without or with cirrhosis is needed.

The present study proposed to externally validate on the cohort of Bondy-Hospital (France) the previously published sequential algorithm combining, FibroTest (FT) and two multianalyte-tests for liver cancer risk (LCR1-LCR2 patents pending) which increased the performance of AFP alone as shown in the construction and validation cohorts FibroFrance (NCT01927133; Peta V. et al Aliment Pharmacol Ther 2018).

Background: Authors hypothesized that certain FibroTest components mediating hepatoprotection could be associated with the development of HCC.

The aim was to externally validate the sensitivity (Se) and the 5-years prognostic value of FT-LCR1-LCR2 sequential algorithm compared to the standard AASLD surveillance (F4+/+-AFP).

Method: Patients of the ongoing prospective cohort of Bondy-Hospital, France, who had paired frozen serum with HCC prospectively detected (cases) were matched to controls who had not developed HCC during a similar follow-up (≥ 1 control for 1 HCC) using gender, age and FibroTest fibrosis stages, blindly to LCR1-LCR2 results. The performance of FT-LCR1-LCR2 algorithm {high LCR2 (LCR2+) in pts with cirrhosis (F4+/LCR2+), or in pts without cirrhosis but with high LCR1 (F0123/LCR1+/LCR2+)}, was assessed and compared (Se and 5-yr survivals without HCC) with the standard AASLD surveillance (F4+/+-AFP). HCC diagnosis was either confirmed by biopsy, or suggested by non-invasive Barcelona criteria, or reported by death certificate.

Results: 159 patients were followed prospectively (median 5.1yr (IQR 2.5-7.1)), including 51 who had developed HCC (31 with cirrhosis and 20 without) and 108 controls (56 with cirrhosis and 52 without).

The sensitivity of FT-LCR1-LCR2 algorithm was higher vs standard surveillance: 78.4 vs 60.8 (p=0.002} (Table), and the 5 years-survival without HCC was 0.90 (0.81-0.99) vs. 0.77 (0.67-0.86; Logrank P=0.003) according to FT-LCR1-LCR2 predetermined cutoff respectively. Similar results were observed in patients of 50 years of age or older (Table).

In pts with HCC occurrence only 4/51 (7.8%) had disappearance of the algorithm signal vs 15/108 (13.9%) of controls when repeated in the same 159 pts, 1.5 yr (IQR 1.1-2.4) later, associated with an increase per year of LCR2, +0.014 (SE = 0.02) for cases vs 0.00 (0.01) for controls (Kruskal-Wallis P = 0.003).

Conclusion: The FibroTest-LCR1-LCR2 algorithm was validated in an independent external cohort for the prediction of HCC.

Table: Performance of LCR1 in F0123, and sequential LCR1-LCR2 algorithm in all

	ALL n (%)		**50 years of age and older**	
	HCC	**Controls**	**HCC**	**Controls**
LCR1 in F0123	**20**	**52**	**19**	**42**
LCR1 + inclusion	20 (100)	49 (94.2)	19 (100)	42 (100)
LCR1- inclusion	0 (0)	7 (5.8)	0 (0)	0 (0)
FT-LCR1-LCR2 algorithm all	**51**	**108**	**47**	**92**
FT-LCR1-LCR2 + inclusion	40 (78.4)	66 (61.1)	37 (78.7)	62 (67.4)
FT-LCR1-LCR2-inclusion	11 (21.6)	42 (38.9)	10 (21.3)	30 (32.6)
Standard AASLD algorithm all	**51**	**108**	**47**	**92**
Cirrhosis	31 (60.8)	56 (51.9)	28 (40.4)	50 (54.3)
No cirrhosis	20 (39.2)	42 (48.1)	19 (59.6)	42 (45.7)

ORAL COMMUNICATION

PS-191

Parallel session: Non-invasive assessment of liver disease

Saturday, 13 April
09:30 - 09:45

Mass spectrometric analysis of serum haptoglobin fucolysation in patients stratified according to fibrosis stages, and the presence of hepatocellular carcinoma.

V Peta, D Lubman, Z Jianhui, R Keyvan, S Huguet, F Imbert- Bismu, G Bolbach, G Codic, L Matheron, C Housset, T Poynard.

In the present study, BioPredictive's research team proposed to construct a new algorithm (LCR3) in order to improve the performances of current HCC biomarkers.

Background and aims: Serum haptoglobin (Hp) is a reporter molecule for aberrant glycosylation in liver disease. Bifucosylated tetra-antennary haptoglobin glycan (fHp), has been used as a potential marker for primary liver cancer (HCC), but its specificity according to severity of fibrosis has never been assessed.

The aim was to assess if fHp was associated with HCC independently of the fibrosis stage and could increase the performance of the standard test (AFP), and not-standard tests (AFPL3, PIVKA).

Methods: From a prospective cohort, we retrospectively selected patients (Pts) with available frozen serum, 110 with contemporaneous HCC for assessing the sensitivity, and for assessing the specificity in versus 140 controls without HCC, including 81 with non-cirrhotic stages (F0 to F3) and 59 Pts with cirrhosis with the 3 classes of severity (F4.1, F4.2, F4.3), according to FibroTest cutoffs (JHepatol 2014).

Applicability was defined as Hp ≥0.3mg/L enabling the identification of fHp.

LCR3-Algorithms (patent pending) were constructed combining fHp, total Hp, GGT, apoA1, alpha-2-macroglobulin, with and without AFP-AFPL3-PIVKA, adjusted for age and gender. AFP and AFP-L3 were measured on a μTASi30 analyzer (Wako) and PIVKA by Lumipulse® G120 analyzer (Fujirebio). The presence of fHp was assessed by MALDI-TOF analysis of Hp purified using an anti-Hp antibody immobilized HPLC column. The N-glycans were released with PNGaseF, desialylated with neuraminidase, purified and permethylated prior to MALDI-TOF-TOF MS analysis.

Results: are presented in the below Table.

FfHp alone had in intention to diagnose Se=0.57, Sp=0.89 and per protocol Se=0.74, Sp=0.88.

Among these fibrosis-adjusted Pts the best AUROC (95%CI) was obtained by LCR3 algorithm with fHp-AFPL3-PIVK 0.92 (0.86-0.95) vs 0.82 (0.75-0.87;P=0.006) for standard AFP, 0.84 (0.77-0.89; P =0.02) for AFPL3 and 0.85 (0.78-0.90;P=0.04) for PIVKA. The false positive rate was 33% among Pts with severe cirrhosis.

Conclusion: Fucosylated Haptoglobin was strongly associated with the presence of HCC and permitted to improve the performances of current HCC biomarkers.

Table. Results : Applicability, sensitivity (Se), specificity (Sp) of FfHp according to fibrosis stage, age and Gender

Fibrosis stage	HCC n	fHp+ True positive NA (%)/n (% = Se)	Age ≥ 50yr (%)	Male (%)	controls n	fHp+ False positive NA%/n (% = 1-Sp)	Age ≥ 50yr (%)	Male (%)
F0	2	0 (0)/1 (50)	1 (50)	1 (50)	27	0 (0)/0 (0)	12 (44)	12 (44)
F1	4	0 (0)/3 (75)	4 (100)	4 (100)	14	0 (0)/1 (7)	5 (36)	5 (36)
F2	5	0 (0)/4 (80)	2 (5)	2 (40)	21	0 (0)/0 (0)	12 (57)	12 (57)
F3	10	0 (0)/7 (70)	9 (90)	9 (90)	19	1 (5)/1 (5)	11 (58)	11 (58)
F4.1	21	2 (12)/13 (62)	16 (21)	16 (76)	19	4 (21)/4 (21)	16 (84)	16 (84)
F4.2	36	11 (31)/18 (50)	31 (86)	31 (86)	19	8 (42)/2 (11)	17 (90)	17 (90)
F4.3	24	11 (46)/11 (46)	22 (24)	22 (92)	21	7 (33)/7 (33)	14 (67)	21 (68)
Total	**102**	**24 (14)/58 (57)**	**91 (89)[2]**	**85 (83)[1]**	**140**	**20 (14)/15 (11)**	**87 (62)**	**87 (62)**

NA: not applicable [1]P < 0.001 between HCC and controls [2]P = 0.005 between HCC and controls

POSTER

THU-484

Poster: Liver tumours: Experimental and pathophysiology

Thursday, 11 April
09:00 - 19:00

Comparison of CAP, MRI-PDFF, SteaTotest, FLI and HSI performances for diagnosing NAFLD and NASH in morbidly obese patients undergoing bariatric surgery

P Garteiser, L Castera, M Coupaye, S Doblas, D Calabrese, S Ledoux, P Bedossa, M Esposito-Farese, F Dib, S Msika, B van Beers, P Jouet

The present abstract has proposed the direct comparison of the performances for assessing NAFLD steatosis and NASH of the main noninvasive methods, imaging and serum biomarkers, in morbidly obese patients undergoing bariatric surgery.

Background and aims: Non-invasive methods for diagnosing NAFLD and NASH have not been well studied in morbidly obese patients.

The aim of the present study was to compare prospectively the performance of MRI-PDFF, CAP, SteatoTest, hepatic steatosis index (HSI) and fatty liver index (FLI) for diagnosing NAFLD (steatosis > 5%), grading steatosis and detecting non-alcoholic steatohepatitis (NASH) in morbidly obese patients undergoing bariatric surgery.

Method: Liver biopsy (central reading by PB) was used as reference for steatosis grading (absent, mild > 5%, moderate > 33%, and severe > 66%) and NASH diagnosis (FLIP algorithm). MRI-proton density fat fraction (PDFF) and T2* relaxation rate were measured in an open-bore, vertical field 1.0T scanner. The controlled attenuation parameter (CAP) was measured using transient elastography (TE, FibroScan, Echosens, France), using the XL probe. Diagnostic performances were measured using area under ROC curve (AUC) and compared using the DeLong methods.

Results: One hundred and fifty two patients underwent liver biopsy of whom 128 out of 130 had successful MRI (failure rate: 1.5%) and 112 out of 142 had successful CAP and TE (failure rate: 21%; TE vs MRI failure rates $p < 0.0001$). Finally, 97 patients (mean age 41 ± 10 yrs, female gender 86 %, BMI 44.4 ± 5.4) had all tests without fail and available. Histology was as followed: steatosis absent 23; > 5%: 21; > 33% 25; > 66% 28; NASH 31%. Fibrosis: F0 48%; F1 40%; F2 10%; F3 2%.

Comparative performances of the 5 methods are shown in Table 1.

MRI-PDFF had significantly better diagnostic accuracy than CAP for moderate ($p < 0.003$) and severe steatosis ($p < 0.002$) and NASH ($p < 0.006$), but not for mild steatosis. MRI-PDFF also outperformed the three biological scores for mild and moderate steatosis. Regarding severe steatosis, MRI-PDFF performed better than HSI and FLI but not better than SteatoTest. CAP performance did not differ from those of biological scores.

Conclusion: In morbidly obese patients undergoing bariatric surgery, MRI-PDFF is an accurate diagnostic method for grading steatosis and detecting NASH. CAP has performance similar to that of MRI-PDFF for detecting mild steatosis and could be used as a first-line diagnostic method for the diagnosis of NAFLD in these patients.

Figure:

AUC (95% CI)	MRI-PDFF	CAP	SteatoTest	HSI	FLI
NAFLD (S > 5%)	0.97 (0.94-1.00)	0.82 (0.70-0.94)	0.77 (0.66-0.88)	0.74 (0.62-0.85)	0.74 (0.63-0.86)
S > 33%	0.97 (0.94-1.00)	0.78 (0.69-0.88)	0.77 (0.68-0.86)	0.72 (0.61-0.83)	0.68 (0.57-0.79)
S > 66%	0.93 (0.88-0.98)	0.75 (0.65-0.85)	0.81 (0.72-0.90)	0.72 (0.62-0.82)	0.70 (0.60-0.81)
NASH	0.82 (0.70-0.90)	0.68 (0.57-0.79)	NA	NA	NA

POSTER

SAT-280

Poster: NAFLD: Diagnostics and non-invasive assessment

Saturday, 13 April
09:00 - 17:00