



Two new blood tests for identifying patients with chronic liver diseases, at high risk of primary liver cancer

T. Poinard^{1,2}, V. Peta³, M. Munteanu³, J. Moussalli¹, M. Rudler¹, P. Lebray¹, J. Massard¹, R. Pais¹, L. Bonyhay¹, F. Charlotte¹, V. Thibault¹, O. Lucidarme¹, D. Eyraud¹, E. Savier⁴, O. Scatton¹, M.A. Valantin¹, Y. Ngo⁵, A. Ngo⁵, F. Drane⁵, F. Bismut⁴, L. Fartoux⁴, O. Deckmyn⁵, P. Cacoub⁴, O. Rosmorduc⁴, C. Housset⁶, D. Thabut⁴, V. Ratziu⁴. ¹APHP, Hepatology, Paris, France; ²UPMC, UMR938; ³BioPredictive, Research, Paris, France; ⁴APHP; ⁵BioPredictive; ⁶UPMC Email: tpoinard@teaser.fr

Background and Aims: The identification of patients (pts) with chronic liver disease and a high-risk profile of primary liver cancer (PLC) is needed. We hypothesized that certain FibroTest (FT) components mediating hepatoprotection could be predictive of the development of PLC. The main aim was to assess the predictive value of two new blood tests in pts with chronic liver disease who underwent FT in the prospective FibroFrance cohort NCT01927133 since 1997.

Method: 2 panels of components were constructed (Patents pending) in a baseline population (P0) using AUROCs and logistic regression, one (HR-Test) to identify pts with a high-risk profile and one combining HR and alpha-fetoprotein (HR-AFP). Their prognostic values were longitudinally assessed using KaplanMeier, Cox model and AUROCs in pts who did not develop PLC at least 1 year (yr) after baseline (P1), and in a subpopulation who received at least 2 tests to assess intra-patient variability (P2).

Results: 9,925 pts were included in P0, 34%, 20%, 12%, 5% and 29% with CHC, CHB, NAFLD, ALD and other or mixed causes, respectively. The HR-Test for the diagnosis of 134 contemporaneous PLC had an AUROC (95%CI) = 0.903 (0.874–0.926) that was higher than FT (0.877 (0.845–0.903 p = 0.01) and AFP 0.810 (0.725–0.862 p = 0.03). In P1, 226 incident PLC (98% HCC) occurred/9791 pts, with a 15-yr-survival without PLC (SwC) 95%CI = 90% (88–92). Pts with an HR-Test <0.25 (HR- n = 6020) had SwC = 99.3% (99.0–99.6) at 10yr and 97.7% (96.2–99.1) at 15yr (28 PLC), compared to pts ≥0.25 (HR+ n = 3771) 91.1% (89.6–92.5) at 10yr and 84.5% (80.9–88.1) at 15yr (198 PLC). The risk (hazard-ratio) of PLC was 12.7 (9.6–16.6 p < 0.0001) times greater in the HR+ than HR- pts (Figure). PLC occurred less often in HR- than in HR+ pts, whatever the cause of liver disease: 14/1727 vs 114/1637, 6/1532 vs 27/475, 4/682 vs 20/416, and 2/159 vs 27/317, in CHC, CHB, NAFLD, and ALD respectively (all p < 0.001). HR-AFP had an AUROC = 0.860 (0.833–0.883) which was higher than that of single tests: AFP (0.740; 0.698–0.778; p = 0.01), HR1 (0.802; 0.772–0.828 p = 0.0001) and FT (0.813; 0.784–0.838 p = 0.0001). In P2, among 1818 pts with at least 2 repeated HR-tests, 16 incident PLC occurred at 10yr; (SwC = 70%; 49–91). When repeated 5.2yr (5.0–5.4) later, the HR-Test had a higher AUROC than the first test 0.851 (0.796–0.892) vs 0.772 (0.699–0.829) at baseline (p = 0.001). The results of Cox sensitivity analyses, which take into account the repeated tests, the impact of antiviral treatment, and HIV infection were similar. These results were confirmed by internal validation but external validation must be performed.

Conclusion: The HR-Test identified a group of pts at high risk of PLC among those with CHC, CHB, NAFLD and ALD. Combining the HR-Test and a specific cancer marker such as AFP significantly increased the value of a single test.

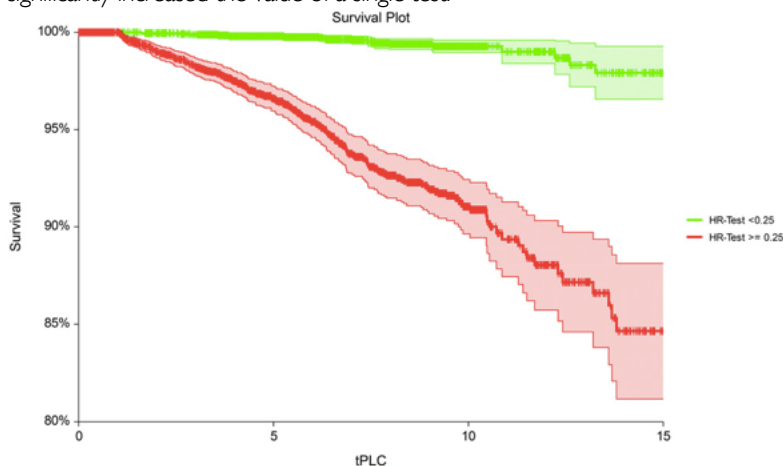


Figure 1: 15-year survival without occurrence of primary liver cancer (95% CI) in patients with HR-Test <0.25 versus those ≥ 0.25

POSTER
FRI-128

HCC

Fri Apr 13th

Appropriateness of inclusion criteria according to transaminases ALT in studies assessing performances of non-invasive tests in type-2 diabetes patients (T2D)

T. Poynard¹, F. Charlotte¹, V. Paradis¹, Y. Ngo², M. Munteanu², V. Peta², R. Pais³, V. Ratziu³, C. Laouenan⁴, P. Stanislas³, C. Boitard⁵, D. Valla³. ¹APHP, Hepatology, Paris, France; ²BioPredictive, Research, Paris, France; ³APHP, Hepatology, France; ⁴APHP, Statistics; ⁵APHP, Diabetology Email: tpoynard@teaser.fr

Background and Aims: In NASH diagnostic studies, biopsies are performed for routine clinical care in the investigation of abnormal liver function tests, often defined as "increased ALT" (iALT). This criteria, which varied according to age and gender, can impact the estimation of NASH-test performances by selecting risk factors not representative of the T2D context of use. The risk of significant fibrosis (F2F3F4), a recognized definition of significant liver disease, according to ALT value, is unknown (DiabetesCare 2017). To assess this risk, we compared T2D with and without iALT using non-invasive tests such as FibroTest (FT), routinely used in France since 2002 and validated as alternatives to biopsy for F2F3F4 diagnosis (LancetGastro 2017).

Method: We retrospectively analyzed T2D (receiving T2D treatment, or with fasting glucose ≥ 7 , in the prospective FibroFrance cohort (NCT01927133). iALT was defined as ALT > 30 IU for men, and > 20 IU for women. T2D were followed by liver tests to assess F2F3F4 with standard cut-offs (Fibrotest 0.48, Elastography TE-M, TE-XL or SWE, all 7.1 kPa). The primary endpoint was the presence of F2F3F4 in non-iALT, and any significant difference in the main prognostic characteristics between the 2 groups: gender, age, and severity defined as the Kaplan-Meier overall survival at 10 yr. Prognostic value of iALT was also assessed after taking into account age and gender by Cox model.

Results: 230 consecutive T2D without other cause of liver diseases, were included. During a mean follow-up of 7 years 157/230 (68%) had iALT and 73/230 (32%) had non-iALT. 77 pts had at least one liver biopsy. The risk of significant liver disease in the non-iALT was not negligible, with 45% of significant activity A2A3A4 among pts with biopsy, and prevalence of F2F3F4 35%, 30% and 62%, by biopsy, FT and TE, respectively. The spectrum was significantly different, with more women, more pts younger than 65 years of age, and with a higher 10- year overall survival rate in iALT group (26 deaths) vs non-iALT group (35 deaths) (Table 1), but the significant difference disappeared when adjusted by age and female gender; risk-ratio = 0.69 (95%CI 0.40–1.16; p = 0.16).

Conclusion: T2D without increased ALT should be included in diagnostic studies evaluating NASH-tests to prevent a spectrum effect and a biased control population.

p = 0.16.

Table 1: characteristics of T2D patients with or without increased ALT transaminases

	Increased ALT n = 133	Not increased ALT n = 97	P value
10-yr cumulative survival (95% CI)	70% (58–82)	56% (43–69)	0.02
Age younger than 65 years	95/133 (71%)	57/97 (59%)	0.04
Female gender	65/133 (49%)	24/97 (25%)	0.0002
F2F3F4 FibroTest > 0.48	58/133 (44%)	29/97 (30%)	0.04
F2F3F4 Elasticity ≥ 7.1 kPa	62/80 (78%)	28/45 (62%)	0.10
Stage F2F3F4 FLIP-CRN biopsy	31/52 (60%)	8/23 (35%)	0.08
Grade A2A3A4 FLIP biopsy	40/52 (77%)	10/22 (45%)	0.01
No steatosis or steatosis $< 5\%$ biopsy	6/54 (17%)	4/23 (11%)	0.45

POSTER
FRI-435

NASH

Fri Apr 13th

Screening for liver fibrosis using transient elastography by fibroscan and fibrotest in type 2 diabetic patient

J. Sandler, E. Vinnitskaya, I. Bakulin, V. Keyan, A. Polukchina, T. Chaimenova. Moscow Clinical Scientific Center, Hepatology, moscow, Russian Federation Email: sandlerjulia2012@gmail.com

Background and Aims: Patients with type 2 diabetes (T2D) are at risk for non-alcoholic fatty liver disease (NAFLD) leading to advanced fibrosis, cirrhosis, and liver cancer. We examined the efficacy of a screening strategy with noninvasive fibrosis biomarkers, FibroTest and FibroMax (FT, BioPredictive, France) and transient elastography (TE, Fibroscan, Echosens, France) in patients with T2D without previous history of liver disease.

Method: We prospectively studied 104 patients without a history of liver disease seen for T2DM. The biomarker data were obtained, and patients with presumed advanced fibrosis were reinvestigated by a hepatologist using, if necessary, ultrasonography, endoscopy, or liver biopsy in order to confirm fibrosis.

Results: 104 patients were included, mean age 56.4 Å 9.5yrs. (range of 29–82), 60.6% females, mean (range) BMI 33.3 Å 5.1 (22–47), 72.1% (> = 30 kg/m). According to the FibroTest biomarkers, advanced fibrosis was diagnosed in 44 out of 104 patients (42%), while the TE biomarkers confirmed the diagnosis in 45% of cases (47/104). Among of 104 patients advanced fibrosis was confirmed in 42 subjects (40%), liver cirrhosis - in 11 patients (10.6%), including 2 cases of esophageal varices, 9 cases of splenomegaly and thrombocytopenia. According to SteatoTest 66% patients had advanced steatosis (cutoff score > = 0.76) and 39.8% according to CAP (dB/m), cutoff score > = 302.0. In patients who were 50 years or older, the prevalence of confirmed advanced fibrosis was 38.5% (p-value = 0.00023 versus p-value = 0.04249). FibroTest diagnosed F4 in 10 subjects (10.4%). The comparative analysis between these results and those of the TE showed discordance in 21 cases (20.2%). The TE performed false positive diagnosis in 9 cases, while FT only in 3. At the same time, FT registered 1 case of false negative result, while TE indicated it in 4 patients. Among 44 patients with advanced fibrosis (F2-F4) according to FT normal ALT level was in 29.6% cases (p-value = 0.58267) and 45.5% (p-value = 0.00034) had normal GGT.

Conclusion: Noninvasive fibrosis biomarkers, FT and TE, might be used for the detection of advanced fibrosis in patients with T2DM. ALT and GGT are not a reliable markers to detect fibrosis.

Improvement of liver steatosis achieved by probiotics in patients with nonalcoholic fatty liver disease

I. Copaci, A. Franculescu, L. Micu, G. Chiriac, M. Mihaila, E.L. Iliescu. Fundeni Clinical Institute, Department of Internal Medicine, Bucharest, Romania Email: laurentiumicu2000@yahoo.com

Background and Aims: Diet-induced weight loss and probiotics are associated with changes in the gut microbioma composition in humans and mice. The aim of the study was to assess the efficacy of this combination in patients with nonalcoholic fatty liver disease (NAFLD).

Method: In a prospective observational study, 92 overweight subjects (54 men, 38 women) with steatosis were recruited after excluding other etiologies. Patients were assigned a moderate caloric restriction (1200–1500 Kcal/day), with less than 30% calories from fat. Group A (40pts) received a combination of B. longum and L. rhamnosus (ZirComBi, Alfasigma), 1 sachet/day, 12 days/month for six months. Group B (52 pts) remained only on diet. Blood samples (biochemistry, HOMA-IR, cytokine levels, steatostest) were collected at entry and at months 6 and 12. All subjects underwent abdominal CT to assess visceral and subcutaneous adipose tissue area (VAT/SAT).

Results: After 12 months, baseline descriptive characteristics (weight, BMI, waist circumference) decreased significantly. Biochemical parameters that decreased significantly in group A vs group B were: GGT (32.2 Å 14 vs 43 Å 18; p = 0.01), ALT (33.8 Å 14.3 vs 59.1 Å 22.5; p = 0.05) and HOMA-IR (3 Å 0.43 vs 4.83 Å 0.65; p = 0.018). Steatostest improved significantly (0.38 Å 0.13 vs 0.68 Å 0.16; p = 0.02). Modification of cytokine levels was significant for leptin (5.9 Å 2.8 vs 13.6 Å 4.7 ng/ml; p = 0.018), adiponectin (11.6 Å 4.9 vs 7.1 Å 3.1 µg/ml; p = 0.003) and IL-6 (1.2 Å 0.3 vs 2.8 Å 2.2 pg/ml; p = 0.02). VAT/SAT did not differ significantly. Multivariate logistic regression showed the following factors related to improved steatosis: BMI < 25 kg/m², ALT < 42 IU/l, leptin < 10.5 ng/ml, adiponectin > 8.4 µg/ml, and treatment with probiotics.

Conclusion: 1. A 6-month course of lifestyle intervention and probiotics reduces steatosis. 2. Association of probiotics significantly influences ALT, HOMA-IR, IL-6, adipocytokines and steatosis.

POSTER
FRI-473

NASH

Fri Apr 13th

POSTER
FRI-491

NASH

Fri Apr 13th

Prognostic value of 2D-shear wave elastography for staging cirrhosis in chronic liver diseases in two severity classes according to liver-related complications

P. Pollo-Flores¹, M. Munteanu², A. Ngo³, Y. Ngo³, E. Luckina⁴, T. Phim⁵, H. Perazzo⁶, L. Bonyhay⁷, M. Rudler⁷, P. Lebray⁷, D. Thabut⁸, V. Ratziu⁸, T. Poynard⁸. ¹CAPEs, UFF Internal Medicine Department, Niteroi, Brazil; ²Biopredictive, APHP, Paris, France; ³Biopredictive, APHP, Paris, Brazil; ⁴APHP, Inserm; ⁵APHP, Biopredictive; ⁶FIOCRUZ, Infectious National Institute, Rio de Janeiro, Brazil; ⁷APHP, Paris, France; ⁸APHP, UPMC, Paris, France Email: priscilapollo96@gmail.com

Background and Aims: In chronic liver disease (CLD), FibroTest (FT, BioPredictive), and transient elastography (TE M-probe, Echosens), are associated with increased overall and liver-related mortality and morbidity. Moreover, FT and TE-M were validated as markers of occurrence of cirrhosis without complications (F4.1), oesophageal varices (EV) grade 2 or more (F4.2), and severe complications (SC) (F4.3) – EV rupture, encephalopathy, ascites and hepatocellular carcinoma (HCC) (J Hepatol 2014). The aim of this study was to extend the validation of elastography by 2D-shear wave elastography (2DSWE), as a prognostic marker of occurrence of cirrhosis without complications (F4.1) versus cirrhosis with EV and SC (F4.2-F4.3).

Method: 3,853 patients (pts) with CLD were pre-included prospectively from Jan-2012 to Dec-2013. 3627pts had 2D-SWE, and 2686pts (74.1%) had all methods. Appli-2D-SWE was defined after excluding minimal stiffness <0.2 kPa. Cirrhosis was defined by FibroTest ≥ 0.74 and TE-M ≥ 12.5 kPa respectively. The applicable 2D-SWE, TE-M, -XL and M or XL and FT were, respectively, 90.4%, 80.0%, 90.8%, 94.5% and 99.5%.

Results: 585pts with applicable-2D-SWE and cirrhosis as per FT or TE-M-XL were followed up for a median (range) 30(0–62.3) months and 13(4.2%) died. None had history of complications, after 30 months had occurred 47 varices (F4.2, incidence of 8.0%) and 50 severe complications (F4.3 8.6%), including HCC in 20 (3.4%). The survivals (95%CI) without EV/SC were: 78.8% (69.4–88.2) in the group F4.23 (2D-SWE ≥ 20 kPa); 89.9% (84.3–95.5) in F4.1 (12.5 kPa \geq 2DSWE < 20 kPa, $p = 0.025$ vs F4.23); and 94.5% (91.4–97.6) in the group without cirrhosis (noF4) ($p = \text{NS}$ vs F4.1). (Figure 1). Among pts with concomitant appli-TE, FT and 2D-SWE, the prognostic AUROCs (95% CI) for esophageal varices and severe complications were: 0.94 (0.90–0.97), 0.92 (0.87–0.95, $p = \text{NS}$ vs TE) and 0.79 (0.69–0.86, $p < 0.01$ vs TE and vs FT), respectively.

Conclusion: Liver biomarkers, such as 2D-SWE, have prognostic values in patients with CLD for predicting varices and severe complications in cirrhotic patients. Previously validated FT and TE predictions of varices and severe complications were comparable and both were superior to 2D-SWE.

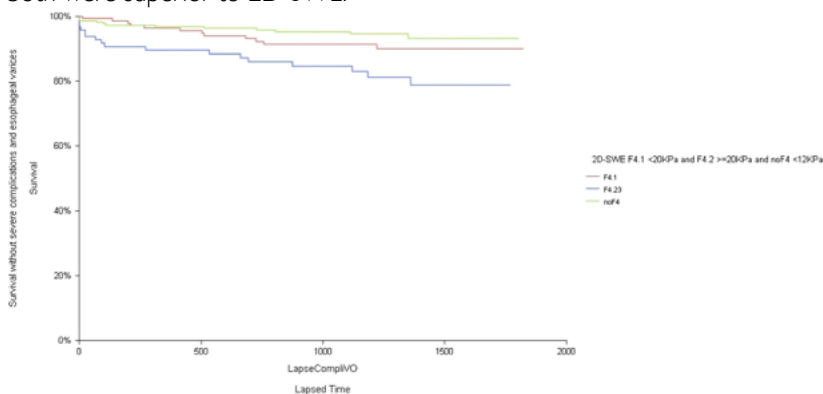


Figure 1: (abstract: SAT-066): Survival Curves according to 2D-SWE classes of liver disease severity.

POSTER
SAT-066

PROGNOSIS

Sat Apr 14th

Long term prognostic value of the FibroTest in patients with non-alcoholic-fatty-liver disease (NAFLD), compared to chronic hepatitis C (CHC), B (CHB), and alcoholic liver disease (ALD)

M. Munteanu¹, J. Moussalli², M. Rudler², P. Lebray², H. Perazzo², J. Massard², R. Pais², F. Charlotte², V. Thibault², L. Olivier², L. Hannoun², M.A. Valantin³, Y. Ngo¹, F. Drane¹, Fl. Bismut³, O. Deckmyn¹, C. Housset⁴, D. Thabut⁴, V. Ratziu⁵, T. Poynard². ¹BioPredictive, Research, Paris, France; ²2APHP, Hepatology, Paris, France; ³3APHP, MIT, Paris, France; ⁴INSERM, UMR938, Paris, France; ⁵UPMC, Hepatology, France Email: tpoynard@teaser.fr

Background and Aims: Although the FibroTest (FT) has been validated as a biomarker for the diagnosis of the stages of fibrosis in NAFLD with results similar to those in CHC, CHB and ALD, it has not yet been confirmed for the prediction of liver related death (Lrd), possibly due to the lower incidence of Lrd and the higher non-liver-related causes of mortality (APT 2014). The primary aim was to assess the long-term prognostic value of FT for Lrd in NAFLD.

Method: All patients (pts) in the prospective FibroFrance- NCT01927133 cohort who underwent a FT between 1997 and 2012 were pre-included. Mortality status was obtained from the physician, the hospital or the national register. The cause of death was classified as Lrd, "cardiovascular" (CVrd) and "other". Survival analyses (events defined as death or transplantation) were based on univariate (KaplanMeier, Logrank, AUROC) and multivariate (Cox-Risk-Ratio (CRR)) analyses, taking into account age, gender and response to antiviral treatment as covariates. The independent prognostic value of each FT component was assessed for each liver disease. The main endpoint was the performance of the FT (AUROC/CRR), for Lrd, compared to results observed in CHC, the most validated population.

Results: A total of 7,012 pts were included; 1,070, 3,420, 2,027 and 495 with NAFLD, CHC, CHB, and ALD, respectively. At baseline, NAFLD pts were older than those with CHC (median;95%CI), 57(56-58) vs 48 (47-49) years old; ($p = 0.0001$), similar for male prevalence 57% vs 59%; ($p = 0.30$), and had a lower severity of fibrosis presumed by FT (mean FT;95%CI and % cirrhosis (F4) (0.24;0.22-0.25;6.8% F4) vs (0.45;0.43-0.46; 21.7% F4); ($p = 0.0001$). Mean follow-up was 7 years. Survival at 15 years without Lrd (SwLrd) in patients with NAFLD was 94% (91-97; 38 Lrd) and 91% (89-92; 223 Lrd; $p = 0.007$) in CHC. The prognostic value (AUROC/CRR) of FT for SwLrd in patients with NAFLD was highly significant ($p = 0.0001$). .92(0.87-0.95)/1638(342-7839) and not different from CHC. 89(0.87-0.91)/2657(993-6586). Staging of NAFLD into 7 categories using FT predicted decreasing 5- year SwLrd in F4.3 vs F4.2 and F4.1 (Figure) as validated previously in CHC and CHB (J Hepatol 2014). The prognostic value of FT in NAFLD. 56(0.51-0.60)/3.9(2.4-6.4) for overall survival (OS) (n death = 249), was significant ($p = 0.0001$) but lower than that observed in CHC (n =489)0.76(0.73-0.78)/32(22-46), as expected because of the lower incidence of Lrd in NAFLD vs CHC. FT was also significant ($p = 0.0001$) for the prediction of CVrd. .62(0.53-0.70)/vs. 58(0.51-0.65) in CHC, driven by a decrease in Apo1 and older age. Using CHB/ALD instead of CHC reported the same results.

Conclusion: The FibroTest has a high predictive value for survival without liver disease or transplantation in patients with NAFLD, similar to that observed in patients with CHC, CHB, and ALD.

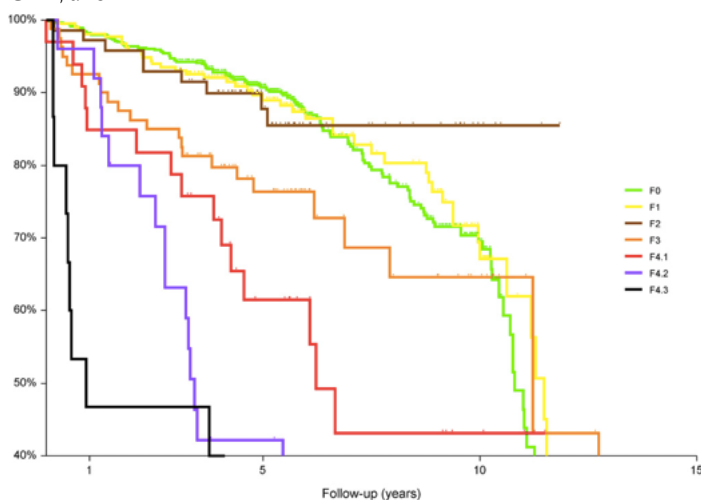


Figure: Survival according to 7 stages of fibrosis presumed by the FibroTest in 1,070 NAFLD patients.

ORAL SESSION
PS-183

THIERRY POYNARD

NASH

Sat Apr 14th
09:30-09:45

PARALLEL SESSION:
NAFLD, DIAGNOSTICS
AND NON-INVASIVE
ASSESSMENT

SOUTH 2

Use of noninvasive biomarkers to assess fibrosis regression in cirrhotic patients during nucleos(t)ide therapy

C. Pan¹, N. Izumi², P. Angus³, A. Duseja⁴, E. Nurmukhametova⁵, R. Balabanska⁶, T. Nguyen⁷, J. Yang⁸, L. Lin⁸, A. Gaggari⁸, J.F. Flaherty⁸, M. Subramanian⁸, S. Ryder⁹, W.-L. Chuang¹⁰, P. Marcellin¹¹. ¹NYU Langone Medical Center, NYU School of Medicine, New York, NY, USA; ²Japanese Red Cross Musashino Hospital, Tokyo, Japan; ³Austin Health, Heidelberg, Victoria, Australia; ⁴Postgraduate Institute of Medical Education and Research, Chandigarh, India; ⁵Infectious Clinical Hospital #1 of Moscow Healthcare Department, Moscow, Russia; ⁶Tokuda Hospital, Sofia, Sofiya, Bulgaria; ⁷Research and Education, Inc., San Diego, CA, USA; ⁸Gilead Sciences, Inc., Foster City, CA, USA; ⁹Nottingham University Hospital, Nottingham, England, UK; ¹⁰Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; ¹¹Université Paris Diderot, Hôpital Beaujon, Clichy, France Email: cpan100@gmail.com

Background and Aims: Noninvasive serum biomarkers for the assessment of liver fibrosis are used in monitoring fibrosis progression in CHB patients. However, limited data is available on the usefulness of these biomarkers in evaluating regression of fibrosis in CHB patients with advanced fibrosis or cirrhosis. The aim of this study is to evaluate commonly used and novel serum biomarkers as a tool in monitoring regression of fibrosis in CHB patients with advanced fibrosis on NUC therapy.

Method: Data from patients with baseline FibroTest score ≥ 0.75 were pooled across 2 Phase 3 studies evaluating TAF and TDF (GS-US-320-0108 and GS-US-320-0110). Differences in noninvasive biomarkers were evaluated using descriptive statistics of absolute and change from baseline at Weeks 48 and 96 in all patients. Effect of liver inflammation on the noninvasive biomarkers was evaluated in a subgroup analysis between patients with normal and abnormal ALT per AASLD criteria at Week 48. Noninvasive biomarkers evaluated include: FibroTest, AST-to-platelet ratio index (APRI), fibrosis index based on four factors (FIB-4). Additional analysis using enhanced liver fibrosis panel (ELF), and plasma collagen type III (Pro-C3) will be presented.

Results: 118 patients had FibroTest score ≥ 0.75 at baseline. The mean (SD) absolute values for FibroTest, APRI, and FIB-4 at Weeks 48 and 96 are shown in the Table. All biomarkers showed an improvement (decline) from baseline at Weeks 48 and 96, with the greatest decline occurring during the first 48 weeks. At week 48, 49 patients had normal ALT and 59 patients had abnormal ALT. Patients with normal ALT had numerically lower FibroTest, FIB-4, and APRI at Week 48 compared to those with abnormal ALT. Patients with abnormal ALT at Week 48 had a greater improvement in fibrosis biomarkers from Week 48 to Week 96 compared to those with normal ALT with mean (SD) FIB-4 of -0.22 (0.81) and APRI of -0.08 (0.60).

Conclusion: Improvement observed with FibroTest, FIB-4, and APRI during the first 48 weeks of initial therapy may over estimate improvement of fibrosis and instead show the impact of liver inflammation. Assessment of these biomarkers compared to ELF and Pro-C3 will be presented.

Table: Serum Marker for Fibrosis in Overall Population and Subset of Patients Stratified by ALT Levels at Weeks 48 and 96

Mean (SD) Absolute Value	FibroTest	FIB-4	APRI
Overall	n = 118	n = 111	n = 111
Baseline	0.84 (0.06)	3.71 (2.31)	2.40 (1.95)
Week 48	0.70 (0.17)	2.23 (1.32)	0.71 (0.55)
Week 96	0.70 (0.17)	2.02 (1.28)	0.63 (0.73)
Normal ALT at Week 48	n = 49	n = 48	n = 48
Week 48	0.63 (0.18)	1.86 (0.95)	0.44 (0.27)
Week 96	0.63 (0.19)	1.79 (1.16)	0.41 (0.28)
Abnormal ALT at Week 48	n = 58	n = 56	n = 58
Week 48	0.76 (0.13)	2.55 (1.50)	0.94 (0.61)
Week 96	0.75 (0.12)	2.15 (1.24)	0.80 (0.91)

POSTER
FRI-310

FIBROSIS REGRESSION

Fri Apr 13th

Long-term follow up of patients with chronic HCV and F2 or F3 fibrosis after achieving SVR with DAA-based therapy: results from the Gilead SVR registry

S. Zeuzem¹, M.B. Ferret^{2,3}, E. Gane⁴, I. Jacobson⁵, S.C Gordon⁶, M. Sulkowski⁷, B. Mcnabb⁸, F. Chen⁸, H. Dvory-Sobol⁸, A. Osinusi⁸, D. Brainard⁸, M. Subramanian⁸, A. Ramji⁹, K. Agarwal¹⁰, R. Reddy¹¹, M. Bourliere¹². ¹Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany; ²Hospital Universitario Vall d'Hebron, Barcelona, Spain; ³CIBERehd; ⁴New Zealand Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand; ⁵Department of Medicine, New York University Medical Center, New York, United States; ⁶Henry Ford Health System, Detroit, United States; ⁷Johns Hopkins University School of Medicine, Baltimore, United States; ⁸Gilead Sciences, Inc., Foster City, United States; ⁹Division of Gastroenterology, University of British Columbia, Vancouver, Canada; ¹⁰Kings College Hospital NHS Trust Foundation, London, United Kingdom; ¹¹University of Pennsylvania, Philadelphia, United States; ¹²Department of Hepato-Gastroenterology, Hôpital Saint-Joseph Marseille, Marseille Email: brian.mcnabb@gilead.com

Background: HCV infected patients with F0-F1 fibrosis experienced minimal liver-related morbidity and mortality following sustained virologic response (SVR) with direct-acting antiviral (DAA) therapy. Less is known about the clinical progression of liver disease among HCV-infected patients with F2 or F3 fibrosis who have achieved SVR with DAA regimens.

Methods: Patients enrolled in the Gilead SVR Registry were included in this analysis if they were deemed to have F2 or F3 fibrosis pre-DAA treatment as measured by FibroTest (0.32–0.58 or 0.59–0.72, respectively). Patients could be enrolled upto 60 weeks after initiating DAA-treatment that lead to SVR, and study visits occurred every 24 weeks for up to 144 weeks. Assessments for signs of jaundice, ascites, hepatic encephalopathy (HE), varices, and hepatocellular carcinoma (HCC) and measurement of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Bili), albumin (ALB), prothrombin time (PT), and platelets (PLT), occurred at each visit.

Results: A total of 1,489 and 857 patients with F2 and F3 fibrosis were enrolled, with median (range) registry follow up times of 1.9 (0–3.3) and 1.8 (0–3.2) years, respectively. Of these, 57% and 72% were male and the mean (range) ages were 55 (19–80) and 57 (19–82) years for F2 and F3 patients, respectively. There were 2 and 4 cases of HCC reported in 2509 and 1371 person-years of follow-up time for patients with F2 and F3 fibrosis, respectively. Overall, the prevalence of liver-related events was low at all visits, remaining stable for F2 and numerically decreasing over time for F3 patients (Table). At Week 144, 1 (0.1%) patient with F2 fibrosis had evidence of varices reported and 1 (0.3%) patient with F3 fibrosis had evidence of jaundice reported. Mean week 144 ALT, AST, Bili, ALB, PT, and PLT were within normal limits and comparable to baseline values. Three patients with F2 and 3 patients with F3 fibrosis died, with no causes of death due to liver disease. No liver transplants were reported. There were 4 patients with F2 and 3 patients with F3 fibrosis who experienced virologic failure during follow up; all but one of these patients had clear virologic evidence for reinfection by sequencing.

Liver-Related Event, n (%)	Registry Baseline		Week 48		Week 96		Week 144	
	F2 n = 1,489	F3 n = 857	F2 n = 1,159	F3 n = 640	F2 n = 916	F3 n = 484	F2 n = 677	F3 n = 367
Jaundice	0	1 (0.1)	0	0	0	0	0	1 (0.3)
Ascites	1 (<0.1)	4 (0.5)	0	1 (0.2)	1 (0.1)	0	0	0
Hepatic Encephalopathy	0	1 (0.1)	0	1 (0.2)	0	0	0	0
Varices	0	3 (0.4)	0	2 (0.3)	3 (0.3)	1 (0.2)	1 (0.1)	0

Conclusion: In HCV-infected patients with F2 or F3 fibrosis who achieve SVR with DAA therapy, events including liver-related complications, HCC, death and HCV relapse are rare in the first 144 weeks of follow-up. These data support early treatment of HCV infection and may be useful in guiding monitoring strategies for HCC and other liver-related events following SVR.

POSTER
FRI-366

FIBROSIS REGRESSION

Fri Apr 13th

Prediction of fibrosis improvement in patients with advanced fibrosis due to NASH using a machine learning approach: Unravelling the placebo response

A. Sanyal¹, T. Nguyen², L. Wang², Y. Xiao², C. Jia², R. Xu², S. Djedjos², M. Subramanian², R. Myers², V. Ratziu³, N. Afdhal⁴, J. Bosch⁵, S. Harrison⁶, Z. Goodman⁷. ¹Virginia Commonwealth University, Richmond, VA, USA; ²Gilead Sciences, Inc., Foster City, CA, USA; ³Hôpital Pitié-Salpêtrière, Paris, France; ⁴Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA; ⁵Inselspital, Bern University, Switzerland, and IDIBAPS, University of Barcelona, Spain; ⁶Pinnacle Clinical Research, San Antonio, TX, USA; ⁷Inova Fairfax Hospital, Falls Church, VA, USA Email: asanyal@mcvh-vcu.edu

Background: Fibrosis improvement (FI) is an important endpoint in clinical trials of therapies for NASH. Our aim was to identify predictors of FI using machine learning in patients with advanced fibrosis due to NASH who received the ineffective therapy simtuzumab (SIM).

Methods: A machine learning algorithm (GUIDE v26.4) was applied to data from two Phase 2b trials of SIM in adults with NASH and advanced fibrosis (NASH CRN F3-F4) to develop predictive models for ≥ 1 -stage FI at Week 48 (W48). The trials were stopped due to lack of efficacy so treatment groups were combined for this analysis. We used clinical, histologic, and serum fibrosis marker data to construct models including only baseline (BL) data or BL plus longitudinal data through W48. A variable importance score (VIS) assessed the aggregated variable contribution across the intermediate nodes of a GUIDE tree. Variables with VIS ≥ 0.7 in $\geq 75\%$ of 100 bootstrapped GUIDE trees were considered to be associated with FI. The predictive performance of the models (AUROCs and misclassification error rates) was calculated using 100 bootstrapped GUIDE trees with 10-fold cross validation.

Results: 410/477 randomized subjects (86%) with complete clinical and histologic data were included. 48 subjects (12%) had FI at W48 (F3, 18%; F4, 6.5%). Predictive models including only noninvasive BL data performed well and similarly to full models including histological data (AUROCs 0.79–0.82; Table). Addition of longitudinal data only slightly improved model performance. Variables associated with FI in the full BL model (in $>90\%$ of bootstrap trees) included lower NASH CRN and Ishak fibrosis stage and hepatic α -smooth muscle actin expression. Noninvasive variables identified in both models included lower BL AST, ELF, hyaluronic acid, APRI, FIB-4, FibroTest ($\geq 95\%$ of bootstrap trees), $\alpha 2$ -macroglobulin, NAFLD fibrosis score, TIMP-1, PIII-NP, and serum LOXL2 (75–95% of trees). The optimal GUIDE tree categorized subjects according to BL AST \leq vs. >30 U/l (AUROC 0.70; 95%CI 0.63–0.77) independent of fibrosis stage. FI was identified in 27% (30/110) of subjects with BL AST ≤ 30 U/l vs only 6% (18/300) of those with AST >30 U/l. Similar findings were observed with models restricted to subjects with bridging (F3) fibrosis.

Conclusion: Machine learning models suggest that spontaneous FI over 48 weeks in subjects with advanced fibrosis due to NASH is greatest in those with lower disease severity at BL. These data suggest that the placebo response in clinical trials can be minimized via refinement of patient selection using noninvasive markers

Table: Model Performance for FI at W48

Model	Model Parameters	AUROC (95% CI)	Error Rate (95% CI)
Baseline	Full	0.79 (0.67, 0.86)	0.27 (0.15, 0.52)
	Noninvasive	0.79 (0.70, 0.85)	0.27 (0.17, 0.47)
Longitudinal	Full	0.82 (0.72, 0.89)	0.25 (0.16, 0.39)
	Noninvasive	0.81 (0.73, 0.89)	0.26 (0.14, 0.41)

ORAL SESSION
PS-178

ARUN SANYAL

NASH

Sat Apr 14th
08:15-08:30

PARALLEL SESSION:
NAFLD, DIAGNOSTICS
AND NON-INVASIVE
ASSESSMENT

SOUTH 2

Usage of antiplatelet agents is inversely associated with liver fibrosis in patients with cardiovascular disease

K. Schwarzkopf¹, J. Bojunga¹, S. Rueschenbaum¹, Y. Martinez¹, M.M. Muecke¹, F. Seeger², F. Schoelzel¹, S. Zeuzem³, M. Friedrich-Rust¹, C. Lange¹. ¹Department of Internal Medicine I, J.W. Goethe-University Hospital, Frankfurt, Germany; ²St. Elisabeth Hospital Ravensburg, Department of Cardiology, Ravensburg, Germany; ³University of Frankfurt, Department of Medicine, Frankfurt, Germany Email: katharina.schwarzkopf@kgu.de

Background and Aims: In animal models platelets participate in the development of liver fibrosis, but little is known about the benefit of antiplatelet agents in preventing liver fibrosis in humans. We therefore aimed to explore the relationship between usage of antiplatelet agents and liver fibrosis in a prospective cohort study of patients at high risk of liver fibrosis and cardiovascular events.

Method: Consecutive patients undergoing elective coronary angiography at the University Hospital Frankfurt were prospectively included in the present study. Associations between usage of antiplatelet agents (acetyl salicylic acid, P2Y₁₂ receptor antagonists) and liver fibrosis were assessed in regression models. Furthermore, the relationship between PDGF- β serum concentration, platelets, liver fibrosis and usage of antiplatelet agents was characterized.

Results: Out of 505 included patients, 337 (67%) received antiplatelet agents and 134 (27%) had liver fibrosis defined as a FibroScan® transient elastography value ≥ 7.9 kPa. Usage of antiplatelet agents was inversely associated with the presence of liver fibrosis in uni- and multivariate analyses (multivariate OR = 0.67, 95% CI = 0.51–0.89; p = 0.006). Usage of antiplatelet agents was inversely associated with FibroTest values as well (beta = -0.38, SD beta = 0.15, p = 0.02). Furthermore, there was a significant correlation between platelet counts and PDGF- β serum concentration (rho = 0.33, p < 0.0001), but PDGF- β serum levels were not affected by antiplatelet agents.

Conclusion: There is a protective association between the usage of antiplatelet agents and occurrence of liver fibrosis. A randomized controlled trial is needed to explore the potential of antiplatelet agents as anti-fibrotic therapy in patients at risk for liver fibrosis progression.

ORAL SESSION

PS-109

**KATHARINA
SCHWARZKOPF**

NASH

Fri Apr 13th
17:00-17:15

PARALLEL SESSION:
NAFLD, CLINICAL AND
THERAPY

MAIN PLENARY