FibroScan® FibroMeter™

Clinical Handbook

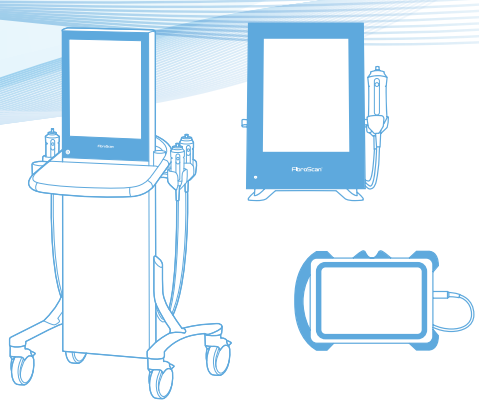
MAIN PUBLICATIONS
BY ETIOLOGIES & APPLICATIONS

echosens™

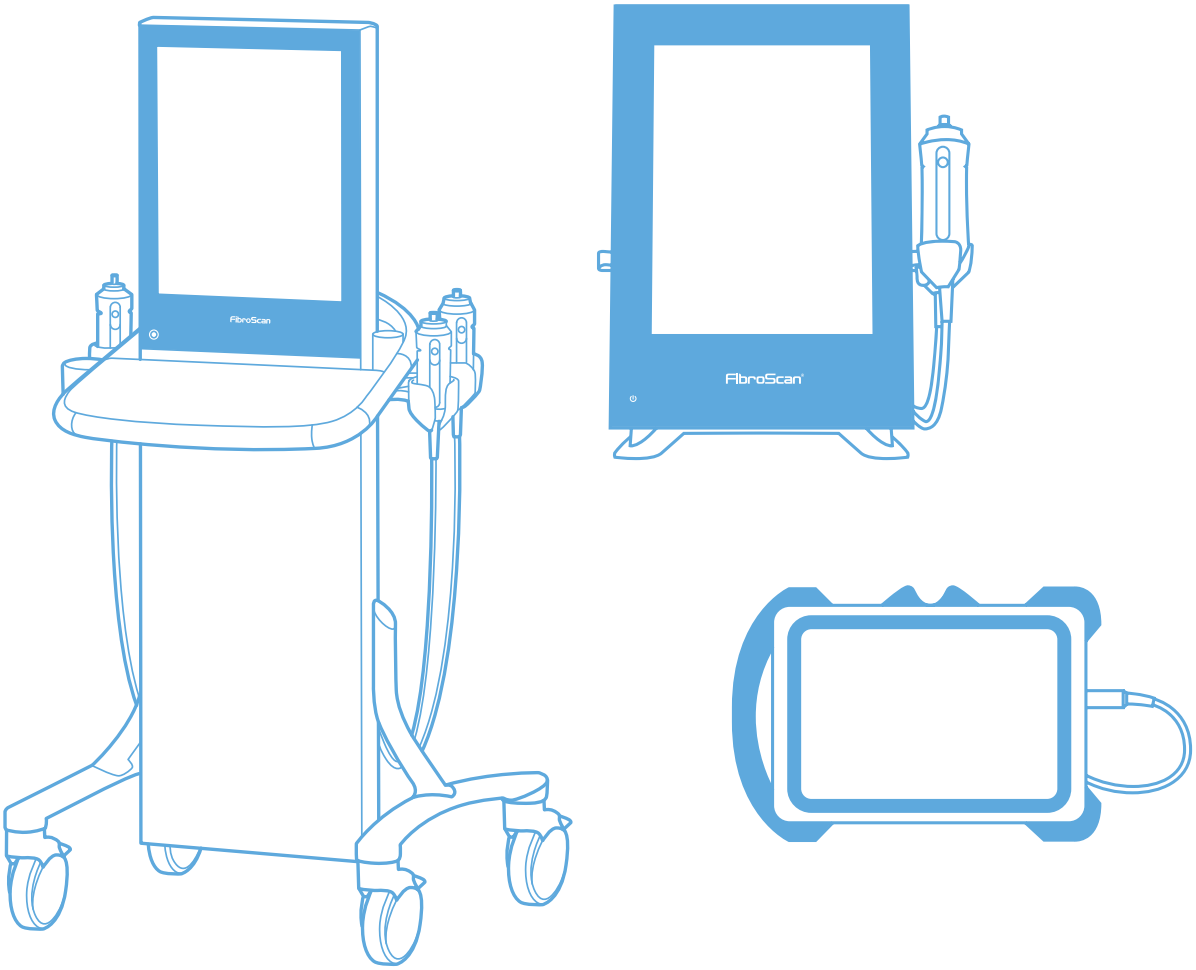
Summary

FibroScan®

FibroMeter™



FibroScan®

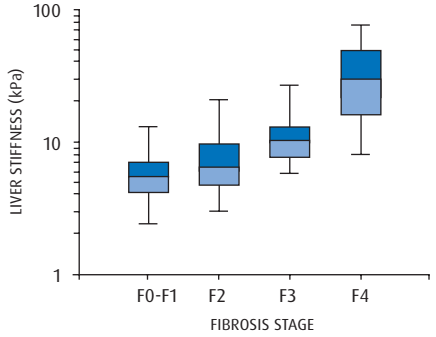


Liver Stiffness Measurement (LSM)

Chronic Viral hepatitis

Chronic Viral hepatitis

Chronic hepatitis C

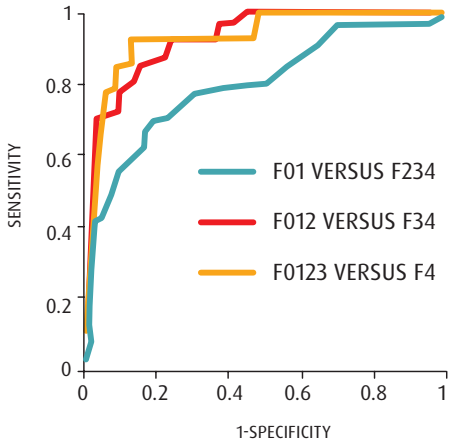
REFERENCE	**Non-invasive assessment of liver fibrosis by stiffness measurement: a prospective multicenter study in patients with chronic hepatitis C.** Ziol et al. (2005). *Hepatology* 41(1): 48-54.
OBJECTIVES	• To compare the accuracy of FibroScan® with biopsy
METHOD	• Prospective multicenter study (4 centers) • 327 consecutive patients with chronic hepatitis C enrolled • FibroScan® performed within 6 months of the liver biopsy **Inclusion criteria:** → presence of HCV RNA in the serum → at least transiently elevated ALAT **Exclusion criteria:** → patients with ascites
PATIENTS ANALYZED	• 251 HCV patients with both FibroScan® and liver biopsy
RESULTS	• Good diagnosis accuracy of liver stiffness measurement for severe fibrosis and excellent in cirrhosis compared to biopsy • The study demonstrates a good efficiency of the FibroScan® in chronic viral hepatitis C for fibrosis detection
GRAPHICS	 **Diagnosis** / **AUROC (95% CI)** METAVIR F ≥ 2 — 0.79 (0.73-0.84) METAVIR F ≥ 3 — 0.91 (0.87-0.96) METAVIR F = 4 — 0.97 (0.93-1.00)
ASSOCIATED PUBLICATIONS	• Arena et al. (2008). Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. Gut 57(9): 1288-1293. • Shaheen et al. (2007). FibroTest and FibroScan® for the Prediction of Hepatitis C-Related Fibrosis: A Systematic Review of Diagnostic Test Accuracy. American Journal of Gastroenterology: 1-12. • Castera et al. (2005). Prospective comparison of transient elastography, Fibrotest, APRI and liver biopsy for the assessement of fibrosis in chronic hepatitis C. Gastroenterology 128: 343-350.

Chronic Viral hepatitis

Chronic hepatitis B

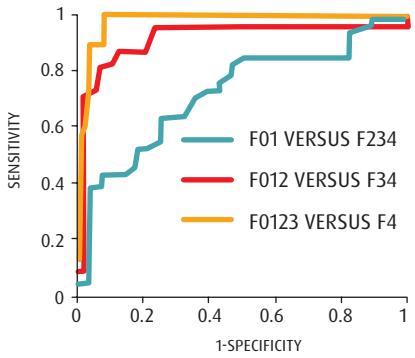
REFERENCE	**Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B.** Marcellin et al. (2009). *Liver International* 29 (2): 242-247.
OBJECTIVES	• To assess the accuracy of FibroScan® in chronic hepatitis B patients
METHOD	• Prospective multicenter study (5 centers) • 202 consecutive patients with chronic hepatitis B • FibroScan® performed within 3 months of the liver biopsy
	Inclusion criteria: → presence of hepatitis B surface antigen → serum HBV-DNA levels >10^5 copies/ml → liver histology compatible with chronic hepatitis **Exclusion criteria:** → patients with chronic alcohol intake → patients with HCV-HBV co-infection → patients with ascites
PATIENTS ANALYZED	• 173 patients with both FibroScan® and liver biopsy
RESULTS	• Good correlation between liver stiffness measurements and biopsy • The role of necro inflammatory activity must be further investigated as in case of acute inflammation or flare, stiffness value may increase without change in fibrosis stage • FibroScan® detects with reliability fibrosis and cirrhosis in HBV patients and seems to achieve similar performances than in HCV
GRAPHICS	

Diagnosis	Cut-off (kPa)	SE	SP
METAVIR F ≥ 2	7.2	0.70	0.83
METAVIR F ≥ 3	8.1	0.86	0.85
METAVIR F = 4	11.0	0.93	0.87



Chronic Viral hepatitis

HIV-HCV coinfection

REFERENCE	**Diagnosis of hepatic fibrosis and cirrhosis by transient elastography (FibroScan®) in HIV-hepatitis C virus-coinfected patients.** de Ledinghen et al. (2006). *Journal of Acquired Immune Deficiency Syndromes* 41(2): 175-179.
OBJECTIVES	• To assess the accuracy of FibroScan® in HCV-HIV co-infected patients • To compare the accuracy of FibroScan® with other non-invasive methods
METHOD	• Prospective multicenter study (5 centers) • 77 patients enrolled **Inclusion criteria:** → presence of HCV RNA and HIV antibodies in serum **Exclusion criteria:** → none
PATIENTS ANALYZED	• 72 patients with HIV-HCV co-infection with both FibroScan® and liver biopsy
RESULTS	• Co-morbidity as HIV do not impair the relationship between liver stiffness and liver fibrosis • The accuracy of the tool in HIV-HCV patients for fibrosis evaluation is as good as in HCV monoinfected patients • FibroScan® accuracy for the diagnosis of cirrhosis is significantly better than platelet count, AST/ALT ratio, APRI or FIB-4 indexes
GRAPHICS	
ASSOCIATED PUBLICATIONS	• De Ledinghen et al. (2008). Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy. *Journal of viral hepatitis* 15(6): 427-33. • Vergara et al. (2007). The use of transient elastometry for assessing liver fibrosis in patients with HIV and hepatitis C virus coinfection. *Clinical Infectious Diseases* 45(8): 969-74. • Kirk et al. (2009). Assessment of liver fibrosis by transient elastography in persons with hepatitis C virus infection or HIV-hepatitis C virus coinfection. Clin Infect Dis 48(7): 963-72

Diagnosis	Cut-off (kPa)	SE	SP
METAVIR F = 4	11.8	1.00	0.93

Chronic Viral hepatitis

Chronic Hepatitis B inactive carriers

REFERENCE	**Transient elastography and biomarkers for liver fibrosis assessment and follow up of inactive hepatitis B carriers** Castera et al., *Alimentary Pharmacology and Therapeutics,* 2011, Vol 33, *455-465*
OBJECTIVES	• To evaluate longitudinally liver stiffness measured by FibroScan VCTE and biomarkers for liver fibrosis assessment and follow-up of hepatitis B virus (HBV) inactive carriers.
METHOD	**Definition of inactive carrier (IC) state:** → HBV viral load <20.000 copies/mL and persistent normal ALT levels during the past 6 months* **Examinations performed:** → Liver biopsy (use of METAVIR scoring system) → FibroScan liver stiffness measurement (LSM) → Fibrosis blood markers (FibroTest, APRI) → All examinations were performed the same day * : Definition of IC at the time of the study (2009)
PATIENTS ANALYZED	• 128 Chronic Hepatitis B patients: → Inactive carrier group (n=201) → CHB patients (n=128)
RESULTS & GRAPHICS	**Comparison of fibrosis markers between IC and CHB patients (HBEAg negative)** → Liver stiffness measured by VCTE (median 4.8 vs. 6.8 kPa, p < 0.0001, cf Figure 1)), Fibrotest results (0.16 vs. 0.35, p< 0.0001) and APRI values (0.28 vs. 0.43, p < 0.0001) were significantly lower in inactive carriers (IC) compared to CHB patients.

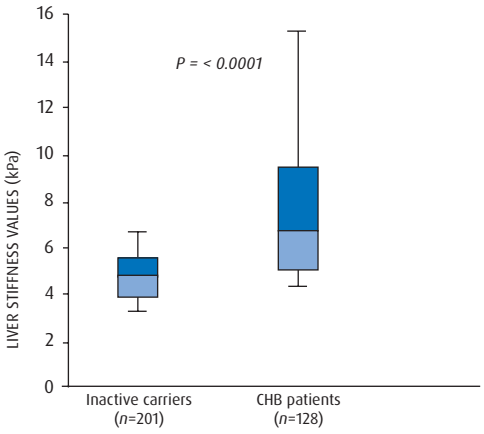


FIGURE 1: BOX PLOTS OF LSM (KPA) IN THE IC GROUP (N=201) AND THE CHB GROUP (N=128). THE TOP AND BOTTOM OF THE BOXES ARE THE FIRST AND THIRD QUARTILES RESPECTIVELY. THE LENGTH OF THE BOX THUS REPRESENTS THE IQR WITHIN WHICH 50% OF THE VALUES WERE LOCATED. THE LINE THROUGH THE MIDDLE OF EACH BOX REPRESENTS THE MEDIAN.

Comparison of LSM measured by FibroScan and biomarkers according to HBV DNA levels in the IC group*

→ Among IC patients, repartition of HBV DNA levels was as follows:

Category	HBV Viral load	N (%)
1	undetectable (<12 IU/mL)	33 (16)
2	Between 12 and 2000 IU/mL	139 (65)
3	Between 2000 and 20.000 IU/mL	39 (19)

*: 81% of the patients are considered as IC based on the recent 2009 EASL definition (Viral load<2000 UI/mL)

→ IC did not differ according to serum HBV DNA levels for baseline characteristics (age, gender, BMI, ALT and AST) as well as for LSM, FibroTest and APRI values

Longitudinal evaluation

→ 82 out of the 201 IC patients underwent at least a second noninvasive evaluation of fibrosis (median interval between the 2 evaluations: 11.5 months (range 3.3-26.8 months), and 48 underwent a third evaluation (median: 23.1 months; range: 10.1–34.7).

→ There was no significant change of LSM (cf Figure 2), of AST, ALT and HBV DNA levels during follow up compared to baseline (p=ns for all)

→ However there was a significant increase of median FT values (+0.03, p= 0.012) during follow up (*possibly due to fluctuations of total bilirubin or alpha2 macroglobulin during follow up*), as well as a significant decrease of median APRI values (-0.01, p<0.05).

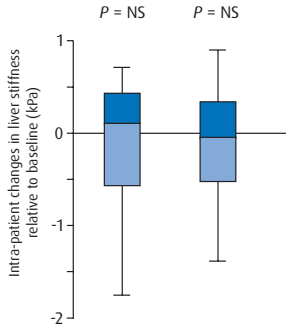


FIGURE 2: EVOLUTION OF LSM IN THE 48 IC PATIENTS WHO UNDERWENT THREE CONSECUTIVE EVALUATIONS OVER THE TIME

KEY POINTS

→ Non-invasive tools for liver fibrosis assessment, particularly LSM measured by FibroScan (VCTE), could be useful, in addition to HBV DNA and transaminase levels, for follow-up of HBV inactive carriers patients.

→ LSM measured by FibroScan could be used to better select right candidates for liver biopsy in the HBV inactive carrier population.

NAFLD & ALD

NAFLD

Non-Alcoholic Fatty Liver Disease

REFERENCE

Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease

Wong et al. (2010). *Hepatology* 51(2)

OBJECTIVES

- To assess the accuracy of FibroScan® and biochemical tests for the diagnosis of fibrosis and cirrhosis in NAFLD patients
- To test if liver stiffness is impaired by hepatic steatosis, inflammation and obesity
- To identify factors associated with discordance between liver stiffness measurements and histology

METHOD

Inclusion criteria:

- → consecutive patients with NAFLD undergoing liver biopsy within one week after FibroScan®
- → patients> 18 years

Exclusion criteria:

- → men consuming more than 30g of alcohol per week
- → women consuming more than 20g of alcohol per week
- → secondary cases of hepatic steatosis
- → positive hepatitis B surface antigen or antihepatitis C virus antibody
- → histologic evidence of other concomitant chronic liver diseases
- → clinical and radiological evidence of cirrhosis

PATIENTS ANALYZED

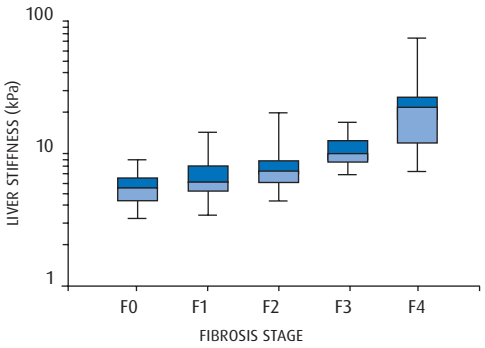
- 246 NAFLD patients with FibroScan® and liver biopsy

RESULTS

- Liver stiffness is not affected by hepatic steatosis, necroinflammation or body mass index
- FibroScan® seems to have a good accuracy to distinguish NASH patients into NAFLD population
- Only liver biopsy length is an independent factor associated with discordance between FibroScan® and histology
- FibroScan® performs significantly better than all studied blood markers (AST/ALT, APRI, FIB-4, NAFLD fibrosis score, BARD score) for both F3 and F4

GRAPHICS

Diagnosis	AUROC (95% CI)
Brunt F ≥ 2	0.84 (0.79-0.90)
Brunt F ≥ 3	0.93 (0.89-0.96)
Brunt F = 4	0.95 (0.91-0.99)



ASSOCIATED PUBLICATIONS

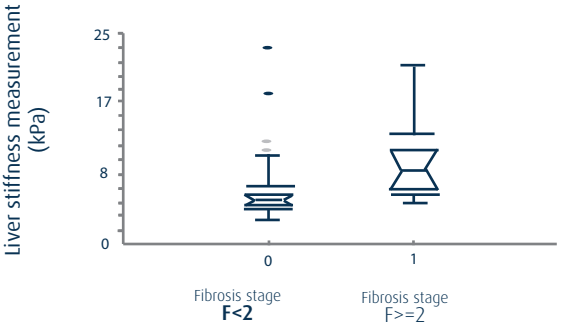
- Yoneda, M. et al., Transient elastography in patients with non alcoholic fatty liver disease (NAFLD). Gut, 2007. 56(9): p 1330-1331
- Yoneda, M. et al., Non invasive assessment of liver fibrosis by measurement of stiffness in patients with non-alcoholic fatty liver disease (NAFLD).Digestive & Liver Disease, 2008. 40 (5): p. 371-378
- Nobili, V. et al., Accuracy and reproductibility of transient elastography for the diagnosis of fibrosis in pediatric non-alcoholic steatohepatitis. Hepatology, 2008. 48(2): p. 442-448

NAFLD

NAFLD patients candidates for bariatric surgery

REFERENCE	**The diagnostic accuracy of Transient Elastography (TE) for the diagnosis of liver fibrosis in bariatric surgery candidates with suspected NAFLD** Naveau et al., Obesity Surgery; May 2014
OBJECTIVES	• To evaluate the diagnostic value of liver stiffness measurement (LSM) by TE in candidates for bariatric Surgery with suspected NAFLD.
METHOD	Patients enrolled: • Candidates for bariatric surgery with suspected NAFLD. • Presence of severe obesity (BMI ≥35kg/m2) with co morbid conditions or morbid obesity alone (BMI ≥40kg/m2) and resistance to medical treatment. • Absence of excessive drinking or chronic viral disease. Liver biopsy: • Evaluated by using the Kleiner Scoring system • 10 mm length required or presence of at least 10 portal tracts LSM by FibroScan® • Performed within 15 days preceding liver biopsy, and 1 year after • Use of either M or XL probe according to the manufacturer's recommendations (Skin to liver capsule distance measurement). • Reliability criteria: At least 10 valid measurements required, IQR/Median ratio <30% only if Median LSM >7.1 kPa
PATIENTS ANALYZED	• 100 patients, suspected NAFLD
RESULTS & GRAPHICS	**Factors associated with Fibroscan LSM:** • By multivariate analysis, **HOMA index (p<0.005), fibrosis stage (p<0.01) and amount of steatosis (p<0.05) were significantly and independently correlated with LSM.** **Fibroscan LSM values according to fibrosis stages:** • **LSM values were significantly higher in patients with fibrosis stage F≥2 (10.4 ± 0.8 kPa)** compared to patients with fibrosis stage below F2 (6.1 ± 0.4 kPa), (p<0.001, cf Figure 1).

Box plots for LSM for stage F<2 and stage F>=2



Diagnostic performances of Fibroscan LSM:

- AUROC of Fibroscan LSM to predict F≥2 was 0.81 ± 0.05, with an optimal cut off at 7.2 kPa (Sensitivity 73%, Specificity 78%, PPV of 48% and NPV of 91%.
- **AUROC of Fibroscan LSM to predict F≥3 was 0.85 ± 0.04.**
- AUROC Obuchowski measure of Fibroscan was 0.78 ± 0.03.

Change of Fibroscan LSM 1 year after bariatric surgery (n=38):

- Second LSM performed on 38 patients only 1 year after surgery
- LSM was significantly lower 1 year after surgery (5.37±0.45 kPa) that before the surgery (6.95±0.7 kPa, p<0.01).
- **Changes in LSM were significantly correlated with HOMA index only (r=0.43, p=0.01) but not with patient BMI or weight.**

KEY POINTS	• Results suggest that Fibroscan LSM could be used as a surrogate marker of insulin resistance, thus helping to identify subgroup of NAFLD patients at higher risk of progressive disease. • Fibroscan could be used for early diagnosis of fibrosis in patients with severe obesity, since highly discriminating for identification of patients with F≥2.

ALD

Diagnostic utility in alcoholic liver disease

REFERENCE

Transient Elastography (TE) alone and in combination with FibroTest for the diagnosis of hepatic fibrosis in alcoholic liver disease

Voican, et al., *Liver International 2017*;37(11):1697-1705.

OBJECTIVES

- To validate the diagnostic utility of TE for advanced fibrosis and cirrhosis in a large multicenter prospective cohort of patients with excessive alcohol consumption
- To evaluate the possible added diagnostic value of FibroTest® (FT) when combined with TE

METHOD

Study details

- Multicenter (4), prospective cross-sectional study

Main inclusion criteria:

- Patient with high serum aminotransferase levels [(AST) ≥1.5xN and (ALT) >N] or suspected cirrhosis
- Patients with at least a 80g per day of alcohol consumption over a period of at least 5 years

Examinations performed:

- FibroScan by Transient Elastography (within 15 days of liver biopsy)
- Liver biopsy (reference standard)
- Prompt Gamma-Ray Activation Analysis (PGAA)
- Blood markers (FT, APRI, Forns Index)

PATIENTS ANALYZED

- 217 Patients with Alcoholic Liver Disease (ALD)

RESULTS & GRAPHICS

Diagnostic value of TE and combination with of TE-FT for advanced fibrosis (F≥3) and cirrhosis (F=4)

- For the diagnosis of advanced fibrosis (F≥3) and cirrhosis (F4), performances of the FibroTest® and combination TE-FibroTest® were not significantly different from the AUROC of FibroScan TE alone (Figure 1).

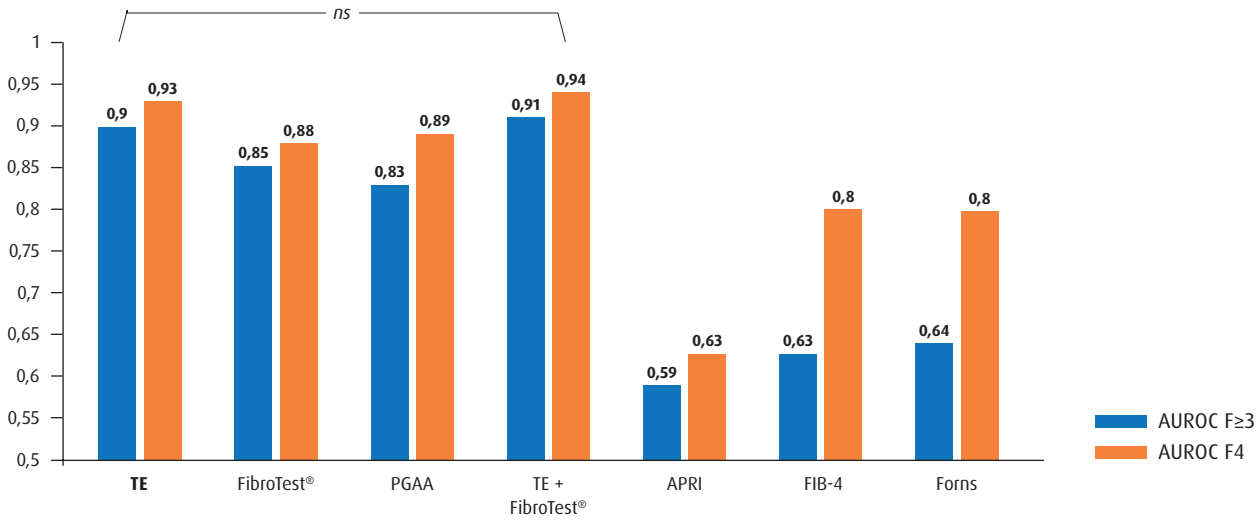


FIGURE 1: DIAGNOSTIC ACCURACY OF NONINVASIVE MARKERS FOR DIAGNOSING ADVANCED FIBROSIS AND CIRRHOSIS VERSUS HISTOLOGY

Optimal cut-offs:

- When using 12 kPa (NPV 84.8%, PPV 86.8%) as an optimal cut-off for advanced fibrosis, 85.5% of the patients were correctly diagnosed by TE versus 77.8% for FT and 80.6% for the combination TE-FT.
- When using 15 kPa (NPV 98.6%; PPV 52.9%) as an optimal cut-off for cirrhosis, TE correctly diagnosed 86.5% of patients vs 81.7% for FT and 86.7% for combination TE-FT.

RESULTS & GRAPHICS

Influence of other histological parameters on TE: hepatic steatosis and presence of alcoholic hepatitis

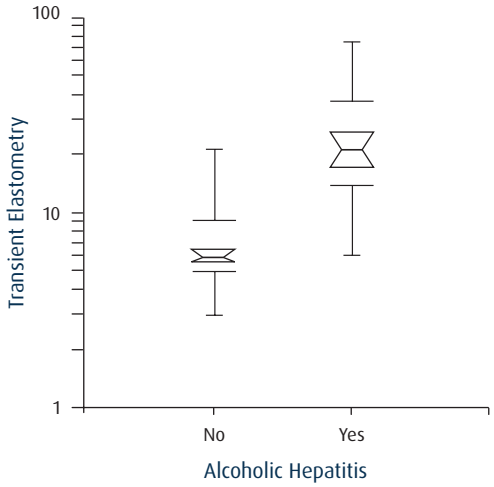


FIGURE 2: TE VALUES (KPA) AS FUNCTION OF PRESENCE OF ALCOHOLIC HEPATITIS

- By multiple linear regression analysis, only the stage of fibrosis and the presence of Alcoholic Hepatitis were independently correlated with the Liver Stiffness measurement (and not the hepatic steatosis).
- Excluding patients with high GGT values (>332 UI/L) ameliorates the performances of TE for diagnosing cirrhosis (AUROC = 0.98).

KEY POINTS

- TE showed excellent diagnostic accuracy for cirrhosis and advanced fibrosis with AUROCs of 0.93 and 0.90, respectively in ALD patients
- TE has excellent diagnostic value for liver fibrosis in alcoholic liver disease. The combined use of TE-FibroTest or TE-PGAA does not improve the performance of TE alone.
- In case of alcoholic hepatitis, TE result should be interpreted with caution since it may also be influenced by inflammation due to ongoing heavy drinking.

ALD

Meta-analysis in alcoholic liver disease

REFERENCE

Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease

Pavlov et al., *The Cochrane database of systematic reviews*, 2015, *Vol 1*

OBJECTIVES

- To determine the diagnostic accuracy of transient elastography (TE) for diagnosing and staging hepatic fibrosis in people with alcoholic liver disease using liver biopsy as a reference.

METHOD

→ Meta-analysis of individual prospective and retrospective studies.

Study selection criteria:

→ Use of TE and liver biopsy for each patient (time interval of 3 months maximum between the 2 exams)

→ Patients with excessive alcohol intake (quantity and duration) and clinical evidences of liver diseases (physical examination and laboratory tests)

Study exclusion criteria:

→ Patients with concomitant liver diseases (viral infection, NAFLD, autoimmune diseases...)

PATIENTS ANALYZED

- 834 patients (14 studies)

RESULTS & GRAPHICS

Diagnostic performances of TE to stage liver fibrosis:

→ **Diagnostic of significant fibrosis F≥2**

Studies (patients)	Optimal cut-off (kPa)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)*	LR- (95% CI)*
7 (338)	**7.5**	0.94 (0.86-0.97)	0.89 (0.76-0.95)	8.2 (3.6-18.5)	0.07 (0.03-0.17)

* LR+: Positive Likelihood Ratio, LR-: Negative Likelihood Ratio

TABLE 1: POOLED DIAGNOSTIC PERFORMANCES OF TE TO STAGE F≥2

→ **Diagnostic of advanced fibrosis F≥3**

Studies (patients)	Optimal cut-off (kPa)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)*	LR- (95% CI)*
8 (564)	**9.5**	0.90 (0.86-0.95)	0.69 (0.46-0.92)	2.9 (0.8-5.1)	0.14 (0.06-0.22)

* LR+: Positive Likelihood Ratio, LR-: Negative Likelihood Ratio

TABLE 2: POOLED DIAGNOSTIC PERFORMANCES OF TE TO STAGE F≥3

With a 0.90% sensitivity and a 0.69 specificity, TE may rule out the presence of advanced fibrosis, considering the prevalence of 61%.

→ **Diagnostic of cirrhosis F4**

Studies (patients)	Optimal cut-off (kPa)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)*	LR- (95% CI)*
5 (306)	**12.5**	0.94 (0.87-0.97)	0.76 (0.63-0.85)	3.8 (2.5-6.0)	0.08 (0.04-0.17)

* LR+: Positive Likelihood Ratio, LR-: Negative Likelihood Ratio

TABLE 3: POOLED DIAGNOSTIC PERFORMANCES OF TE TO STAGE F4

With a 0.94% sensitivity and a 0.76 specificity, TE may rule out the presence of cirrhosis and to avoid unnecessary liber biopsies.

KEY POINTS	
	→ Transient elastography may be used as a diagnostic method to rule out advanced fibrosis (F3) and liver cirrhosis (F4) in people with alcoholic liver disease. → The use of transient elastography for severe fibrosis and cirrhosis may lead to a reduced need for liver biopsy. → Use of liver biopsy or another noninvasive test may remain an option if certainty to rule in or out stage of fibrosis is not sufficient for the clinician. → Proposed cut-offs may be used in clinical practice, but with caution since are only the most common cut-offs used by study authors.

Treatments

Treatments

Prognostic value of LSM after successful antiviral therapy

REFERENCE	**Predicting Liver-Related Events (LRE) Using Transient Elastography in Chronic Hepatitis C Patients with Sustained Virological Response (SVR)** Lee et al., *Gut and Liver,* 2015 | 10 | 429-36
OBJECTIVES	• To investigate whether liver stiffness (LS) values obtained using Transient Elastography at SVR, can predict LRE development in patients with Chronic hepatitis C who achieved SVR
METHOD	**Treatment protocol and follow up:** → Treatment with PEG-INF + Ribavirin → Post treatments visits scheduled every 3 to 6 months for screening of HCC and other portal hypertension complications **Definition of Liver related events (LREs):** → Cirrhotic complications (ascites, variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome), HCC and/or liver related mortality
PATIENTS ANALYZED	• 256 patients with chronic hepatitis C
RESULTS & GRAPHICS	**Baseline characteristics** → Cirrhosis was identified in 44.7% of patients (n=85), all were Child Pugh A → Mean LS value at SVR by FibroScan was 7.1±5.4 kPa **Liver related events (LREs)** → 10 of patients (5.3%) experienced LREs development → Cumulative incidence rates of LRE development at 1, 2 and 3 years were 0.5%, 1.1%, and 2.1% respectively → Median time between SVR and HCC diagnosis was 19.4 months. **Comparison between patients with or without LRE development after SVR** → LS values were significantly higher in patients with LRE development versus those without (16.6 vs 6.8 kPa, p<0.001) **Risk factors for LRE development** → Age ≥65 years (Hazard ratio 8.23, p=0.024) → AFP level≥6 ng/mL (Hazard ratio 11.363, p=0.025) → Liver stiffness value by TE ≥ 7 kPa (Hazard ratio 9.472, p=0.048) → Cumulative incidence rates of LRE development increased significantly in patients with older age, higher AFP level, and higher LS values at SVR (log-rank test, all p<0.05)

RESULTS & GRAPHICS

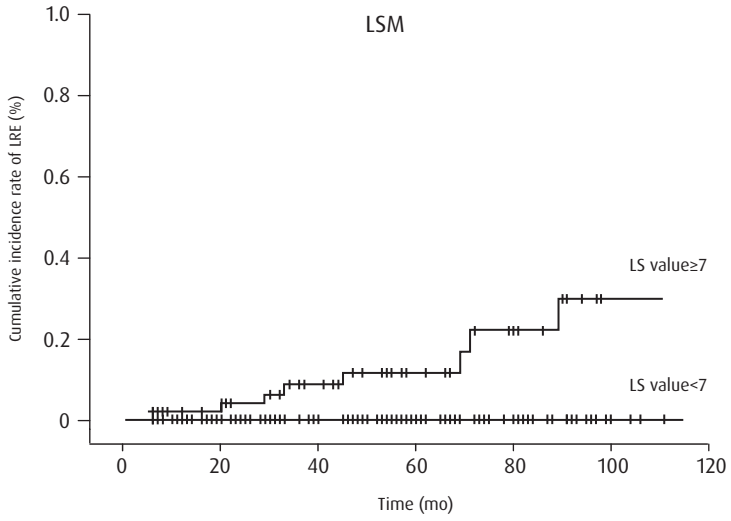


FIG1: CUMULATIVE INCIDENCE RATE OF LRES DEVELOPMENT BASED ON STRATIFIED STIFFNESS VALUES

→ 3 year cumulative incidence rate of LRE was higher in older patients, those with higher AFP levels, and those with LS values >7 kPa (Hazard Ratio 24.562, p=0.003, cf Figure 1)

→ Patients with LS value ≥7.0 kPa, AFP ≥6 ng/mL and age ≥65 years at SVR had 9-, 11- and 8-fold higher risk for LRE development than their counterparts

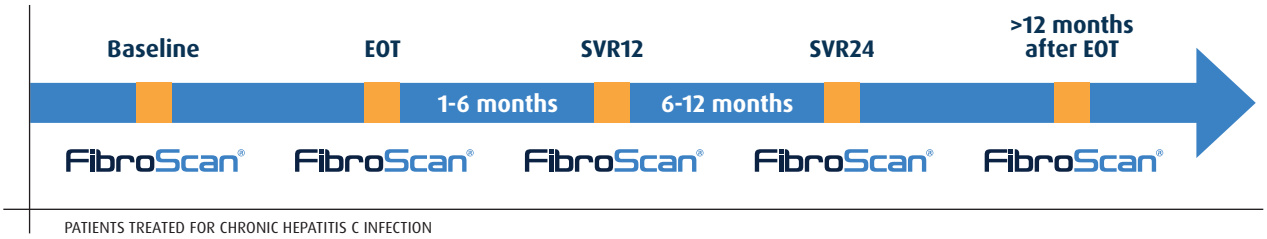
KEY POINTS

- Liver stiffness value at SVR by Transient Elastography can independently predict future LRE development.
- HCC development can last for a prolonged time after SVR achievement and highlight the importance of long-term periodic surveillance for HCC in spite of SVR achievement.
- LRE surveillance strategies might be optimized according to liver stiffness values at SVR, even with complete viral eradication.

Treatments

HCV treatment follow-up

REFERENCE	**Magnitude & Kinetics of Decrease in LS After Antiviral Therapy in Patients with Chronic Hepatitis C: A Systematic Review & Meta-analysis** Singh, et al., *Clinical Gastroenterology & Hepatology* 2018;16(1):27-38.e4.
OBJECTIVES	• To estimate the decrease in liver stiffness, measured by VCTE, in patients with HCV infection who achieved SVR, as compared with pretreatment liver stiffness • To assess temporal evolution of change in Liver Stiffness after SVR • To identify factors that may influence magnitude of change of LS6M-LS12M after end of treatment (EOT)
METHOD	**Study details** • Meta-analysis of observational studies and randomized controlled trials between 2005 and 2016 • Patients were treated with interferon based therapy in 8 studies, with DAAs in 6 studies **Main inclusion criteria for studies:** • Conducted in adults (>18 years) with HCV who received antiviral therapy (with either DAAs or interferon-based therapies) • Underwent LSM using VCTE before therapy initiation } Paired LSM using VCTE • At least 1 follow-up VCTE performed after completion of therapy **Serial measurements during patient follow up:**
PATIENTS ANALYZED	• Patients treated for chronic hepatitis C infection



RESULTS & GRAPHICS

Evolution of LS as function of SVR (Figure 1)

- Liver stiffness decreases significantly, in 6–12 months after achieving viral eradication; in contrast, liver stiffness remains unchanged in patients who do not achieve SVR.

Factors Influencing Magnitude of Change in LS 6-12 months after EOT (15 studies)

- **Type of treatment**: Patients treated with DAA agents had a more significant decrease vs patients with interferon-based therapy (-4.5 kPa vs -2.6 kPa, p = 0.03).
- **Cirrhosis at baseline**: Patients with cirrhosis at baseline had a more significant decrease of 5.1 vs patients without cirrhosis at baseline (-5.1 kPa vs - 2.8 kPa; p = 0.02).
- **LSM at baseline**: Among patients with baseline LSM >9.5 kPa (classified as advanced fibrosis or cirrhosis), 47% achieved posttreatment LSM of <9.5 kPa.
- **ALT at baseline**: Patients with higher mean ALT at baseline ad a more significant decrease vs those with lower mean ALT (p<0.001).

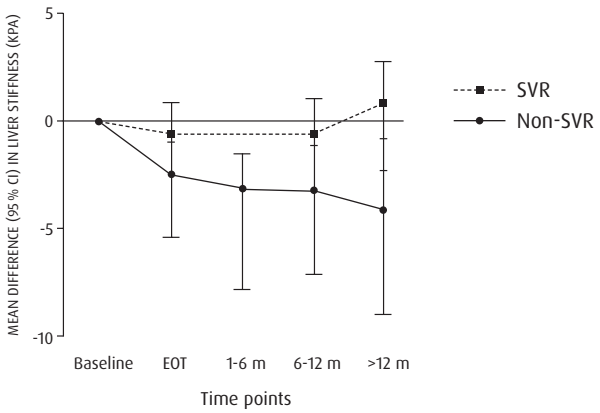


FIGURE 1: CHANGE OF LIVER STIFFNESS OVER TIME, IN PATIENTS WHO ACHIEVED SVR VERSUS PATIENTS WHO DO NOT ACHIEVED SVR. EOT: END OF TREATMENT

Temporal evolution of change in LS patients achieving SVR (Figure 1)

- Mean LSM decrease by 2.4 kPa, at end of therapy (EOT) [9 studies]
- Mean LSM decrease by 3.1 kPa, 1 – 6 months after therapy including SVR12 [5 studies]
- Mean LSM decrease by 3.2 kPa, 6 – 12 months after therapy, including SVR24; median relative decline in LS was 28.2% [15 studies]
- Mean LSM decrease by 4.1 kPa, 12 months or more after therapy [8 studies]

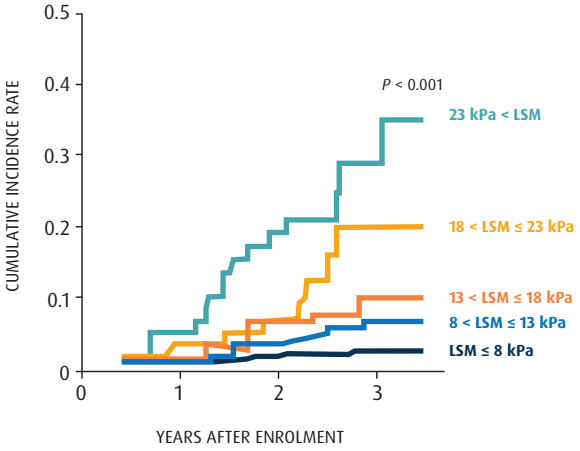
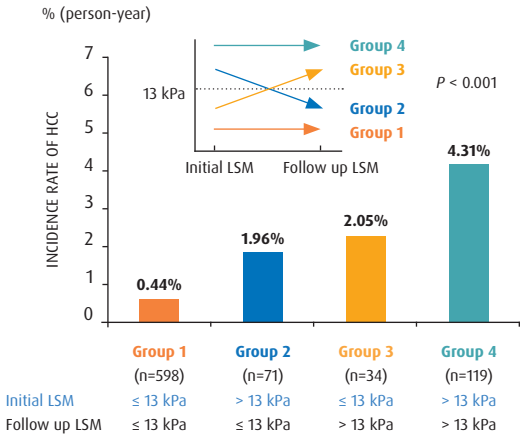
KEY POINTS

- Liver stiffness measured by VCTE decreases significantly on patients achieving SVR (median decrease of 28.2%) and magnitude of the decline is incremental after completion of therapy.
- 47% of patients with F3/F4 before treatment have a decline of LSM below 9.5 kPa post treatment.
- It is conceivable that this decline of liver stiffness may be associated with a decrease of liver related complications.

Cirrhosis, Portal Hypertension & Prognosis

Cirrhosis, Portal Hypertension & Prognosis

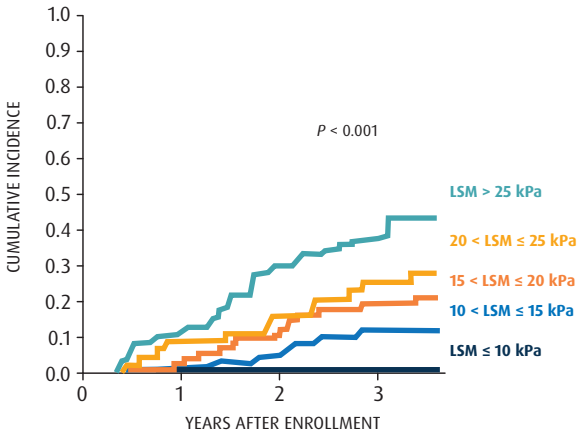
Prognostic value for HCC

REFERENCE	**Risk assessment of Hepatitis B virus-related Hepatocellular Carcinoma Using Liver Stiffness measurement (FibroScan®)** Jung et al.(2011). *Hepatology* 3: 885-893
OBJECTIVES	• To assess the usefulness of Liver Stiffness Measurement (LSM) for assessing the risk of Hepatocellular carcinoma (HCC) development in a large cohort of patients with Chronic Hepatitis B.
METHOD	• Prospective longitudinal study • 1130 consecutive patients with Chronic Hepatitis B • LSM using FibroScan® and blood tests performed at baseline and during patient follow up (median follow-up of 30.7 months) • Population stratified in 5 groups according to LSM results: → ≤ 8kPa → 8.1-13 kPa → 13.1-18kPa → 18.1-23 kPa → >23 kPa • Screening for HCC (based on AASLD guidelines) performed every 3 to 6 months after enrolment.
PATIENTS ANALYZED	• 1130 patients screened for HCC development
RESULTS	• High LSM value, Older Age, Male Sex, Lower albumin level, HBE Ag positivity, and heavy alcohol consumption are independent predictors of HCC development. • Correlation between high LSM and HBV-related HCC development remains significant, even if HBV related HCC can develop on non-cirrhotic livers. • In comparison to previous studies, HCC development hazard ratio seems to be lower in patients with Chronic Hepatitis B than in patients with Chronic hepatitis C.
GRAPHICS	**Risk analysis of HCC development according to LSM baseline value**  Cumulative incidence rates of HCC based on stratified LSM **Risk analysis of HCC development according to LSM change**  Incidence rates of HCC according to LSM change
KEY POINTS	• Results suggest than LSM can be used as a dynamic indicator of risk of HCC development. • LSM could then be used as a noninvasive predictor of HCC development in patients with CHB.

Cirrhosis, Portal Hypertension & Prognosis

Prognostic value for HCC

REFERENCE	**Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography** Masuzaki et al. (2009). *Hepatology* 495(6): 1954-1961
OBJECTIVES	• Prospectively evaluate the efficacy of Liver Stiffness Measurement (LSM) by transient elastography using FibroScan® as a predictor of HCC development among a cohort of patients with hepatitis C with various degrees of liver fibrosis
METHOD	• Prospective study • Patients separated in five groups according to LSM baseline value • Screening for HCC development according to LSM baseline value
PATIENTS ANALYZED	• 866 consecutive patients with Chronic Hepatitis C
GRAPHICS	**Cumulative incidence of HCC according to LSM baseline value**



- The incidence rate of HCC differed significantly among the five groups (p<0.001), increasing in accordance with liver stiffness
- Patients who developed HCC tended to be older and had a higher AFP level at the time of entry in the same rank of LSM
- Factors associated with HCC development by multivariate analysis:
  - → LSM was revealed to be at a significantly higher risk for HCC development, as compared to LSM ≤10 kPa.

LSM Value	Hazard ratio	p
10.1-15	16,7 (3.71-75.2)	<0.001
15.1-20	20,9 (4.43-98.8)	<0.001
20.1-25	25,6 (5.21-126.1)	<0.001
>25	45,5 (9.75-212.3)	<0.001

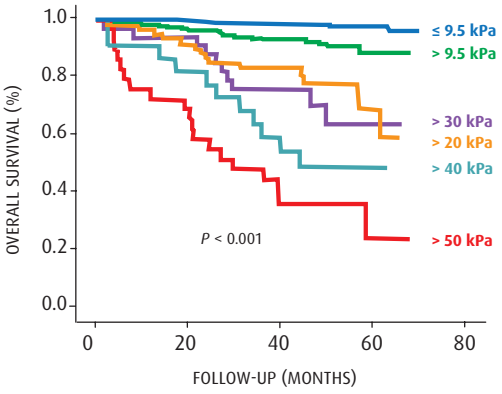
  - → Presence of clinical cirrhosis, older age, male gender and serum albumin level were also associated with HCC development

RESULTS	• LSM is a significant risk factor of HCC development independent of those already identified (older age, male gender, heavy alcohol intake, high BMI, cirrhosis, lower platelets count, higher AFP level, lower serum albumin level and higher ALT level.) • LSM should be used in complements to other laboratory test to identify high-risk patients of HCC • The utility of LSM is not limited to a surrogate for liver biopsy but can be applied as a dynamic indicator of the risk of HCC development • Cirrhosis can be further stratified with clinical relevance based on LSM

Cirrhosis, Portal Hypertension & Prognosis

Survival rate in chronic hepatitis c

REFERENCE	**Non-invasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C** Vergniol et al., *Gastroenterology 2011*, 140, 1970-79
OBJECTIVES	• Evaluate the 5-year prognostic value of liver stiffness, FibroTest (FT), APRI and FIB-4 for predicting survival and liver related death in patients with chronic hepatitis C
METHOD	• Prospective longitudinal study • Patient follow up: → Liver Stiffness Measurement (LSM), APRI, FibroTest (FT) and liver biopsy performed at baseline → 5 years patient follow-up for evaluation of survival without death or liver-related death (including death-related to liver disease and liver transplantation)
PATIENTS ANALYZED	• 1453 HCV patients • Patient groups: → 663 patients with all liver fibrosis scores available (core group) → 794 other patients (non core group)
GRAPHICS	**Survival:** → The overall number of death/transplantation was 93 (6.4% of the cohort, 53 liver-related and 40 not liver related) → The 5-year overall survival in the overall population was 0.917 (0.897-0.938) → The 5-year survival without liver-related death was 0.961 (0.939-0.984) → Overall survival and survival without liver-related deaths were significantly associated with LSM and FT whatever age and treatment, with an additive prognostic value, when fibrosis stage (estimated using liver biopsy) and necro activity inflammation (Actitest) were taken into account **Prognostic performances** → Combination of LSM and FT had an AUROC for prediction of survival of 0.907 (95% CI 0.825-0.952) in the core group and 0.871 (95% CI 0.810-0.914) in the non-core group → No significant difference between LSM (AUROC= 0.848) and FT (AUROC= 0.839) for the prediction of survival (p<0.61)
KEY POINTS	• First study showing that liver stiffness has a prognostic value for overall survival and survival without liver-related death in patients with HCV infection • **LSM and FT have better prognosis values than liver biopsy, FIB-4 and APRI** • In patients with cirrhosis, an increasing LSM is associated with a worse prognosis, introducing for the first time the concept of non-invasive prediction of survival in cirrhotic patients with LSM • **LSM, as a good predictor for survival, may help physician** → **to evaluate earlier the severity of chronic liver diseases** → **to decide with stronger arguments of a liver transplantation or a portosystemic shunt** → **to evaluate more precisely the surgical risk of cirrhotic patients**
LINK TO THE PUBLICATION	• http://www.ncbi.nlm.nih.gov/pubmed?term=21376047



Survival rate of patients according to baseline LSM values

Cirrhosis, Portal Hypertension & Prognosis

Meta analysis: evaluation of portal hypertension

REFERENCE	**Transient elastography: a meta analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease** Shi et al., *Liver International*, 2013, Vol 33, *62-71*
OBJECTIVES	• To assess the performance of LSM in the evaluation of significant portal hypertension as well as the presence and the size of esophageal varices in patients with chronic liver diseases (CLD).
METHOD	**Study selection criteria for meta analysis:** • At least 30 patients in the study cohort • Study evaluating accuracy of LSM using FibroScan® for prediction of significant portal hypertension, esophageal varices in patients with CLD • Measurement of portal pressure performed with HVPG, and use of endoscopy as a reference standard for the diagnosis of varices. • Reported data allowing to calculate true positive, false positive, true and false negative diagnostic results of LSM for diagnosis of varices **Quality of studies** • Graded using the QUADAS system, dedicated to assess the validity of diagnostic accuracy studies included in systematic reviews.
PATIENTS ANALYZED	• 3644 patients (18 studies)
RESULTS & GRAPHICS	**Accuracy of LSM for detection of significant portal hypertension** → Evaluated in 5 studies → Global diagnostic performance (HSROC) was 0.93 (95% CI 0.90-0.95), cf Figure 1. → Assuming the prevalence of significant portal hypertension was 61.4%, PPV* of LSM was 0.88 and NPV* was 0.88 **Accuracy of LSM for the detection of oesophageal varices** → Evaluated in 12 studies → Global diagnostic performance (HSROC) was 0.84 (95% CI 0.80-0.87), cf Figure 1. → Assuming the prevalence of oesophageal varices was 49%, PPV of LSM was 0.79 and NPV was 0.64 **Accuracy of LSM for the detection of large oesophageal varices** → Evaluated in 9 studies → Global diagnostic performance (HSROC) was 0.78 (95% CI 0.74-0.81), cf Figure 1. → Assuming the prevalence of large oesophageal varices was 32%, PPV of LSM was 0.79 and NPV was 0.66 * PPV: Positive Predictive Value, NPV: Negative Predictive Value

Accuracy of LSM and CLD aetiology for detection of varices

Subgroup analysis was conducted on patients with viral CLD (4 studies with CHB or CHC):

- → Cut offs ranged from 17.1 to 26.5 kPa,
- → Pooled Sensitivity was 0.87 (not different from that it was for all etiologies, p=0.16)
- → Pooled Specificity was 0.71 (significantly higher that it was for all etiologies, p<0.001)
- → Diagnostic accuracy was also significantly higher compared to all aetiologies

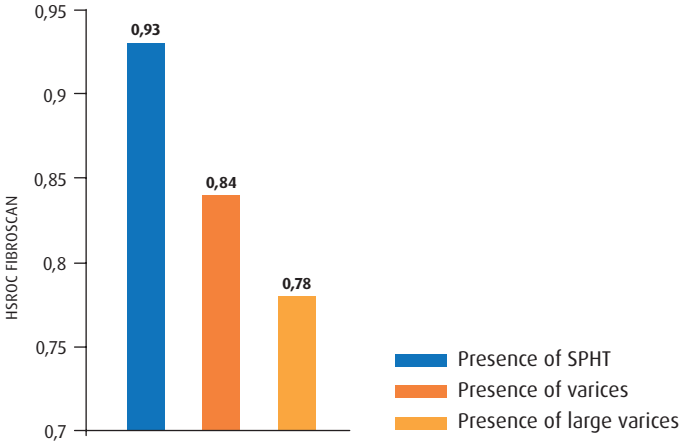


FIGURE 1: GLOBAL PERFORMANCES OF FIBROSCAN FOR DETECTION OF CIRRHOSIS COMPLICATIONS (HSROCS)

KEY POINTS

- → LSM using FibroScan® presents a high accuracy for detection of significant portal hypertension
- → FibroScan® could therefore be integrated in the detection of significant portal hypertension in untreated patients, and could be useful to select suspicious patients with CLD for HVPG measurements.
- → In patients with significant portal hypertension, FibroScan® might be used in monitoring the hemodynamic response and the effect of drugs reducing portal pressure

Surgery & transplantation

Surgery and transplantation

Fibrosis evaluation post-tranplant

REFERENCE	**Performance of transient elastography and serum fibrosis biomarkers for non-invasive evaluation of recurrent fibrosis after liver transplantation (LT): A meta-analysis** Bhat, et al., PLoS ONE 2017; 12(9):e0185192.
OBJECTIVES	• To perform a meta-analysis of the diagnostic accuracy of simple serum biomarkers, and TE for the prediction of recurrent liver fibrosis in the post-LT setting.
METHOD	**Study details** • Systematic literature search from 2003 and May 2017 • Sources: electronic databases (PubMed, Medline, Embase, Cochrane), conference abstract books (AASLD, ILTS, EASL, ATC, DDW, APASL). **Main inclusion criteria for studies:** • Adults or children population • TE, FIB4 and APRI available • Liver biopsy used as a reference standard with comparable fibrosis staging system
PATIENTS ANALYZED	• Liver transplanted patients, multietiology
RESULTS & GRAPHICS	12 studies with TE included in the meta-analysis (1196 patients) **Diagnostic accuracy of TE after LT for significant fibrosis** • TE exhibited AUC ranging from 0.75 to 0.96 depending on individual studies. • Summary odds ratio for TE was the best, at 21.17 (95% CI: 14.10-31.77, p <0.001) having excluded one study due to publication bias. • When compared to other noninvasive tests (APRI and FIB4), there was a significant difference between TE and APRI (p<0.05), and between TE and FIB4 (p<0.05)
KEY POINTS	• Identification of significant liver fibrosis is relevant in LT recipients, indicating both recurrence of primary disease (ie hepatitis C, NASH) or *de novo* disease. • This work represents the first meta-analysis evaluating use of noninvasive markers after LT, including all aetiologies of liver disease (ALD, HCV, NAFLD, cholestatic diseases) • TE has good accuracy in detecting significant liver fibrosis in LT recipients and outperforms simple serum biomarkers, such as APRI and FIB-4.

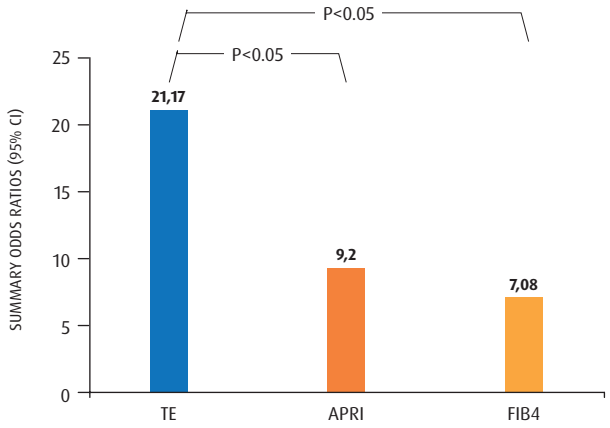


FIGURE 1: DIRECT COMPARISON OF DIAGNOSTIC ACCURACY OF NONINVASIVE TESTS (SUMMARY ODDS RATIOS) FOR PREDICTION OF F≥2 AFTER LT.

Publication Bias

For TE, there was evidence of publication bias in one study. No publication bias was demonstrated for the 11 other remaining studies (Egger test; p>0.05)

Surgery and transplantation

Predictive value for outcomes after hepatic resection

REFERENCE

Value of Transient Elastography Measured With FibroScan in Predicting for clinical outcomes after Hepatic Resection for Hepatocellular Carcinoma (HCC).

Cescon et al., Annals of Surgery 2012; 256:706-713

OBJECTIVES

- To evaluate the predictive role of LS measurement by FibroScan for postoperative liver failure (PLF) in patients undergoing hepatectomy for HCC.

METHOD

Study details

→ HCC patients candidates for resection enrolled
→ Patients with recurrent tumors excluded

Postoperative liver failure (PLF)

Presence of at least one of the parameters listed in the classification of Dindo et al. (*refractory ascites, elevated bilirubin levels, alteration of coagulation factors with INR>1.5, renal impairment requiring loop diuretics, dopamin/telapressin treatment or dialysis*).

Liver stiffness measurements (LSM)

→ Performed the day before surgery
→ 6 hours of fasting required
→ Performed by 2 experienced operators by using the FibroScan® M probe

PATIENTS ANALYZED

- 92 patients with hepatectomy prescribed for HCC

Postoperative complications

→ Median hospital stay was 9 days (3-40), and PLF occurred in 26 patients (28.9%)
→ In all patients, FibroScan exhibited AUROC of 0.865 to predict PLF, with associated cut off of 15.7 kPa (Se 96.1, Sp: 68.7%, PPV: 55.6%, NPV: 97.8%)
→ No patient with LSM <14.8 kPa developed PLF.
→ In subgroup of cirrhotic patients, FibroScan exhibited AUROC of 0.817 to predict PLF, with associated cut off of 17.6 kPa (Se 91.4, Sp: 60%, PPV: 59.3%, NPV: 91.7%)

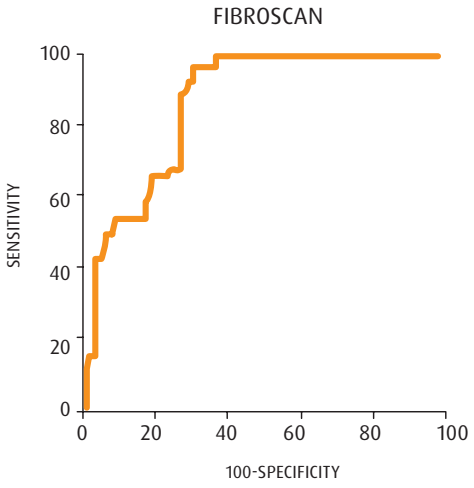


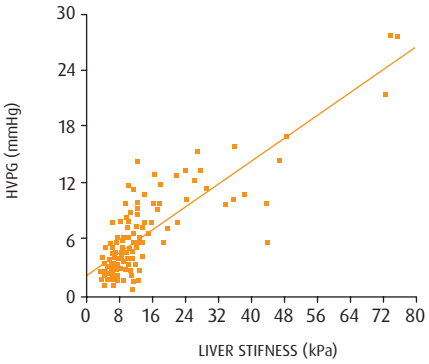
FIG 1: PERFORMANCE OF LSM BY FIBROSCAN TO PREDICT OCCURENCE OF PLF

[Publi_Cescon_2012] - Revision date [03/11/2015] - FibroScan® is a class IIa medical device according to Directive EC/93/42 and is manufactured by Echosens. Assessment of its conformity with the essential requirements of the Directive EC/93/42 is established by the LNE-G-MED (n°0459)- France - . FibroScan® is indicated for the non invasive measurement of liver stiffness (E) and controlled attenuation parameter (CAP) in humans. It is expressly recommended to carefully read the guidance within the users' guide and labeling of the device. FibroScan® examination must only be performed by operators certified by the manufacturer or its accredited local representative. The values obtained with FibroScan® must be interpreted by a physician experienced in dealing with liver disease, taking into account the complete medical record of the patient.

	Factors affecting postoperative liver failure (PLF) → Multivariate analysis showed that lower preoperative serum sodium levels (p=0.012), **higher stiffness value (p=0.005)** and presence of cirrhosis (p=0.024) were independent predictors of PLF.
KEY POINTS	→ LSM measured by FibroScan seems to be the best predictor of hepatic decompensation in patients undergoing liver resection for HCC → Cut off of 15.7 kPa showed sufficient accuracy in discriminating between populations at different risks of liver insufficiency → Given its accessibility, reliability of results and simplicity of use, FibroScan should be added to routine preoperative workup of patients candidates for surgery for HCC

Surgery and transplantation

HCV recurrence after liver transplantation

REFERENCE	**Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation.** Carrion et al. (2006). *Liver Transplantation* 12: 1791-1797.
OBJECTIVES	• To assess the accuracy of FibroScan® in HCV patients after liver transplantation • To compare the accuracy of FibroScan® with liver biopsy and by hepatic venous pressure gradient (HVPG)
METHOD	• 135 consecutive transplanted patients with occurrence of HCV **Inclusion criteria:** → HCV infected patients with liver transplantation → undergoing liver biopsy and/or hepatic hemodynamics **Exclusion criteria:** → Body Mass Index> 35kg/m^2 → clinically evident ascites
PATIENTS ANALYZED	• 124 consecutive HCV-infected transplanted patients with liver biopsy, FibroScan® and HVPG
RESULTS	• There is an excellent correlation between liver stiffness and HVPG (no patients with significant portal hypertension were bellow 8,74 kPa) • FibroScan® seems to have a good predictive value for occurrence of complications in transplanted patients • FibroScan® is a useful and efficient tool for a close and non invasive follow up of transplanted patients
GRAPHICS	

Diagnosis	AUROC (95% CI)
METAVIR F ≥ 2	0.90 (NR)
METAVIR F ≥ 3	0.93 (NR)
METAVIR F = 4	0.98 (NR)

ASSOCIATED PUBLICATIONS	• Corradi et al. (2008). Assessment of liver fibrosis in transplant recipients with recurrent HCV infection: Usefulness of transient elastography. *Digestive & Liver Disease In Press*. • Rigamonti et al. (2008). Transient elastography predicts fibrosis progression in patients with recurrent hepatitis c after liver transplantation. *Gut* 57(6): 821-827.

Paediatric liver diseases

Paediatric liver diseases

Fibrosis evaluation in children

REFERENCE

Serum biomarkers and Transient Elastography as Predictors of Advanced Liver Fibrosis in a United States Cohort: the Boston Children's Hospital Experience

Lee et al., Journal of Pediatrics, 2013, In Press

OBJECTIVES

- To evaluate and compare the ability of serum hyaluronic acid (HA), human cartilage glycoprotein-39 (YKL-40) and Transient Elastography (TE) to predict histologically assessed advanced (F3 or more) hepatic fibrosis in a cohort from a single pediatric center on both children and young adults.

METHOD

TE examination

- Performed with the FibroScan® medium (M probe) or pediatric probe (S probe) according to the manufacturer's recommendations.

Liver biopsy (METAVIR):

- Performed within 12 months of TE examination
- Reading in central lab, minimum length of 15mm required with at least 6 portal tracts

Blood markers: collected within 6 months of TE examination

PATIENTS ANALYZED

128 patients (multietiology cohort)

- 97 patients with TE and blood markers
- 31 patients with blood markers only

RESULTS & GRAPHICS

Diagnostic performances (AUCs) and cut-offs of fibrosis markers for diagnosis of F3-F4 fibrosis stages in comparison with histology (Table 1):

Fibrosis Marker	n	F3-F4 (%)	Cut-off	Se	Sp	Diagnostic accuracy (%)	AUC
Direct measures							
HA (ng/mL)	120	38 (32)	>43	0.66	0.77	73	0.75
YKL-40 (ng/mL)	119	38 (32)	>26.2	0.68	0.43	51	0.51
FibroScan by TE (kPa)	**97**	**34 (35)**	**>8.6**	**0.79**	**0.83**	**81**	**0.85**
Indirect measures							
APRI	113	38 (34)	> 1.45	0.61	0.69	66	0.67
AST/ALT	117	39 (33)	> 0.84	0.69	0.62	44	0.69
AST/GGT	93	32 (34)	> 0.49	0.75	0.30	45	0.44

Table 1: Performances and cut-offs of studied fibrosis markers for fibrosis assessment in comparison with liver biopsy

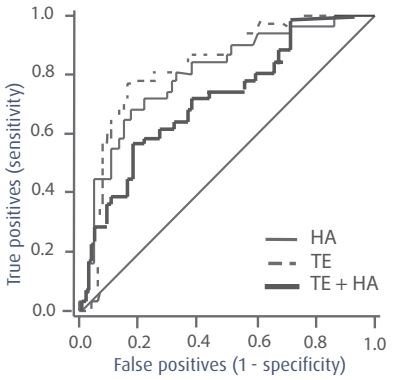


Figure 1: AUCs of TE, HA, and TE-HA combination for diagnosing F3-F4 fibrosis (n=88)

- TE performed better than any of the indirect fibrosis markers (APRI, AST/ALT, AST/GGT).
- Performance of TE by FibroScan® (AUC) was significantly better than HA and YKL-40 (Figure 1)
- Combination of TE+HA did not perform significantly better than TE alone.

KEY POINTS

- Liver stiffness measurement using TE is superior to both HA and YKL-40 for the detection of F3-F4 patients
- TE is safe, well tolerated and successfully performed in the large majority of subjects including infants using M and S probes as appropriate.
- Development of dedicated algorithm using multiple noninvasive tests could be useful to more precisely define the need for primary and serial liver biopsies in children and adolescents with chronic liver disease.

Diabetes

Diabetes

Screening for NAFLD in type 2 diabetes population

REFERENCE	**Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: A prospective cohort study** Kwok et al. Gut, 2015, In press
OBJECTIVES	• To test the strategy of NAFLD and fibrosis screening in patients with type 2 diabetes. • To study factors associated with increased CAP and liver stiffness to guide selection of patients for screening
METHOD	**FibroScan examination** → Steatosis was graded as follows based on CAP results: S1: 222-232 dB/m; S2: 233-289 dB/m; S3: ≥290 dB/m → Fibrosis was graded as follows based on CAP results: → M probe: F≥3: 9.6-11.4 kPa, F4: >11.5 kPa → XL probe: F≥3: 9.3-10.9 kPa, F4: >11 kPa **Liver biopsy** → Performed only for patients with F3 or F4 according to FibroScan results → Use of the Kleiner scoring system → NASH was defined by presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning), with or without fibrosis.
PATIENTS ANALYZED	• 2119 patients • Type 2 diabetes
RESULTS & GRAPHICS	**Proportion of patients with increased CAP and increased liver stiffness** → 72.8% of patients had an increased CAP value >222dB/m suggestive of S≥1 (cf Figure 1) → 17.7% of patients had an increased stiffness value suggestive of advanced fibrosis or cirrhosis → Increased stiffness was more common on patients with increased CAP (20.6%) compared to patients with normal CAP values (6.9%, p<0.001)

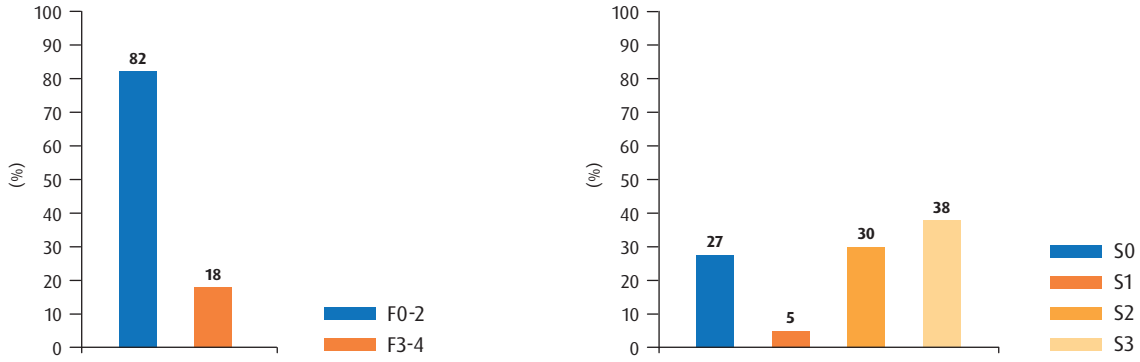


FIGURE 1: PREVALENCE OF FATTY LIVER AND OF ADVANCED FIBROSIS OR CIRRHOSIS IN THE STUDY COHORT

Factors associated with increased CAP

- → By multivariate analysis, increased CAP value was independently associated with female gender, elevated BMI, no use of insulin, fasting blood glucose, ALT and triglycerides levels.
- → Increased CAP value was found in 54.6% of patients with BMI<25, 82.7% of patients with BMI between 25 and 30, and 94.6% of patients with BMI>30 kg/m2, respectively (p<0.001, cf Figure 2)

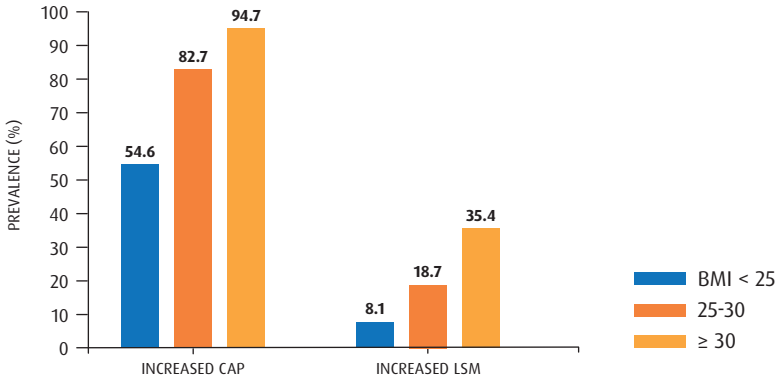


FIGURE 2: INCREASED CAP AND STIFFNESS (LSM) VALUES AS FUNCTION OF PATIENT'S BMI

Factors associated with increased stiffness

- → By multivariate analysis, increased stiffness value was independently associated with longer duration of diabetes, lower level of HDL cholesterol, elevated BMI and ALT and spot urine albumin creatinine ratio.
- → LSM was significantly increased as function of patient BMI (p<0.001, cf Figure 1)

Liver biopsy results

- → Performed on 94 patients
- → 56% of patients were diagnosed as NASH
- → 21% of patients had advanced fibrosis (F3) and 29% had cirrhosis (F4).

KEY POINTS

- → Diabetic patients at hospital of primary care have a high prevalence of NAFLD and advanced liver fibrosis.
- → Patients with high BMI and dyslipidemia are at high risk and may be a target for liver assessment.
- → FibroScan is a reasonable tool for primary liver assessment in type 2 diabetes patients.

Miscellaneous

Miscellaneous

Prognostic value in patients with heart failure

REFERENCE

Liver stiffness (LS) reflecting right-sided filling pressure can predict adverse outcomes in patients with heart failure

Taniguchi, et al., *JACC Cardiovascular imaging*, 2018, in Press

OBJECTIVES

- To investigate the prognostic value of liver stiffness for cardiac events in patients hospitalized for heart failure (HF).

METHOD

Main Inclusion criteria:

- Patients hospitalized for heart failure without scheduled surgical treatment

Exclusion criteria:

- Any type of liver disease, alcohol consumption, presence of fibrosis or ascites

Examinations performed

- LSM using FibroScan® (Transient Elastography) with M probe.
- Right sided filling pressure evaluation estimated by LSM (mmHg, obtained with LSM based formula described in previous published data [1])
- Routine Lab tests (B type natriuretic peptide, type IV collagen)
- Echocardiogaphy

Patient follow up:

- By clinical visits or telephone interviews
- Primary endpoint was cardiac death or rehospitalization for treatment of HF

[1] : Taniguchi T., et al. Usefulness of transient elastography for noninvasive and reliable estimation of right-sided filling pressure in heart failure. Am J Cardiol 2014;113:552–8.

PATIENTS ANALYZED

- 171 patients with HF

RESULTS & GRAPHICS

Liver stiffness and right sided filling pressure at baseline

- Median LSM values was 5.6 kPa (2.4-39.7 kPa)
- Right sided filling pressure estimated by LSM was 5.7 mmHg (0.1-18.9)

Predictive value of LS for cardiac events

- Median patient follow up was 203 days, 5% of patients died and 19% were rehospitalized for HF
- Patients in the highest LSM group had a significantly higher probability of cardiovascular event (Figure 1)
- LSM showed a significant predictive value for cardiac events with Hazard ratio per kPa increase of 1.13 (1.09-1.17, p<0.001)
- Right sided filling pressure (estimated by LSM) also showed significant predictive value for cardiac events with HR per 1mmHg increase of 1.3 (1.19-1.41, p<0.001)
- Combining BNP and LSM allows a better prognostic value than the model including BNP alone

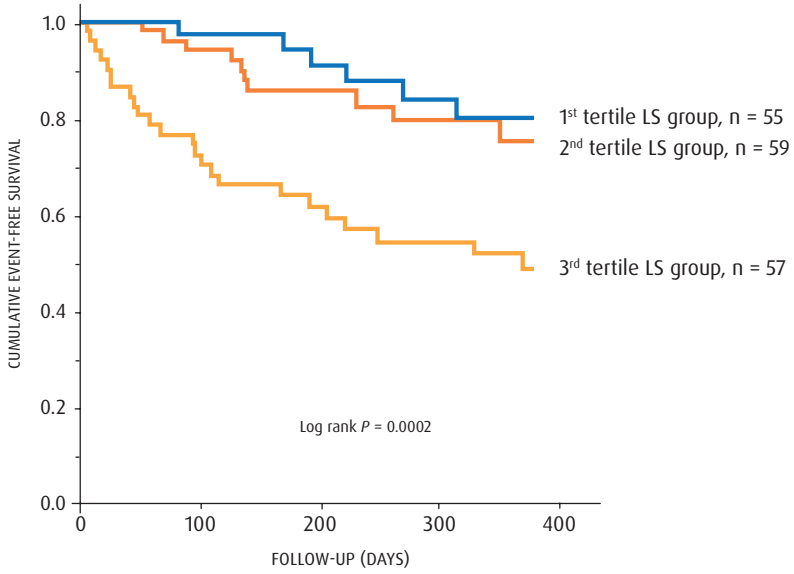


FIGURE 1: CUMULATIVE CARDIAC EVENT FREE SURVIVAL RATE PER TERTILES OF LS VALUES.
PINK LINE: FIRST TERTILE GROUP; GREEN LINE; SECOND TERTILE GROUP; BLUE LINE, THIRD TERTILE GROUP.

RESULTS & GRAPHICS	**Predictive value of LSM for short term cardiac events (90 days of follow-up)** • LS value of 10.1 kPa (and estimated right filling pressure of 9.7 mmHg) yielded a Sensitivity of 0.73 and a Specificity of 0.9 for worse cardiac outcomes, better than the inferior vena cava diameter (IVC)
KEY POINTS	• Liver stiffness measured by TE at discharge is a strong predictor of clinical outcomes, including cardiac death and rehospitalization in patients with heart failure. • Study results suggest that evaluating the liver congestion by TE at discharge may be useful for the management of patients with HF. • These findings may extent the use of TE from hepatology to cardiology.

Miscellaneous

Autoimmune hepatitis

REFERENCE	**Validation of Transient Elastography in autoimmune hepatitis: timing determines the impact of inflammation and fibrosis** Hartl et al., *Journal of Hepatology*, In press
OBJECTIVES	• To assess diagnostic performance of Transient Elastography (TE) in patients with AutoImmune Hepatitis (AIH) • To investigate the impact of disease activity on its diagnostic accuracy
METHOD	**Study design** → Prospective cohort (n=34) → Validation cohort (n=60) **Exclusion criteria:** → BMI>40 kg/m^2 → Severe of fulminant flare at the time of FibroScan examination. **FibroScan examination:** → Performed within 3 months of liver biopsy
PATIENTS ANALYZED	• Prospective cohort: 34 patients, Validation cohort: 60 patients
RESULTS	**Diagnostic performances of LSM measured by TE** • Prospective cohort: → Liver stiffness (LS) was strongly correlated with histological fibrosis stage (p=0.611, p<0.001) → Performance of TE (AUROC) was 0.82 for F2 (SE 0.73, SP 0.91), and 0.92 for F4 (SE 0.83, SP 1) → Optimal diagnostic cut-offs were 5.8 kPa (F≥2), 10.5 kPa (F≥3), and 16.0 kPa (F4) • Validation cohort → LS was also correlated with histological fibrosis stage (p=0.777, p<0.0001) → Diagnostic performance of TE (AUROC) was high for F2 (AUROC 0.96, SE=0.89, SP=1) and for F4 AUROC of 0.92, SE=0.92, SP=1).
GRAPHICS	• Total cohort → Application of diagnostic cut-offs in the validation cohort (n=94)

Histological staging (SCHEUER)	AUROC	Optimal cut-off (kPa)	Sensitivity	Specificity	PPV	NPV
F≥2	0.87	5.8	0.90	0.72	0.83	0.84
F≥3	0.93	10.4	0.83	0.98	0.92	0.91
F4	0.96	16	0.88	1	1	0.98

TABLE 1: DIAGNOSTIC PERFORMANCES IN THE TOTAL PATIENT COHORT (N=94)

GRAPHICS

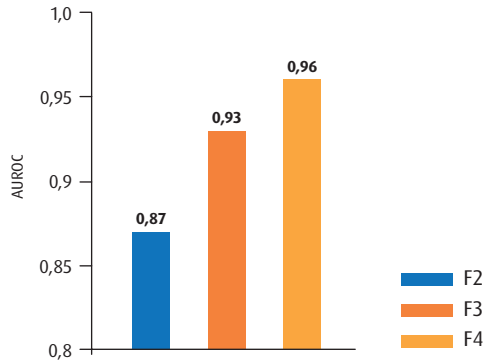


FIGURE 1: DIAGNOSTIC PERFORMANCES OF TE FOR FIBROSIS ASSESSMENT IN AIH VERSUS LIVER BIOPSY IN THE TOTAL COHORT (N=94) (SCHEUER SCORING SYSTEM)

Impact of hepatic inflammation on LS based on duration of immunosuppressive treatment

→ Patients with less than 3 months between LS examination and initiation of immunosuppressive therapy had higher biomarkers of inflammation and histological activity grade vs patients with at least 6 months of treatment before LS examination.

→ Diagnostic performance of LS was also impaired on these patients (*AUROC for diagnosing F2 was 0.68 for patients with less than 3 months between LS and treatment initiation, vs 0.97 for patients with at least 6 month treatment at the time of LS exam, cf Figure 2*).

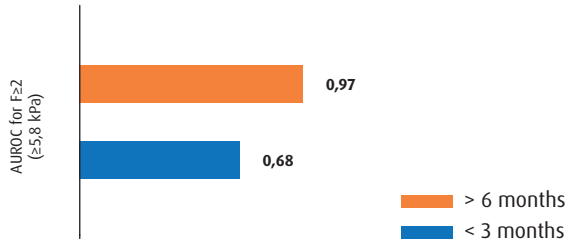


FIGURE 2: DIAGNOSTIC PERFORMANCE OF LSM BY TE AS FUNCTION OF TIME BETWEEN TREATMENT INITIATIONS AND LS EVALUATION (MONTHS)

Impact of biochemical and histological remission on LS

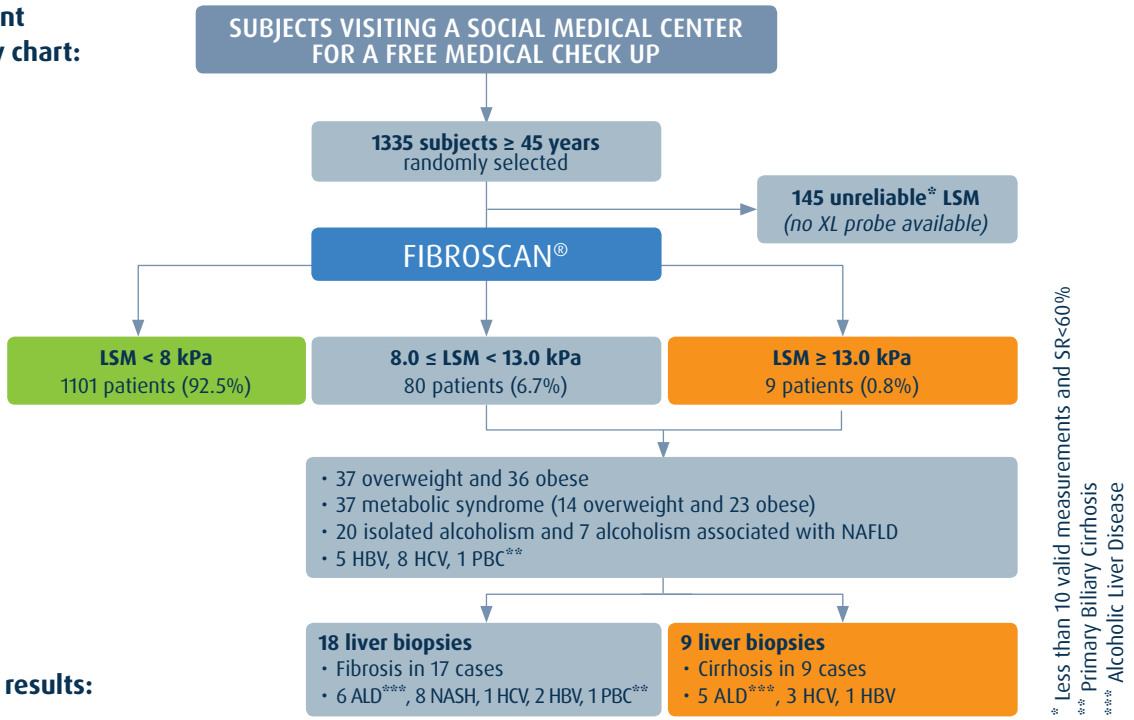
→ No differences in diagnostic performances were found between patient with biochemical remission at the time of LS examination (EASL definition, normal ALT and IgG levels), versus those with no remission.

KEY POINTS

- Liver stiffness measured by TE is a reliable surrogate marker of liver fibrosis in AIH patients treated for six months or longer
- TE has high accuracy for diagnosing cirrhosis F4 and severe fibrosis F3
- Since liver inflammation affects liver stiffness first months of immunosuppressive treatment, result shall be interpreted with caution during this period.

Miscellaneous

Screening in general population

REFERENCE	**Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years** *Roulot et al. (2011), Gut, 60 (7), 977-84*
OBJECTIVES	• To assess the performance of liver stiffness measurement using FibroScan® as a screening procedure for liver diseases in a large unselected community-based population aged 45 years or above.
METHOD	**Study chararecteristics:** • Examinations performed → Routine laboratory tests → Liver stiffness measurement (LSM) using FibroScan® → Patients with LSM ≥ 8kPa were referred to liver centre for further investigation → Liver biopsy was proposed to patients with LSM ≥8kPa • Liver stiffness measurements → Cut off of 8 kPa was chosen for normal values → Cut off of 13 kPa was chosen for cirrhosis
PATIENTS ANALYZED	• 1335 healthy patients over 45 years
GRAPHICS & RESULTS	**Patient study chart:**  **Main results:** • For all 89 subjects with LSM values >8 kPa, a specific cause of chronic liver disease was either documented or highly suspected • Liver biopsy was accepted by 18 patients with 8.0 ≤ LSM < 13.0 kPa and confirmed presence of fibrosis in 17 out of 18 cases (94% of patients) • Liver biopsy was accepted by 9 patients with LSM ≥13 kPa and confirmed cirrhosis in 9 cases (100% of patients)
KEY POINTS	• A relatively high percentage of liver diseases remain undiagnosed in apparently healthy subjects and LSM might contribute to referring these patients to hepatologists • LSM results, when explained to patients, have an obvious psychological impact that help to convince them to accept further investigations • This study validated LSM using FibroScan® as an effective screening procedure for cirrhosis in the general population

Controlled Attenuation Parameter (CAP™)

Multi-etiology

Multi-etiology

Meta-analysis of CAP diagnostic performances for steatosis assessment

REFERENCE

Individual Patient Data Meta-Analysis of Controlled Attenuation Parameter (CAP) Technology for Assessing Steatosis

Karlas et al., Journal of Hepatology, 2016 In Press

OBJECTIVES

- Conduct an individual patient data meta-analysis on CAP accuracy for non-invasive grading of liver steatosis.
- To establish CAP cut off values for distinguishing healthy from affected patients and "mild" from "significant" steatosis.

PATIENTS ANALYZED

- Indication/Etiology: Chronic liver diseases
- Median Age and SD: Adult: 45.4 ± 13.5
- % Male: 63.3%

METHOD

Study details

- Meta-analysis of 19 pooled studies

Sample Size

- 2735

Methodology

- Steatosis was graded histopathologically by evaluating the percentage of affected hepatocytes:
  → S0 (<5 or 10% depending on the trial), S1 (5 or 10-33%), S2 (34-66%), S3 (>66%)
- CAP was performed within 1 day of liver biopsy in 59.7% of patients and within one week in 97.2% of patients
- FibroScan (Liver stiffness, CAP) was performed with the M probe only
- Optimal CAP diagnostic cut offs were determined by maximizing the sum of Sensitivity and Specificity (Youden Index)

RESULTS & GRAPHICS

Diagnostic performances of CAP for steatosis evaluation

- The optimal cut-offs and 95% CI were 248 (237 to 261), 268 (257 to 284) and 280 (268 to 294) dB/m for identifying steatosis grades > S0, > S1 and > S2, respectively.
- 37% of individual had a CAP value≥238 dB/m suggestive of significant steatosis

MODELS	AUC	Sensitivity	False negative rate (1-Sensitivity)	Specificity	False positive rate (1-Specificity)	Optimal cut-off (db/m)
F≥1						
S0 vs. S1-S3	0.823 (0.809-0.837)	0.688 (0.600-0.750)	0.312 (0.250-0.400)	0.822 (0.761-0.897)	0.178 (0.103-0.239)	248 (237-261)
S0-S1 vs. S2-S3	0.865 (0.850-0.880)	0.773 (0.690-0.838)	0.227 (0.162-0.310)	0.812 (0.749-0.879)	0.188 (0.121-0.251)	268 (257-284)
S0-S2 vs. S3*	0.882 (0.858-0.906)	0.882 (0.765-0.956)	0.118 (0.044-0.235)	0.776 (0.720-0.821)	0.224 (0.179-0.280)	280 (268-294)

TABLE 1: DIAGNOSTIC PERFORMANCES OF CAP. RESULTS OF THE RECEIVER OPERATING CHARACTERISTIC (ROC) ANALYSIS.
AUC: AREA UNDER ROC CURVE; S0-S3: STEATOSIS GRADING ACCORDING TO HISTOLOGY.

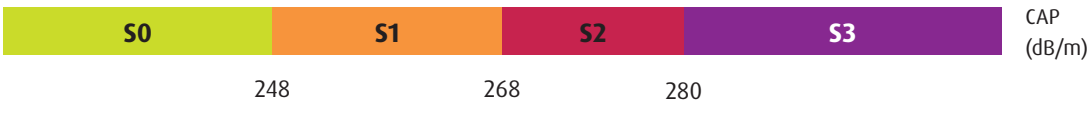


FIGURE 2: OPTIMAL CAP DIAGNOSTIC CUT OFFS (DB/M) FOR EACH HISTOLOGICAL STEATOSIS GRADE

RESULTS & GRAPHICS	**Impact of etiology and covariates on CAP** • BMI, diabetes, and etiology are found are found to have significant and relevant influence on CAP ($p<0.001$) • Although age is nominally significant, the estimate for the coefficient in the model shows that a difference of over 35 years would only account for about 10 dB/m. • NAFLD/NASH CAP values differs significantly from both HBV and HCV, whereas no contrast between HBV, HCV and "other etiologies"differs significantly **Variables associated with discrepancies between CAP and histological assessment of steatosis** • There was a difference of at least 2 categories between steatosis grading based on histology and CAP cut-offs in 15% of cases • BMI was associated with discrepancies, largest dependence was observed for an increase of 10 BMI units (Odds ratio of 2.67) • Etiology, fibrosis staging, diabetes and IQR of CAP were not associated with discrepancies (p=ns for all)
KEY POINTS	• CAP provides a standardized non-invasive measure of hepatic steatosis, with established cut-offs of 248, 268 and 280 dB/m for steatosis grades > S0, > S1 and > S2, respectively • Prevalence, etiology, diabetes, and BMI deserve consideration when interpreting CAP • The recently introduced CAP feature for the transient elastography XL probe may overcome this BMI dependence.

Multi-etiology

Adaptation of CAP on XL probe

REFERENCE	**LIVER STEATOSIS ASSESSED BY CONTROLLED ATTENUATION PARAMETER (CAP) MEASURED WITH THE XL PROBE OF THE FIBROSCAN: A PILOT STUDY ASSESSING DIAGNOSTIC ACCURACY** Sasso et al. Ultrasound Medicine & Biology, 2015, In press
OBJECTIVES	• To adapt the CAP algorithm on the FibroScan XL probe to allow physician to use the same CAP interpretation scale with both probes. • To validate the reproducibility and diagnostic performance of CAP measured using the FibroScan XL probe in a cohort of patients undergoing steatosis quantification assessed by MRI.
PATIENTS ANALYZED	• 59 patients with different grades of hepatic steatosis
RESULTS & GRAPHICS	**Correlation between CAP measurement and fat fraction measured by MRI** CAP was significantly correlated with the MRI-based hepatic fat fraction (ρ= 0.73, ρ<0.0001, and ρ=0.74, ρ<0.0001) for measurements using the M and XL probes, respectively. **Reproducibility of CAP measurements** Intra class correlation coefficient (ICC) for CAP was equal to 0.83 [0.76; 0.89] and 0.84 [0.77; 090] for the M and XL probes, respectively. **Factors associated with CAP** By multivariate regression analysis, only BMI and steatosis (assessed by MRI) were significantly associated with CAP values. CAP was independent of liver stiffness measurement (LSM) for both probes (p>0.10) **Diagnostic performances of CAP for steatosis evaluation (AUROCs)** No statistical differences were found for the diagnostic performances in terms of AUROC between the two probes (p values≥0.5, cf Table 1).

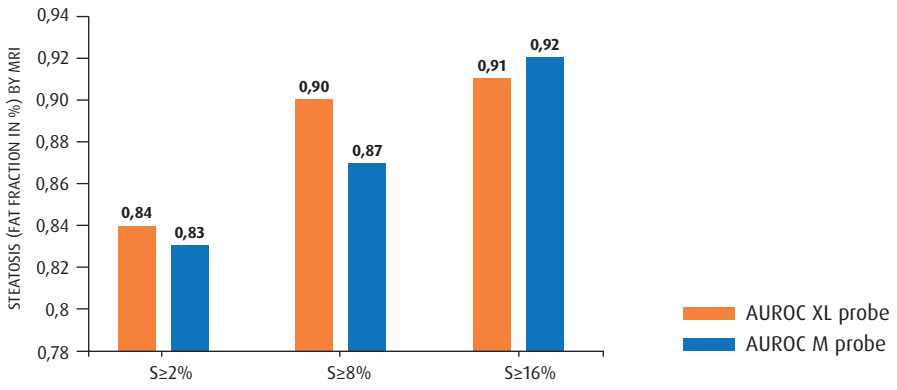


FIGURE 1 : DIAGNOSTIC PERFORMANCES OF CAP M & XL PROBES (AUROCS) VERSUS MRI

Fat fraction S (%) by MRI	CAP with M probe		CAP with XL probe		p value *(Delong Test for statistical difference)*
S≥2%	Cut-off (dB/m): Se (%): Sp (%):	251 78 78	Cut-off (dB/m): Se (%): Sp (%):	254 83 78	0.76 (ns)
S≥8%	Cut-off (dB/m): Se (%): Sp (%):	267 80 79	Cut-off (dB/m): Se (%): Sp (%):	270 88 79	0.50 (ns)
S≥16%	Cut-off (dB/m): Se (%): Sp (%):	299 92 88	Cut-off (dB/m): Se (%): Sp (%):	301 92 81	0.78 (ns)

S=steatosis, Se=sensitivity, Sp=specificity, ns: non-significant

TABLE 1 : DIAGNOSTIC PERFORMANCES OF CAP MEASURED BY FIBROSCAN M AND XL PROBES VS MRI

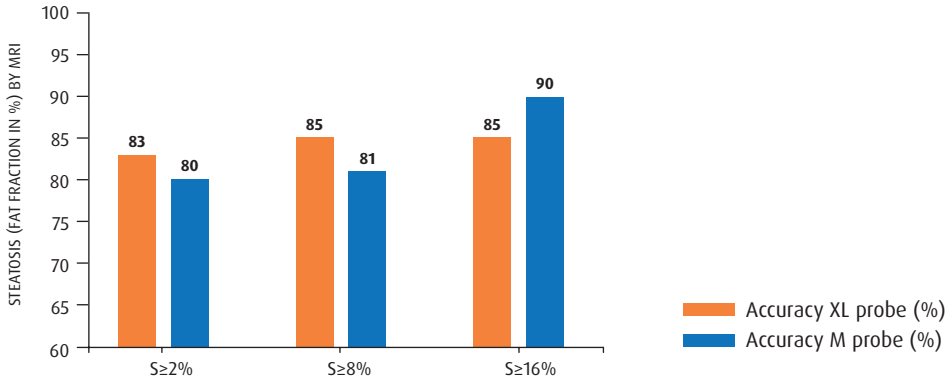


FIGURE 2: % OF WELL CLASSIFIED PATIENTS WHEN USING CAP CUT-OFFS (TABLE 1) TAKING MRI AS REFERENCE

KEY POINTS

- CAP algorithm was successfully adapted for the FibroScan XL probe, and result can be interpreted with the same reading scale as for the M probe.
- Reproducibility was good, and CAP exhibits good to excellent diagnostic performances to quantify hepatic steatosis, taking MRI as a reference.
- CAP can now be assessed properly on overweight and obese patients who are particularly exposed to steatosis.
- NASH patients will benefit from this new development as they can be assed simultaneously for steatosis and fibrosis, regardless of their morphology.

Chronic Viral hepatitis

Chronic Viral hepatitis

Performances of CAP vs histology

REFERENCE

Novel Controlled Attenuation Parameter (CAP™) for non-invasive assessment of steatosis using FibroScan®: validation in chronic hepatitis C.

M. Sasso and al.(2011). *Journal of viral hepatitis*, in press

OBJECTIVES

- To assess the diagnostic accuracy of Controlled Attenuation Parameter (CAP™) for steatosis assessment in a large cohort of patients with chronic hepatitis C in comparison with histology.

METHOD

- Prospective monocenter cross-sectional study
- Steatosis grading by liver biopsy (% of hepatocytes):
  - → S0: <10%
  - → S1: 11-33%
  - → S2: 34-66%
  - → S3: >66%
- Pathologist blinded from CAP™ results.

PATIENTS ANALYZED

- 615 patients with HCV

GRAPHICS & RESULTS

Relationship between CAP™ and histological parameters

By multivariate analysis (including fibrosis, steatosis and activity), steatosis was the only histological parameter significantly related to CAP™ ($\rho<10^{-16}$)

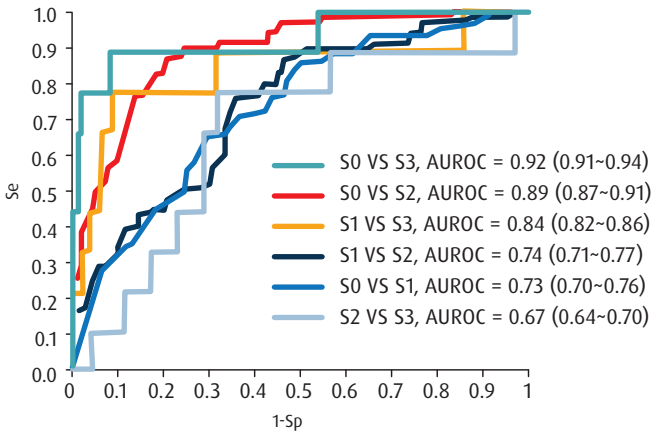
CAP™ performances for steatosis assessment versus histology

Steatosis Grade	AUROC	Optimal cut off*	Se	Sp	PPV	NPV
≥S1	0.80	222 dB/m	0.76	0.71	0.53	0.87
≥S2	0.86	233 dB/m	0.83	0.74	0.33	0.98
≥S3	0.88	290 dB/m	0.78	0.93	0.15	1

* Cut off chosen for maximizing the sum of Sensitivity and Specificity (Se+Sp)

Steatosis quantification using CAP™

- CAP™ showed excellent performance to differentiate S0/S3 (AUROC=0.96)
- CAP™ showed good performance to differentiate S0/S2 and S1/S3 (AUROC=0.89 and 0.84, respectively)
- CAP™ showed poor performance to differentiate S0/S1, S1/S2, and S2/S3 (AUROCs=0.74, 0.73, 0.67 respectively)



KEY POINTS

- CAP™ shows good performance to detect steatosis and to differentiate steatosis grades at ≥ 2 grades apart
- Liver biopsy remains the gold standard for steatosis assessment but it cannot be performed repeatedly
- Compared to Liver Biopsy, CAP™ is less prone to sampling error, and it can explore a liver volume about 100 times larger.
- Both steatosis and fibrosis can be evaluated non-invasively during the same procedure using FibroScan® on patients with chronic hepatitis C.

NAFLD & ALD

NAFLD

CAP vs Magnetic Resonance Spectrospopy (1H-MRS) in NAFLD patients

REFERENCE

Non-Invasive Assessment of Hepatic Steatosis in Patients with NAFLD Using Controlled Attenuation Parameter and 1H-MR Spectroscopy

Karlas et al., Plos One, March 2014, Issue 3, Volume 9

OBJECTIVES

- To compare CAP™ performance and 1H-magnetic resonance spectroscopy (1H-MRS) for diagnosis of hepatic steatosis versus histology as a reference method

METHOD

- Prospective cross-sectional study

Patients

- Study group: biopsy proven NAFLD or NASH patients, exclusion of concomitant diseases
- Healthy group: volunteers without any signs of fatty liver or metabolic syndrome

Examination

- Liver biopsy: use of NAS Score for diagnostic of NASH; steatosis grading: S1 "mild": 5-33%; S2 "Moderate": 33-66%; S3 "Severe":>66%
- FibroScan CAP™ measurement: performed with the FibroScan M probe.
- 1H-MR Spectroscopy: performed within 3 weeks from CAP™ measurement.

PATIENTS ANALYZED

- 50 NAFLD patients (Study Group)
- 15 Healthy volunteers (Control Group)

RESULTS & GRAPHICS

Diagnostic performances of CAP™ and 1H-MRS for steatosis assessment (AUCs) using histology as a reference:

→ CAP and 1H-MRS exhibited comparable performances for staging the different grades of steatosis.

Steatosis grades (histology)

S0 vs S1S2S3 (Steatosis >5%)	FibroScan CAP™	1H-MRS
AUC	**0.93**	**0.87**
Optimal cut off*	233.5 dB/m	3.12% fat fraction
Sensitivity (%)	93	79
Specificity (%)	87	88

S0S1 vs S2S3 (Steatosis >33%)	FibroScan CAP™	1H-MRS
AUC	**0.94**	**0.88**
Optimal cut off*	286.5 dB/m	8.77% fat fraction
Sensitivity (%)	97	91
Specificity (%)	81	77

S0S1S2 vs S3 (Steatosis >66%)	FibroScan CAP™	1H-MRS
AUC	**0.82**	**0.85**
Optimal cut off*	301.2 dB/m	13.69% fat fraction
Sensitivity (%)	82	91
Specificity (%)	76	75

Table 1: Performances of CAP™ versus 1H-MRS for steatosis grading versus histology
**Cut off chosen for maximizing the Youden Index (Se+Sp)*

Cut-offs values of CAP™ for clinical use (Fig1)

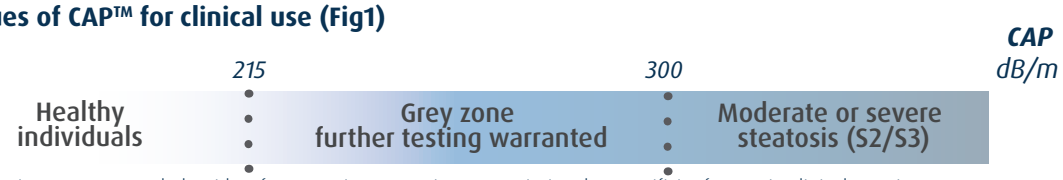


Figure 1: proposed algorithm for CAP™ interpretation to maximize the Specificity for use in clinical practice

→ This proposed CAP™ algorithm allows to correctly classify 50% of patients with no steatosis, or with moderate to severe steatosis (S2 and S3 stages).

KEY POINTS

- CAP™ and 1H-MRS exhibit comparable accuracy for non-invasive assessment of hepatic steatosis.
- CAP™ is a promising tool for steatosis evaluation, since it allows correctly classifying 50% of individuals by using the algorithm proposed in the present study.
- FibroScan®, with concomitant assessment of CAP™ and liver stiffness, represents a fast and easy method for better characterization on patients with NAFLD.

ALD

Steatosis evaluation and effect of alcohol detoxification on CAP

REFERENCE

CAP & Alcoholic Hepatic Steatosis: Diagnostic Accuracy & Role of Alcohol Detoxification

M Thiele, et al., *Journal of Hepatology*, 2018, in Press

OBJECTIVES

- To validate CAP for assessment of biopsy-verified alcoholic steatosis
- To study the effect of alcohol detoxification on CAP

METHOD

Study details

- Main Inclusion criteria:
  - → Patients with a prior or on-going use of alcohol exceeding the max recommended limit [3 units/day for men & 2 unit/day for women] with at least one year of excessive drinking

Examinations performed

- Ultrasound examination
  - → Evaluation of the bright liver echo pattern (BLEP) to define steatosis on B mode ultrasound
- Liver biopsy:
  - → 10 mm minimum required, at last 5 portal tracts
  - → Use of the NASH CRN Scoring system
- FibroScan (TE)
  - → Performed by experienced operator (>500 exams)
  - → 10 measurements minimum required, with IQR/Median ratio for stiffness below 30%
  - → Sub analysis was performed applying CAP IQR as 40 dB/m maximum as a quality criteria

PATIENTS ANALYZED

- 269 patients (for diagnostic cohort)
- 293 patients (for detoxification cohort)

RESULTS & GRAPHICS

Diagnostic performances of LSM by FibroScan vs liver biopsy

- TE diagnosed advanced fibrosis with excellent accuracy

	AUC	Sensitivity	Specificity	PPV	NPV
Fibrosis F≥3	0.96 (0.93-0.98)	91%	94%	90%	95%

TE and CAP were independent from each other

Diagnostic performances of CAP vs liver biopsy

- CAP performances for any steatosis (AUC>=S1 = 0.77) and moderate steatosis (AUC>=S2=0.78) exhibited fair accuracy, whereas performances were good for severe steatosis (AUC S3 = 0.82).
- CAP diagnosed steatosis with higher diagnostic accuracies than BMI, waist circumference and BLEP (p<0.02 for AUC comparisons).
- In posthoc subgroup analyses of CAP IQR as a marker of reliability, the accuracy of CAP to diagnose any steatosis was significantly better if IQR was below 40 dB/m (P= 0.006 for IQR <40 dB/m versus IQR ≥40 dB/m).

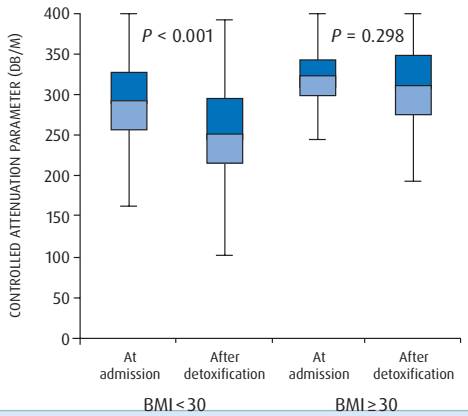
	Any steatosis (S≥1)	Moderate Steatosis (S≥2)	Severe Steatosis (S≥3)
Diagnostic accuracy	0.77 (0.71-0.83)	0.78 (0.72-0.83)	0.82 (0.75-0.88)
Optimal cut off value for 90% Se	220 dB/m	257 dB/m	286 dB/m
Optimal cut off value for 90% Sp	300 dB/m	328 dB/m	339 dB/m
Sub analysis **CAP IQR <40 dB/m (n=143)** **CAP IQR≥40 dB/m**	 0.86 (0.79-0.92) 0.63 (0.48-0.77)	 0.79 (0.66-0.92) 0.81 (0.74-0.88)	 NA*

*No IQR≥40 in S3

RESULTS & GRAPHICS

Effect of detoxification on CAP

- CAP declined during hospitalization (median time 6.3 days) in 76% of the patients (from 293±50 dB/m to 261±56 dB/m, P<0.001), with a mean difference in CAP of 32±47 dB/m.
- Obese patients with BMI >30 kg/m2 had a significantly higher CAP, which did not decrease significantly during detoxification.



KEY POINTS

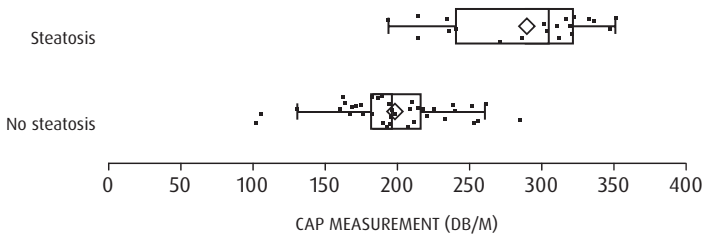
- CAP performed better in the determination of steatosis than regular ultrasonography.
- CAP can be used to detect severe alcoholic steatosis and to rule in any steatosis.
- CAP decreased significantly in non-obese ALD patients after alcohol detoxification.
- Given the potential of CAP to capture the dynamics of alcohol withdrawal, the method can be used in conjunction with TE for monitoring patients during and after alcohol rehabilitation.

Paediatric liver diseases

Paediatric liver diseases

Steatosis noninvasive evaluation in children

REFERENCE	**Comparison of Controlled Attenuation Parameter and Liver biopsy to assess hepatic steatosis in pediatric patients** Desai et al., *The Journal of Pediatrics*, 2016, March
OBJECTIVES	• To assess whether the degree of steatosis as determined by controlled attenuation parameter (CAP) correlates with that observed on liver biopsies in a single-center pediatric and young adult cohort
METHOD	**Study details:** • Patients: → Children and young adults with indication of liver biopsy → Pregnant women and patients with medical implantable devices excluded • Liver biopsy: → Use of the Kleiner scoring system for steatosis assessment → S0: <5% → S1: 5-33% → S2: 33-66% → S3: >66% → Use of Brunt scoring system for fibrosis assessment • FibroScan and blood analyses → Blood analyses were performed within 6 months of CAP examination → FibroScan CAP measurement was performed either with M or XL probe based on manufacturer recommendations (*Patients with thoracic perimeter<75 cm and requiring the use of S probe were excluded*)
PATIENTS ANALYZED	• 69 patients included in the study • Median time between liver biopsy and CAP measurement was 1.3 months
GRAPHICS & RESULTS	**Diagnostic accuracy of CAP** → The mean CAP measurement for patients without steatosis was 198 ± 37 versus 290 ± 47 dB/m for patients with steatosis (p < 0.0001, cf Fig 1) → CAP was also able to distinguish severity of steatosis (cf Fig 2): Mean CAP measurement for patients with no steatosis was 198 ± 37 dB/m compared with 265 ± 53 dB/m for patients with mild or moderate steatosis (P < .0001) and 313 ± 25 dB/m for patients with marked steatosis (p<0.001) → No effect on BMI on CAP measurements (p=0.81)



	N	Mean ± SD	p
Steatosis			
Yes	23	290 ± 47	<.0001
No	46	1980 ± 37	

FIGURE 1: CAP MEASUREMENT AS FUNCTION OF STEATOSIS (PRESENCE/ABSENCE)

GRAPHICS & RESULTS

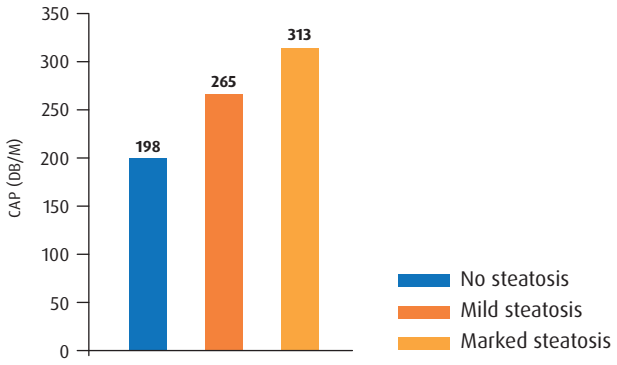


FIGURE 2: CAP MEASUREMENT AS FUNCTION OF SEVERITY OF STEATOSIS

→ Optimal cut point of 225 dB/m for predicting steatosis was identified, with with 0.87 sensitivity, 0.83 specificity, positive predictive value 0.71, negative predictive value 0.93, and area under the curve 0.93 (95% CI, 0.87-0.99).

KEY POINTS

- CAP is a noninvasive tool that may be useful in the detection of steatosis in children
- A CAP threshold of 225 dB/m may be optimal to detect steatosis in a pediatric population

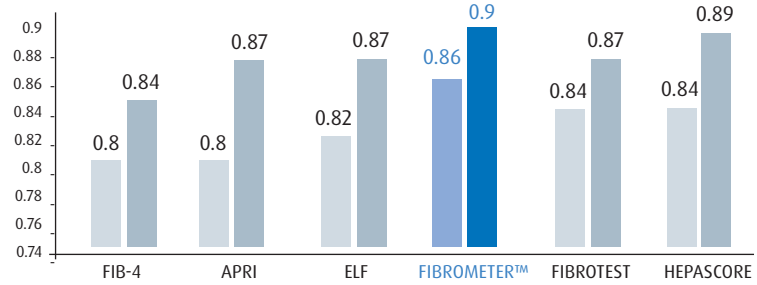
FibroMeter™

Chronic Viral hepatitis

Chronic Viral hepatitis

FibroMeter Virus in Chronic hepatitis C

REFERENCE	**Comparison of 9 blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study** Zarski et al., J Hepatol. 2012 Jan;56(1):55-62
OBJECTIVES	• To perform a prospective independent comparative evaluation of most of the currently best evaluated fibrosis non-invasive markers (Blood tests and FibroScan®) versus liver biopsy in chronic hepatitis C patients.
METHOD	• Multicentre (19 sites) prospective cross sectional study • HCV infected untreated patients, or no treatment during the last 6 months prior to enrollment in the study • Biopsy: reading in central lab by 2 experienced pathologists • Blood tests: FibroMeter™, Hepascore, ELF, Forns, Hyaluronate, APRI, FIB-4, FibroTest, MP3 analysed in a central laboratory • Delay between blood tests and biopsy < 3 months
PATIENTS ANALYZED	• 382 CHC patients with both blood tests and FibroScan® results available
RESULTS	• Diagnostic performances (Areas under ROC curves) → **For diagnostic of significant fibrosis F≥2, performances of FibroMeter were slighty better compared to other biomarkers (FibroTest, Hepascore and APRI)** → For diagnostic of cirrhosis F4, all patented tests were equivalent (cf Figure 1) • Combination of tests → **Algorithm combining FibroMeter™ or one of the best blood tests and Fibroscan® improved the accuracy for significant fibrosis F≥2 and markedly decreased the requirement for biopsy (cf Figure 2)** → Combination between tests does not improve the diagnostic accuracy for the diagnostic of cirrhosis (best markers such as FibroMeter™, FibroScan®, Hepascore or FibroTest could be used alone).
GRAPHICS & RESULTS	



	FIB-4	APRI	ELF	FIBROMETER™	FIBROTEST	HEPASCORE
F ≥ 2	0.80	0.80	0.82	**0.86**	0.84	0.84
F 4	0.84	0.87	0.87	**0.90**	0.87	0.89

Fig1: Diagnostic performances (AUCs) of the 6 best fibrosis blood tests (n=382) for significant fibrosis and cirrhosis in comparison with histology

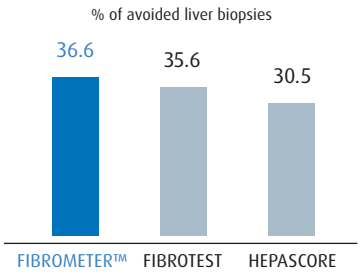


Fig2: Percentage of potentially avoided liver biopsies by using one of the three best fibrosis blood tests in combination with FibroScan® for diagnosis of significant fibrosis

KEY POINTS	• The combination of FibroMeter™ with Fibroscan® improves the diagnostic performance for diagnosing significant fibrosis (F≥2). • For the diagnosis of cirrhosis F4, the best blood tests (including FibroMeter™) or Fibroscan®, when interpretable, can be used alone.

[Publi_Zarski et al.,2012] - Revision date [03/11/2015] - FibroMeter™ Virus is classified as an in vitro diagnostic medical device and is manufactured by BioLiveScale. The FibroMeter score is based on blood parameters and is indicated for the diagnosis and quantification of liver fibrosis in adult patients with chronic liver disease due to virus. It is expressly recommended to carefully read the guidance within the users' guide together with the labeling of the device. Examinations must be performed according to the pre analytical and analytical recommendations from the manufacturer (www.fibrometer.com). Results obtained must be interpreted by a physician experienced in dealing with liver disease, taking into account the complete medical record of the patient. FibroScan® is a class IIa medical device according to Directive EC/93/42 and is manufacturedby Echosens.Assessment of its conformity with the essential requirements of the Directive EC/93/42 is established by the LNE-G-MED (n°0459)-France - . FibroScan® is indicated for the non invasive measurement of liver stiffness (E) and controlled attenuation parameter (CAP) in humans. It is expressly recommended to carefully read the guidance within the users' guide and labeling of the device. FibroScan® examination must only be performed by operators certified by the manufacturer or its accredited local representative. The values obtained with FibroScan® must be interpreted by a physician experienced in dealing with liver disease, taking into account the complete medical record of the patient.

Chronic Viral hepatitis

FibroMeter Virus in Chronic Hepatitis B

REFERENCE	**Prospective evaluation of FibroTest®, FibroMeter®, and Hepascore® for staging fibrosis in chronic Hepatitis B: comparison with hepatitis C.** Leroy et al., *Journal of Hepatology*, 2014, *In Press*
OBJECTIVES	• Compare diagnostic performances of FibroTest™ (FT), FibroMeter™, and Hepascore® (HS) for fibrosis assessment in CHB and CHC.
METHOD	• **Blood markers:** Collected the same day of liver biopsy. • **Liver biopsy (METAVIR):** → à Fragmented samples excluded → à Minimum length of 15mm required → à Reading by single experienced pathologist blinded from biochemical markers
PATIENTS ANALYZED	• 510 patients → 255 CHB patients → 255 CHC patients
RESULTS & GRAPHICS	**Correlation between blood markers and histology (METAVIR)** → All the tests including FibroMeter® were significantly correlated to fibrosis stage in both CHB (r=0.67, p<0.001) and CHC patients (r=0.64, p<0.001). → All blood tests values values tended to be lower in F3F4 patients in CHB compared to CHC (0.74 vs 0.90 respectively, p<0.01)

Diagnostic accuracy of blood markers in CHB and CHC patients (cf Fig 1)

→ In the CHB population (n=255), FibroMeter® demonstrated superiority over both FT and HS for the diagnostic of significant fibrosis F≥2 (Auroc of 0.84 vs 0.79, p<0.001 and vs 0.77, respectively, p<0.001) and of extensive fibrosis F≥3 (AUROC of 0.88 vs 0.83, p<0.02, and vs 0.84, p<0.05, respectively.

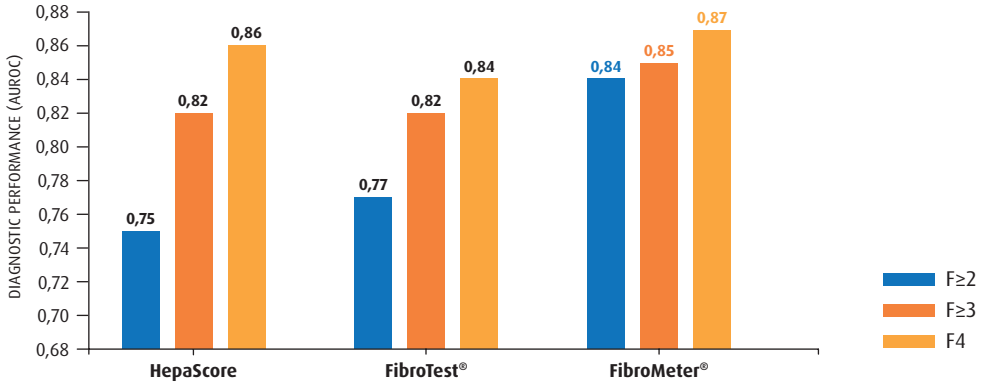


FIG 1: COMPARISON OF BLOOD TESTS FOR FIBROSIS STAGING (AREA UNDER ROC CURVES) IN THE OVERALL POPULATION (N=510).

A P VALUE <0.05 IS CONSIDERED SIGNIFICANT FOR STATISTICAL DIFFERENCE.

→ All studied blood markers exhibited comparable performances for diagnosing cirrhosis (F4).

→ No statistical differences between studied blood tests when CHB and CHC subgroups were studies separately.

→ FibroMeter® exhibiter similar accuracy in CHB compared to CHC patients (cf Table 1)

	F≥2		F≥3		F4	
AUROC FibroMeter®	CHB	CHC	CHB	CHC	CHB	CHC
	0.84	0.85	0.85	0.91	0.87	0.92

TABLE 1: DIAGNOSTIC PERFORMANCES (AUROCS) OF FIBROMETER IN CHB (N=255) AND CHC PATIENTS (N=255)

Definition of optimal cut offs (cf Table 1)

→ Cut offs of blood markers including FibroMeter® were lower in CHB compared to CHC patients (0.47 vs 0.64 for F≥2, 0.69 vs 0.72 for F≥3, and 0.72 vs 0.78 for F4, respectively)

Factors of discordance between blood tests and histology

→ By multivariate analysis, CHB aetiology and low GGT values were independent factors of fibrosis underestimation by blood markers.

KEY POINTS

- FibroMeter® exhibits the best performances than any other studied fibrosis blood markers for the diagnosis of both significant and extensive fibrosis in the overall population.
- Overall performance of blood tests including FibroMeter® is similar in CHB compared to CHC.
- Blood tests values are lower in CHB compared to CHC, potentially due to thiner fibrosis septa in CHB and less frequent sinusoidal fibrosis.
- Blood tests cut-offs including FibroMeter® cut offs should be specifically designed for CHB patients to avoid under diagnosing fibrosis and cirrhosis.

NASH

NASH

FibroMeter NAFLD in NAFLD/NASH Patients

REFERENCE

Performance of Non-invasive Models of Fibrosis in Predicting Mild to Moderate Fibrosis in Patients with Nonalcoholic Fatty Liver Disease (NAFLD)

Siddiqui et al., Alimentary Pharmacology & Therapeutics, 2016, In Press

OBJECTIVES

- To evaluate the performance of a panel of non-invasive models including FibroMeter NAFLD (FM NAFLD) in predicting fibrosis in NAFLD.

METHOD

Study details

- Study type:
  - → Retrospective cross sectional study
- Liver biopsy:
  - → Fibrosis was staged based on the KLEINER/BRUNT scoring system (NASH CRN criteria)
  - → Steatosis was defined by the presence of at least 5% of steatosis
  - → NASH was diagnosed by evaluating presence of steatosis, inflammation and lobular ballooning (NAS Score)
  - → Biopsy was performed by two experts pathologists, consensus was reached in case of discordance
- Blood tests
  - → FibroMeter NAFLD (FM NAFLD), FIB4, APRI, BARD Score, BAAT Score, AST/ALT ratio, NAFLD fibrosis score were computed for all patients
  - → Blood tests were performed with data collected within 2 months of liver biopsy.
- Statistical analysis:
  - → Diagnostic performances were evaluated by using Area Under ROC curves (AUROCs). Comparisons between tests were performed using the Delong method.

PATIENTS ANALYZED

- 145 Non Alcoholic Fatty Liver Disease (NAFLD)

RESULTS & GRAPHICS

Occurrence of steatosis and NASH in the cohort

- → 99 patients were diagnosed as NASH, whereas 46 patients had simple steatosis

Performances for the detection of mild fibrosis (F≤1)

- → Diagnostic performance (AUROC) was greatest for FIB4 (0.821[0.750-0.891]) and FibroMeter NAFLD (0.801[0.718-0.883]), compared to the other tests (Table 1)
- → FibroMeter NAFLD outperformed other models with a diagnostic accuracy ratio (DA) of 80.0% with PPV of 84.9% and NPV of 66.7% (Figure 1)

MODELS	AUROC (95% CI)	Cut-Off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)
F≥1							
FM NAFLD	**0.801 (0.718-0.883)**	**0.151**	**87.4**	**61.9**	**84.9**	**66.7**	**80.0**
APRI	0.762 (0.673-0.851)	0.425	79.6	64.3	84.5	56.3	75.2
FIB-4	0.821 (0.750-0.891)	1.430	60.2	92.9	95.4	48.6	69.7
BARD	0.673 (0.579-0.767)	2.00	68.6	58.5	80.2	43.2	65.7
BAAT	0.676 (0.577-0.774)	2.00	90.4	35.0	77.9	59.7	72.4
AST/ALT Ratio	0.695 (0.602-0.789)	0.738	63.1	71.4	84.4	44.1	65.5
NAFLD Fibrosis	0.740 (0.645-0.834)	0.047	91.3	48.8	81.4	69.5	79.2

TABLE 1: DIAGNOSTIC PERFORMANCES OF STUDIED PANELS FOR THE DIAGNOSIS OF MILD FIBROSIS F≤1

AUROC : area under the ROC curve; 95% CI: 95%confidence interval; PPV: positive predictive value; NPV: negative predictive value; DA: diagnostic accuracy

RESULTS & GRAPHICS

Performances for the detection of advanced fibrosis (F≤3)

- → NAFLD-FM and FIB4 had the highest AUROC with AUROC of 0.862 (0.801-0.923) and 0.866 (0.802-0.931), respectively, significantly higher than the other tests (Table 2)
- → Diagnostic accuracy (DA) was highest for FIB4 (85.5%) followed closely by FibroMeter NAFLD (82.1%, cf Figure 1).

MODELS	AUROC (95% CI)	Cut-Off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)
F≥3							
FM NAFLD	**0.862 (0.801-0.923)**	**0.589**	**74.5**	**86.2**	**74.5**	**86.2**	**82.1**
APRI	0.797 (0.721-0.873)	0.706	64.7	80.9	64.7	80.9	75.2
FIB-4	0.866 (0.802-0.931)	1.961	70.6	93.6	85.7	85.4	85.5
BARD	0.687 (0.594-0.760)	4.00	39.2	90.2	68.5	73.2	72.0
BAAT	0.615 (0.520-0.710)	2.00	94.9	23.8	40.3	89.5	46.3
AST/ALT Ratio	0.728 (0.643-0.813)	0.748	74.5	60.6	50.7	81.4	65.5
NAFLD Fibrosis	0.787 (0.709-0.864)	0.156	80.4	68.8	58.3	86.6	72.9

TABLE 2: DIAGNOSTIC PERFORMANCES OF BLOOD PANELS FOR ADVANCED FIBROSIS F≥3

AUROC : area under the ROC curve; 95% CI: 95%confidence interval; PPV: positive predictive value; NPV: negative predictive value; DA: diagnostic accuracy

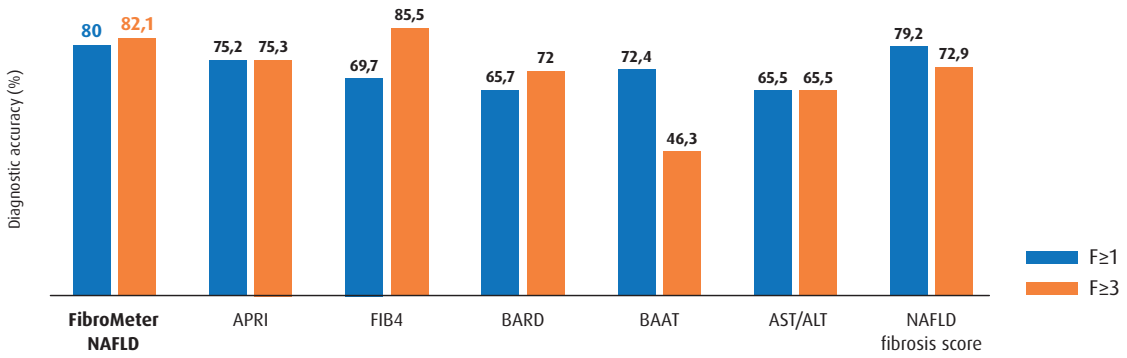


TABLE 1: DIAGNOSTIC ACCURACY OF FIBROSIS BLOOD PANELS FOR F1 AND F3 (% OF WELL DIAGNOSED PATIENTS TAKING THE BIOPSY AS REFERENCE)

Performances with fixed sensitivity and specificity

- → With a fixed sensitivity at 90%, FM NAFLD outperformed other models at predicting F≥1 and F≥3 fibrosis, with higher Specificity (Sp=52.4% for F≥1 fibrosis, PPV 82.3%, NPV 68.8%, and Sp=63.8% for F≥3 fibrosis, PPV 57.5%, NPV 92.%).
- → With a fixed specificity at 90%, FIB4 performed better than other models with higher Sensitivity (Se=60.2% for predicting F≥1 fibrosis, and Se=70.6% for F≥3 fibrosis.)

KEY POINTS

- Non-invasive models can predict presence of mild fibrosis (F≥1) and advanced fibrosis (F≥3) fibrosis with reasonable accuracy in NAFLD.
- FM-NAFLD and FIB4 have the highest performance for diagnosing F≥1 and F≥3 fibrosis compared to other blood panels. FibroMeter NAFLD was the best model to predict mild fibrosis whereas FIB4 was superior to predict advanced fibrosis.

Multi-etiology

Multi-etiology

Added value of FibroMeter VCTE in the main etiologies of chronic liver diseases

REFERENCE	**A Single Test Combining Blood Markers and Elastography is More Accurate Than Other Fibrosis Tests in the Main Causes of Chronic Liver Diseases.** Ducancelle, et al., *Journal of Clinical Gastroenterology* 2017; 51(7):639-649.
OBJECTIVES	• To evaluate the accuracy of combined noninvasive tests (blood test and liver stiffness measurement) for fibrosis assessment, as recommended by international guidelines
METHOD	**Noninvasive tests evaluated:** • **Simple tests** : APRI, FIB4 • **Specialized blood tests** : FibroMeters® (FibroMeter VIRUS, FibroMeter NAFLD, FibroMeter ALD), FibroTest®, Zeng Score, NAFLD fibrosis Score • **LSM tests**: Vibration Controlled Transient Elastography (VCTE) by FibroScan® • **Combined tests**: FibroMeter VCTE (combination of VCTE and FibroMeter) **Inclusion criteria** • Chronic liver disease with a single predominant cause (CHC, CHB, NAFLD, ALD, HIV/CHC coinfection, HIV) • Liver biopsy available • At least 10 calculable noninvasive tests **Exclusion criteria** • Interval > 6 months between biopsy and noninvasive test • Patient on treatment or with complications or liver transplantation **Liver biopsy** • Used as a reference standard • Read by expert pathologists **Statistics** • Diagnostic accuracy was valuated using both Obuchowski Indexes (OIs), and Area Under ROC Curves (AUROCs)
PATIENTS ANALYZED	• Multietiology (CHC, CHB, NAFLD, ALD, HIV/CHC coinfection, HIV)

RESULTS & GRAPHICS

Performances of tests per aetiology (Obuchowski Index)

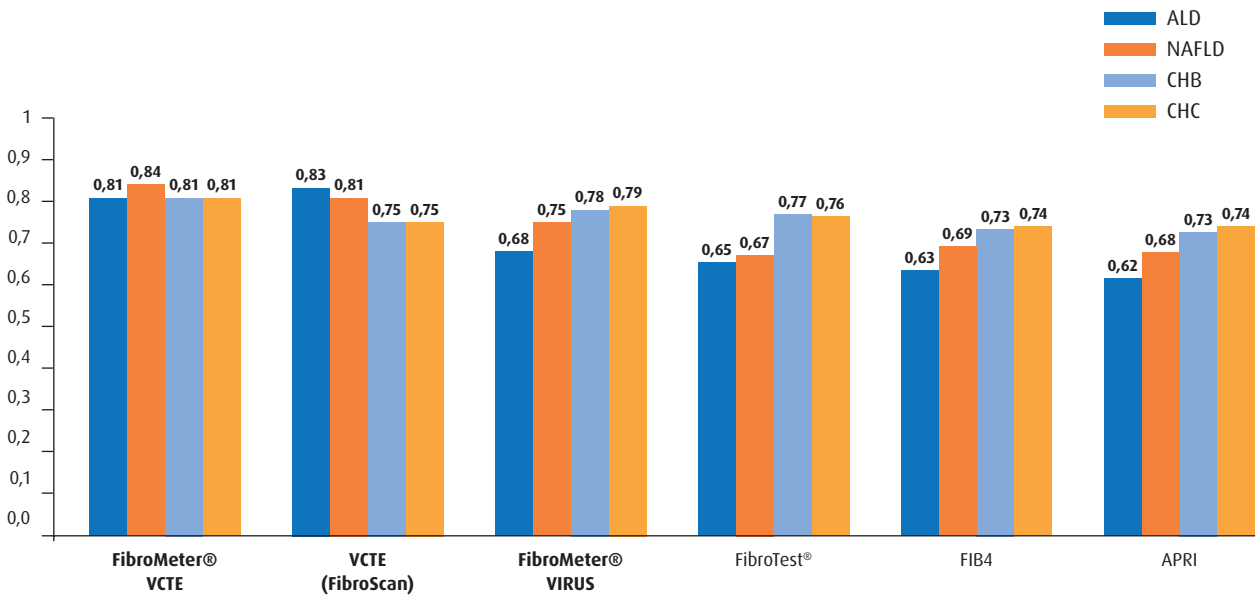


FIGURE 1: OBUCHOWSKI INDEX (OIS) COMPARISON BETWEEN TESTS FOR THE FOUR MAIN ETIOLOGIES OF CHRONIC LIVER DISEASE.

Focus on combined tests (FibroMeter VCTE)

- In CHC (n=641), FibroMeter VCTE had significantly higher indices than their constitutive tests in all diagnostic targets.
- In CHB (n=152), FibroMeter VCTE had significantly higher indices for all diagnostic targets versus VCTE and for cirrhosis diagnosis only versus FibroMeter VIRUS.
- In NAFLD (n=226), FibroMeter VCTE had significantly higher indices than their constitutive tests in all diagnostic targets (except for cirrhosis).
- In ALD (n=150), FibroMeter VCTE had significantly higher indices than FibroMeter VIRUS in all diagnostic targets but there was no advantage compared with VCTE.

	CHC			CHB			NAFLD			ALD		
AUROC	***FM VCTE***	FM	VCTE	***FM VCTE***	FM	VCTE	***FM VCTE***	FM	VCTE	***FM VCTE***	FM	VCTE
F≥2 p	***0.842***	0.798 *0.0001*	0.788 *0.0002*	***0.865***	0.832 *ns*	0.790 *0.0131*	***0.893***	0.839 *0.0122*	0.833 *0.0026*	***0.890***	0.701 *<0.0001*	0.922 *0.0970*
F≥3 p	***0.877***	0.816 *<0.0001*	0.839 *0.0014*	***0.900***	0.856 *ns*	0.828 *ns*	***0.917***	0.807 *0.0002*	0.886 *ns*	***0.855***	0.666 *<0.0001*	0.861 *ns*
F4 p	***0.922***	0.844 *<0.0001*	0.897 *0.0282*	***0.947***	0.909 *0.0402*	0.906 *0.0485*	***0.953***	0.794 *ns*	0.951 *ns*	***0.910***	0.735 *<0.0001*	0.909 *0.3867*

TABLE 1: COMPARISON OF FIBROMETER VCTE VERSUS ITS CONSECTUTIVE TESTS: FIBROMETER VIRUS AND VCTE, RESPECTIVELY;
FM: FIBROMETER, FM VCTE: FIBROMETER VCTE; SIGNIFICANT DIFFERENCES WITH FIBROMETER VCTE ARE SHOWN WITH THE P VALUES IN ITALIC.

KEY POINTS

- Tests combining blood markers and LSM outperformed all other tests in 4 etiologies (except ALD), validating and extending recent guidelines.
- Simple tests such as APRI and FIB-4 are less suitable for use in NAFLD and ALD.
- Combined tests (FibroMeter VCTE) could become the future reference in the main CLD etiologies, especially CHC and NAFLD.

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