



Clinical Handbook

FibroScan[®]

POWERED BY **VCTE**[™]

THE FIRST CLINICALLY VALIDATED DEVICE
USING **TRANSIENT ELASTOGRAPHY**

 **echosens**[™]

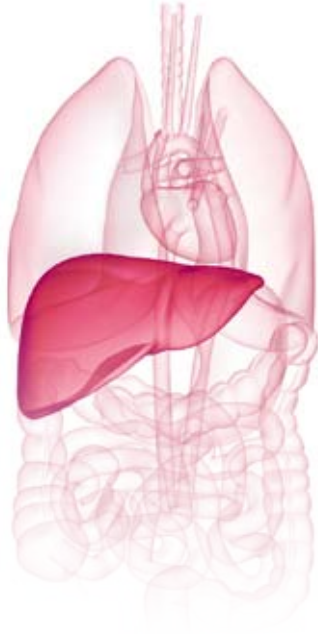


FibroScan® is an **intuitive and easy-to-use** device based on a **robust technology : Vibration-Controlled Transient Elastography (VCTE™)**. It allows a **reproducible and operator independent examination**.✱

- ◆ Deliver **quantitative & immediate results** in kPa
- ◆ Measure **directly & explore a large volume of the liver** (about 100 times larger than the biopsy)
- ◆ Enhance both **patient and practice management** by a large spectrum of applications (from the first diagnosis to the follow up of cirrhosis complications)

“kPa: the only reference unit in **elastography**”

* Fraquelli et al. Gut 2007



Summary

FibroScan®, an adjunct to liver biopsy

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FibroScan® facilitates patient management

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FibroScan®, a reliable tool in hepatology

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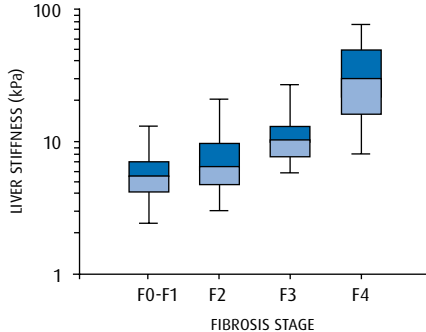
CHRONIC HEPATITIS C

| | | |
|-------------------|---|--|
| REFERENCE | Non-invasive assessment of liver fibrosis by stiffness measurement: a prospective multicenter study in patients with chronic hepatitis C. Ziol et al. (2005). <i>Hepatology</i> 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 \geq 2 | 0.79 (0.73-0.84) |
| METAVIR F \geq 3 | 0.91 (0.87-0.96) |
| METAVIR F = 4 | 0.97 (0.93-1.00) |

ASSOCIATED PUBLICATIONS

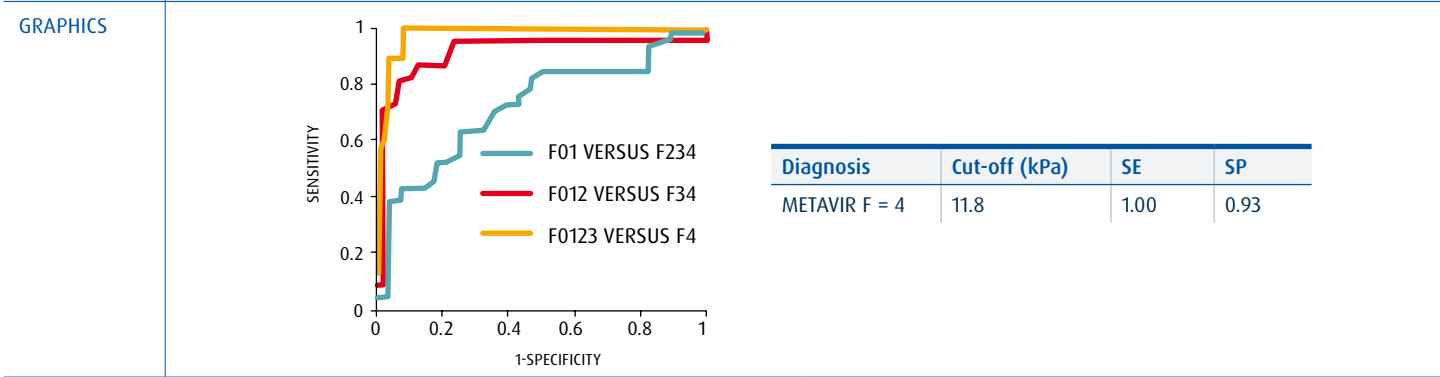
- ♦ Arena et al. (2008). Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. Gut 57(9): 1288-1293.
- ♦ Shaheen et al. (2007). FibroTest and FibroScan® for the Prediction of Hepatitis C-Related Fibrosis: A Systematic Review of Diagnostic Test Accuracy. American Journal of Gastroenterology: 1-12.
- ♦ Castera et al. (2005). Prospective comparison of transient elastography, Fibrotest, APRI and liver biopsy for the assesment of fibrosis in chronic hepatitis C. Gastroenterology 128: 343-350.

HIV-HCV CO-INFECTION

| | | |
|-------------------|---|---|
| REFERENCE | Diagnosis of hepatic fibrosis and cirrhosis by transient elastography (FibroScan®) in HIV-hepatitis C virus-coinfected patients. de Ledinghen et al. (2006). <i>Journal of Acquired Immune Deficiency Syndromes</i> 41(2): 175-179. | |
| OBJECTIVES | <ul style="list-style-type: none">♦ To assess the accuracy of FibroScan® in HCV-HIV co-infected patients♦ To compare the accuracy of FibroScan® with other non-invasive methods | |
| METHOD | <ul style="list-style-type: none">♦ Prospective multicenter study (5 centers)♦ 77 patients enrolled | |
| | <ul style="list-style-type: none">♦ Inclusion criteria:<ul style="list-style-type: none">→ presence of HCV RNA and HIV antibodies in serum | <ul style="list-style-type: none">♦ Exclusion criteria:<ul style="list-style-type: none">→ none |
| PATIENTS ANALYZED | <ul style="list-style-type: none">♦ 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



ASSOCIATED PUBLICATIONS

- ♦ De Ledingham 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

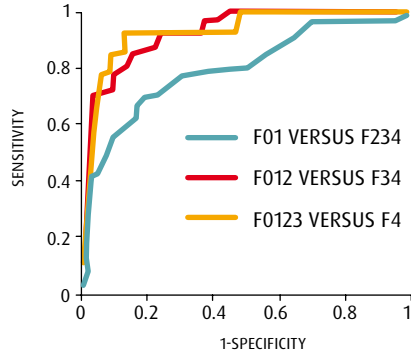
CHRONIC HEPATITIS B

| | | |
|-------------------|---|---|
| REFERENCE | Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. Marcellin et al. (2009). <i>Liver International</i> 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: <ul style="list-style-type: none">→ presence of hepatitis B surface antigen→ serum HBV-DNA levels >10⁵ copies/ml→ liver histology compatible with chronic hepatitis | ♦ Exclusion criteria: <ul style="list-style-type: none">→ 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 |

ASSOCIATED PUBLICATIONS

- ♦ Chang et al. (2008). Prospective evaluation of transient elastography for the diagnosis of hepatic fibrosis in Asians: comparison with liver biopsy and aspartate transaminase platelet ratio index (APRI). *Alimentary pharmacology & therapeutics* 28(1): 51-61.

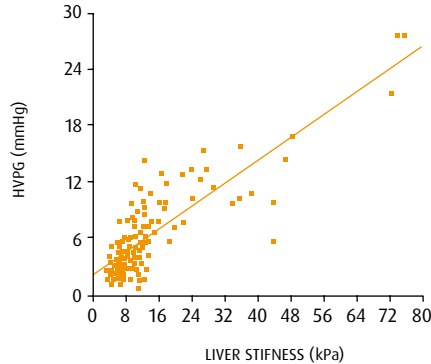
LIVER TRANSPLANTATION

| | | |
|-------------------|--|---|
| REFERENCE | Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. Carrion et al. (2006). <i>Liver Transplantation</i> 12: 1791-1797. | |
| OBJECTIVES | <ul style="list-style-type: none">♦ 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 | <ul style="list-style-type: none">♦ 135 consecutive transplanted patients with occurrence of HCV <ul style="list-style-type: none">♦ Inclusion criteria:<ul style="list-style-type: none">→ HCV infected patients with liver transplantation→ undergoing liver biopsy and/or hepatic hemodynamics | <ul style="list-style-type: none">♦ Exclusion criteria:<ul style="list-style-type: none">→ Body Mass Index > 35kg/m²→ clinically evident ascites |
| PATIENTS ANALYZED | <ul style="list-style-type: none">♦ 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 below 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 \geq 2 | 0.90 (NR) |
| METAVIR F \geq 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.

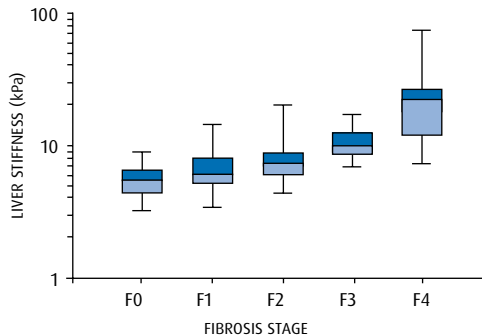
NON-ALCOHOLIC FATTY LIVER DISEASE

| | | |
|-------------------|---|--|
| REFERENCE | Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease Wong et al. (2010). <i>Hepatology</i> 51(2) | |
| OBJECTIVES | <ul style="list-style-type: none">♦ 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 | <ul style="list-style-type: none">♦ Inclusion criteria:<ul style="list-style-type: none">→ consecutive patients with NAFLD undergoing liver biopsy within one week after FibroScan®→ patients > 18 years | <ul style="list-style-type: none">♦ Exclusion criteria:<ul style="list-style-type: none">→ 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 | <ul style="list-style-type: none">♦ 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 \geq 2 | 0.84 (0.79-0.90) |
| Brunt F \geq 3 | 0.93 (0.89-0.96) |
| Brunt F = 4 | 0.95 (0.91-0.99) |

ASSOCIATED PUBLICATIONS

- ♦ Yoneda et al. (2007). Transient elastography in patients with nonalcoholic fatty liver disease (NAFLD). Gut 56(9): 1330-1

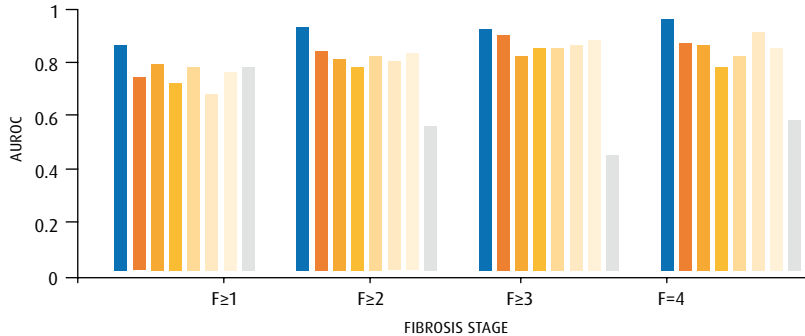
ALCOHOLIC LIVER DISEASE

| | | |
|-------------------|--|--|
| REFERENCE | Assessment of asymptomatic liver fibrosis in alcoholic patients using FibroScan®: prospective comparison with 7 non-invasive laboratory tests. Nguyen-Khac et al. (2008). <i>Alimentary Pharmacology & Therapeutics</i> 28(10): 1188-98. | |
| OBJECTIVES | <ul style="list-style-type: none">♦ To evaluate the performance of FibroScan® in asymptomatic subjects with chronic alcohol intake♦ To determine cut-off values in ALD (Alcoholic Liver Disease)♦ To compare performance of FibroScan® and biological markers in ALD (Alcoholic Liver Disease) | |
| METHOD | <ul style="list-style-type: none">♦ Inclusion criteria:<ul style="list-style-type: none">→ patients aged > 18 years→ chronic consumption of more than 50g per day of alcohol for more than 5 years→ patients agreed to undergo liver biopsy to detect alcoholic liver disease | <ul style="list-style-type: none">♦ Exclusion criteria<ul style="list-style-type: none">→ existence of non-alcoholic liver disease (chronic viral hepatitis C and B)→ refusal to undergo liver biopsy→ ongoing pregnancy→ failure to obtain valid transient elastography measurements→ severe acute alcoholic hepatitis (Maddrey score > 32)→ presence of known or decompensated alcoholic cirrhosis |
| PATIENTS ANALYZED | <ul style="list-style-type: none">♦ 103 patients with FibroScan®, liver biopsy and 7 others biological fibrosis markers | |

RESULTS

- ◆ FibroScan® has a good to excellent accuracy compared to biopsy on severe fibrosis to cirrhosis detection
- ◆ FibroScan® is an efficient tool for the monitoring of stiffness change in case of “diet” or stop in alcohol consumption
- ◆ FibroScan® can have many advantages in the complex follow up of ALD
- ◆ FibroScan® performs better than all other markers tested for all fibrosis stages

GRAPHICS



| Diagnosis | Cut-off (kPa) | SE | SP |
|--------------------|---------------|------|------|
| METAVIR F \geq 2 | 7.8 | 0.80 | 0.91 |
| METAVIR F \geq 3 | 11.0 | 0.87 | 0.81 |
| METAVIR F = 4 | 19.5 | 0.86 | 0.84 |

| | |
|--|---|
| ■ FIBROSCAN® | ■ HYALURONIC ACID |
| ■ FIBROMETER | ■ PGA |
| ■ FIBROTEST | ■ PGAA |
| ■ HEPASCORE | ■ APRI |

ASSOCIATED PUBLICATIONS

- ◆ Nahon et al. (2008). Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. *Journal of Hepatology* 49(6): 1062-8.

Physicians experience feedback

LIVER DISEASE

“Transient Elastography can be performed for the staging of liver fibrosis independent from the underlying liver disease.”

M. Friedrich-Rust et al., EASL 2007.

LIVER COMPLICATIONS

“The FibroScan® is a potentially useful adjunct to assess risk of liver decompensation and complications among liver cancer patients undergoing liver resection.”

L. Lai et al., APASL 2007.

LIVER TRANSPLANTATION

“El FibroScan® es un método simple para cuantificar el grado de FH en pacientes trasplantados hepáticos.”

J.C. Marín Gabriel et al., AEEH 2007.

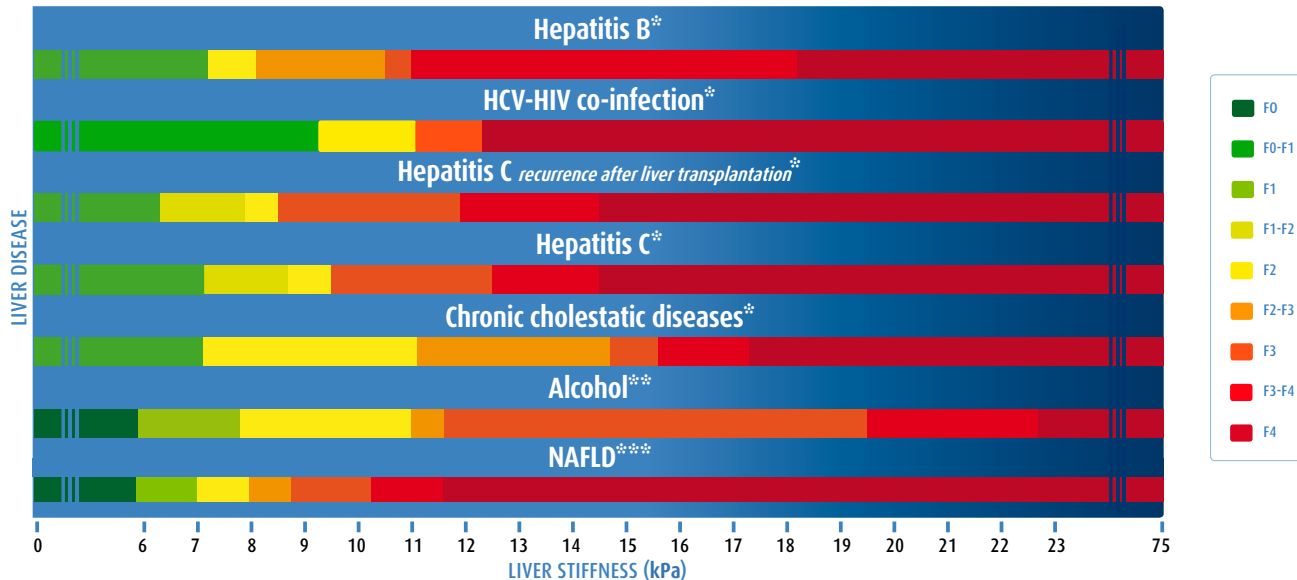
CO-INFECTION DISEASES (HIV)

“Our study confirms the relevance of FibroScan® to evaluate fibrosis in HIV/HBV co-infected patients.”

P. Mialhes et al., CROI 2007.

SCORING CARD

CORRELATION BETWEEN LIVER STIFFNESS (kPa) & FIBROSIS STAGE



*According to Metavir score: Transient elastography (FibroScan): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67

**According to Brunt score: Nahon et al. J Hepatol (2009) 49, 1062-68, Nguyen-Khac et al., Aliment Pharmacol Ther (2008), 28, 1188-98

***According to Brunt score: Wong et al. Hepatology (2010) 51, 454-62 Transient elastography (FibroScan®): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67

Notes

In 2010 we have:

- ▶ More than **800 FibroScan®** worldwide
- ▶ FibroScan® available in more than **59 countries**
- ▶ More than **15,000 patients** included in clinical studies since 2003
- ▶ **296 articles** published or in press including:
 - 204 original contributions
 - 57 review articles
- ▶ **550 oral or poster communications** including:
 - 57 at APASL (including 2010)
 - 106 at EASL
 - 163 at AASLD