2017

2ème Jeunes Hépatologues Conférence

Du 29 juin au 1er juillet 2017

Saint-Maximin-la-Sainte-Baume

Organisée par
Patrick Marcellin et Lawrence Serfaty

Le Couvent Royal Saint Maximin

www.aphc.info

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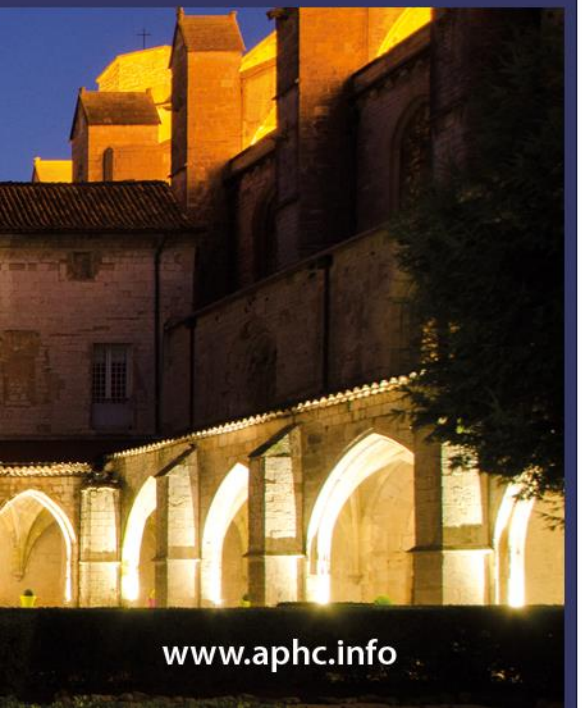

Restitution Atelier 1

Méthodes diagnostiques de la NASH

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Sce Hépatogastroentérologie
Institut de Cardiométabolisme et Nutrition
Hôpital Pitié Salpetrière

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Cas clinique

Mr. D, 62 ans

ATCD : HTA, dyslipidémie, obésité (BMI 34 kg/m2)

TTT : Olmesartan, Simvastatine

OH : 60 g/semaine

Adressé pour hyperferritinémie (450 ng/ml)

ASAT 42 (N < 45)	GGT 149	TP 110
ALAT 57 (N < 60)	PAL 52	Albumine 45g/l
	PLQ 289 G/l	Glycémie 5,8 mmol/l

Echo : stéatose

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Mme T 55 ans

Consulte pour hyperferritinémie à 617 µg/l + SAT à 42%

ATCD

- **Diabète type 2** depuis 10 ans
- **HTA**
- **Ménopausée** depuis 8 ans

Mode de vie

- **Alcool:** 0
- **Tabac:** 0
- **Secrétaire**

Traitement

- **Metformine**
- **Gliclazide**
- **Enalapril**

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Mme T 55 ans

Consulte pour hyperferritinémie à 617 µg/l + SAT à 42%

Clinique

- **IMC=30,5 kg/m²**
- **+8kg/8ans**
- **Hépatomégalie** (14 cm, ferme, non tranchant)

Hépatique

- **ALAT 70 (N<40)**
- ASAT 39 **(N<40)**
- **GGT 200 (N<35)**
- TP 100%; albumine 40 g/l; plaquettes 250 000/mm3

Métabolique

- **Cholestérol 2,6 g/l (N<2 g/dl)**
- **Triglycérides 1,7 g/l (N<1,5 g/dl)**
- **Hb A1c 9% (Objectif <7%)**

What do we want to diagnose and why?

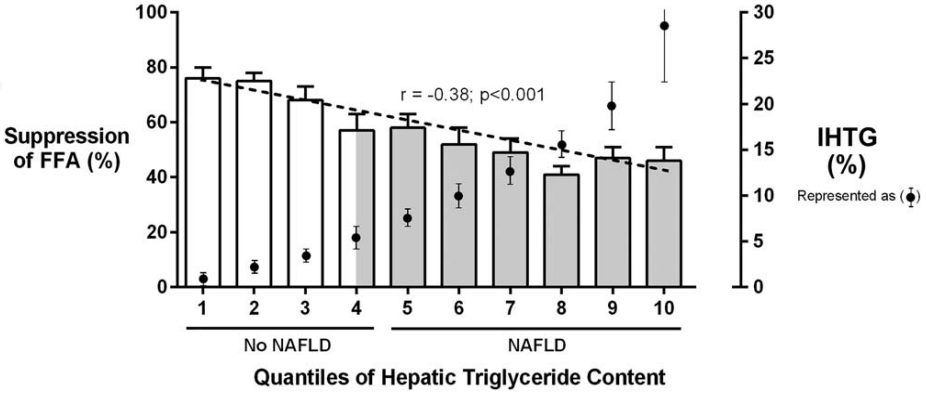
STEATOSIS **STEATOHEPATITIS** **FIBROSIS**

↓

BENIGN
NO PROGRESSION
NO INCREASE IN MORTALITY

→

ADIPOSE TISSUE IR



Bril, Hepatology 2017

Correlation with histological severity/progression?
Interest for clinical trials?

Non invasive diagnosis of steatosis

Ultrasonography

- metanalysis, 34 studies, 2800 pts
- detection of moderate/severe vs. no steatosis (AUROC 0.93, Se 85%, Sp 94%)
- suitable for screening of general population/epidemiologic studies

Hernaez, Hepatology 2011

Controlled attenuated parameter (CAP)

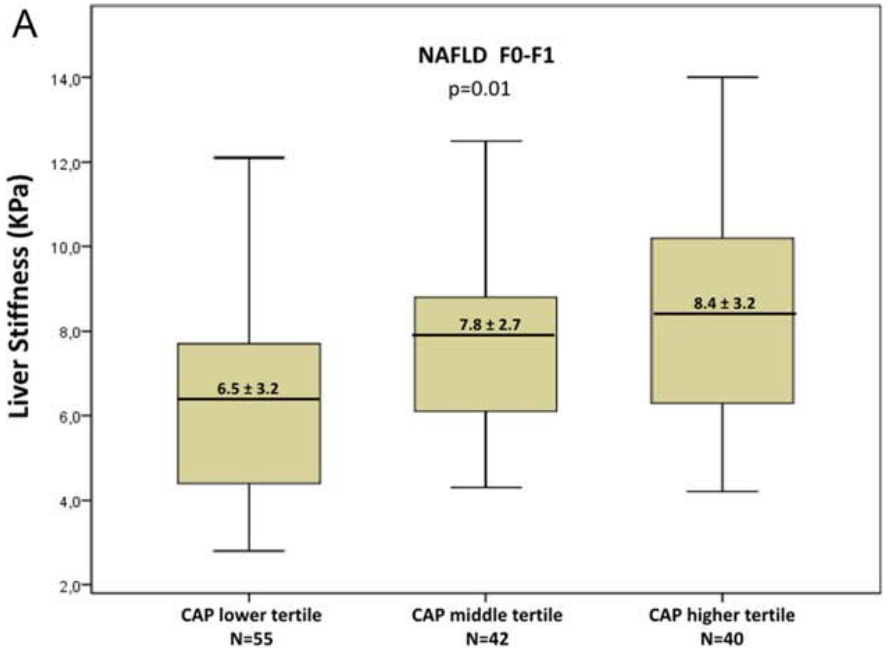
	S0 *vs.* S1–S3
AUC	0.823 (0.809–0.837)
Sensitivity	0.688 (0.600–0.750)
False negative rate (1-sensitivity)	0.312 (0.250–0.400)
Specificity	0.822 (0.761–0.897)
False positive rate (1-specificity)	0.178 (0.103–0.239)
Optimal cut-off, dB/m	248 (237–261)

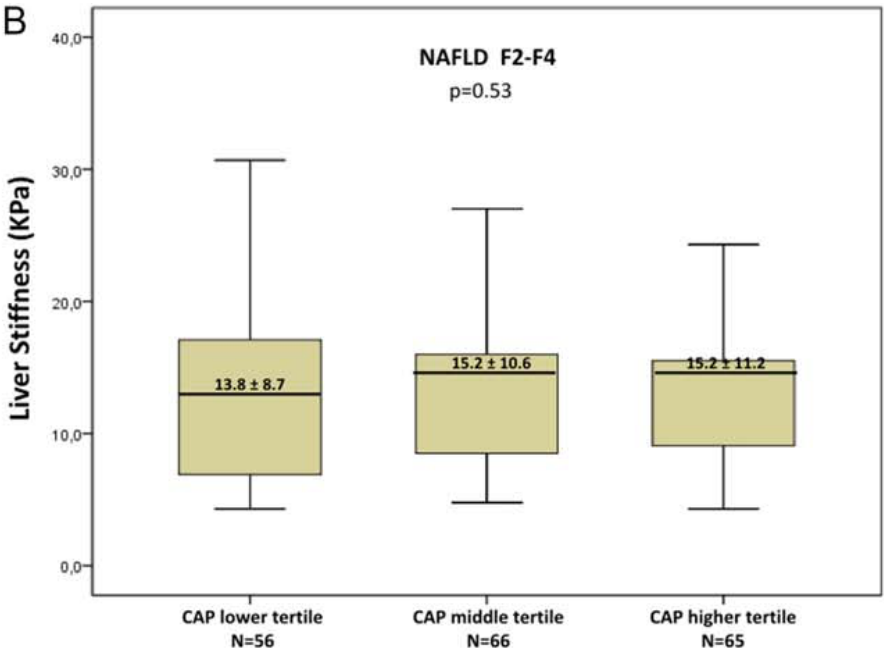
- etiology, diabetes, and BMI deserve consideration when interpreting CAP
- longitudinal data are missing

Karlas, J Hepatol 2017

- **avoid overestimation of liver fibrosis as assessed by LSM**

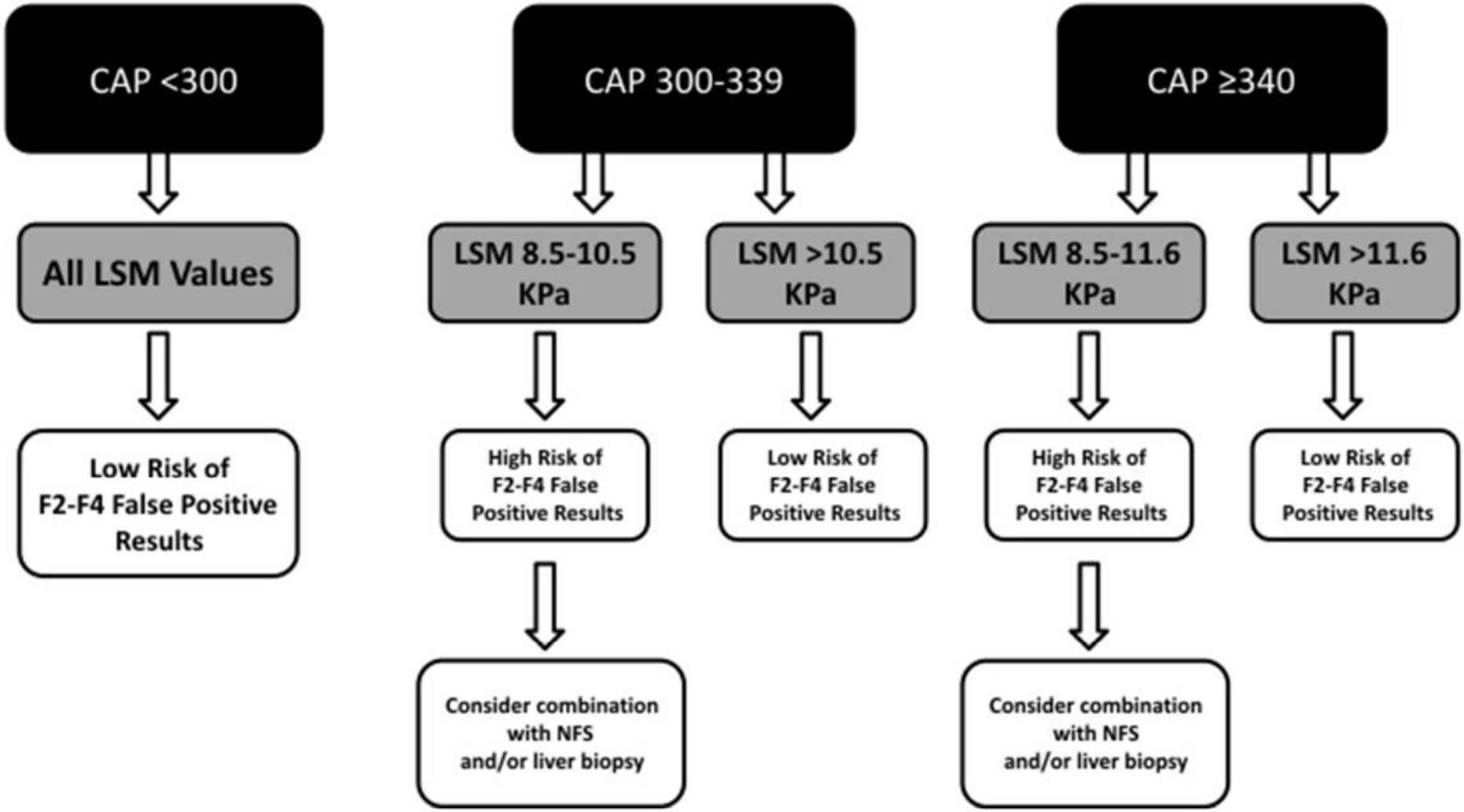
CAP to refine the results of FibroScan





Petta, Hepatology 2017

CAP pour interpréter le Fibroscan



Petta, Hepatology 2017

Non invasive diagnosis of steatosis

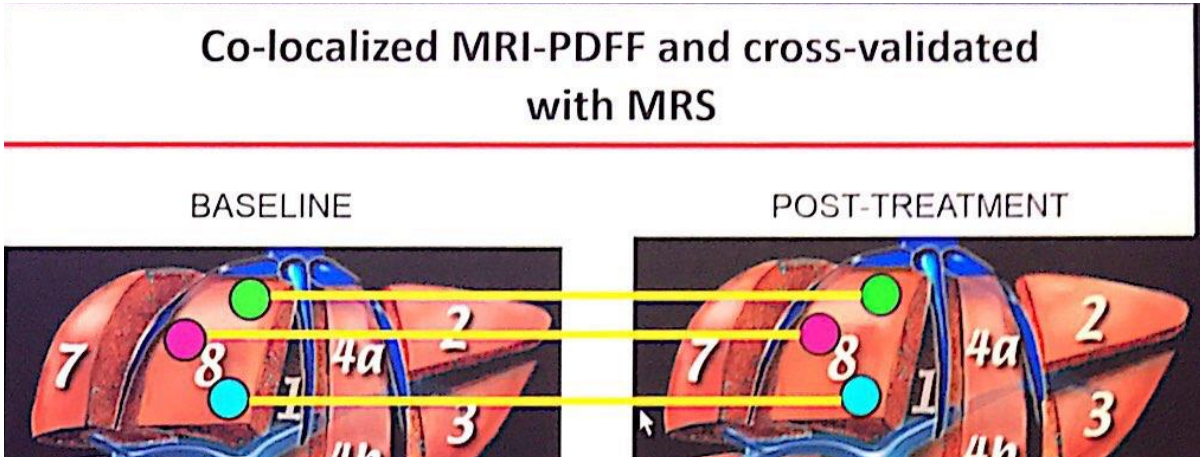
MRI – PDFF

- Good accuracy for any steatosis/adjacent grades

  Imajo, Gastroenterology 2016

  Park, Gastroenterology 2017

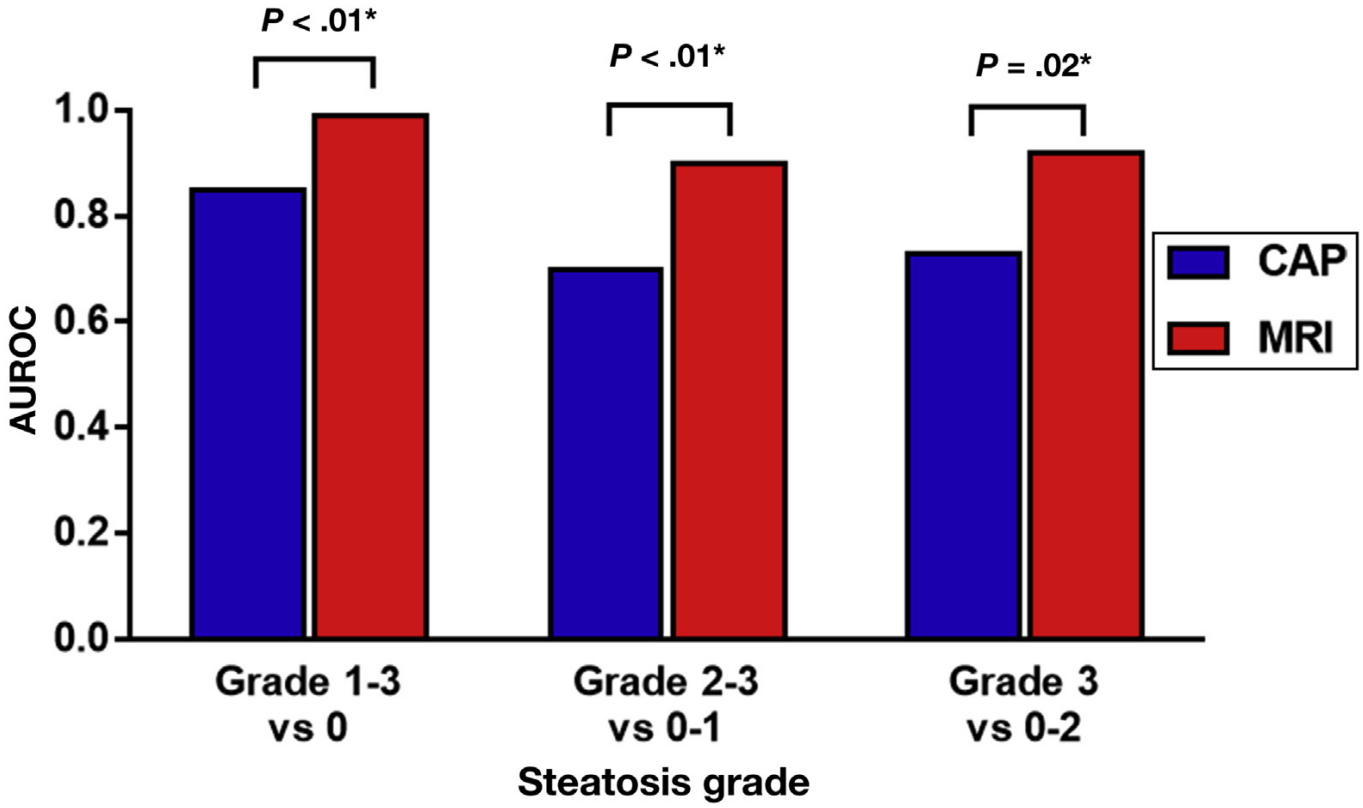
- Longitudinal changes in steatosis (on treatment) ➔ utility for clinical trials (Ezetimibe, Aramchol, Sitaglipin)
- Expensive; reduce availability; used for research purposes



PDFF recorded in region of interest (ROIs)
The same 3 ROIs in each of the 9 liver segments measured at baseline and EOT
Each segment fat fraction = average of 3 ROIs
Total liver fat fraction = average of 27 ROIs

Lee, Hepatology 2012

MRI-PDFF performed better than CAP for all steatosis grades



Park, Gastroenterology 2017

What do we want to diagnose and why?

STEATOSIS

↓

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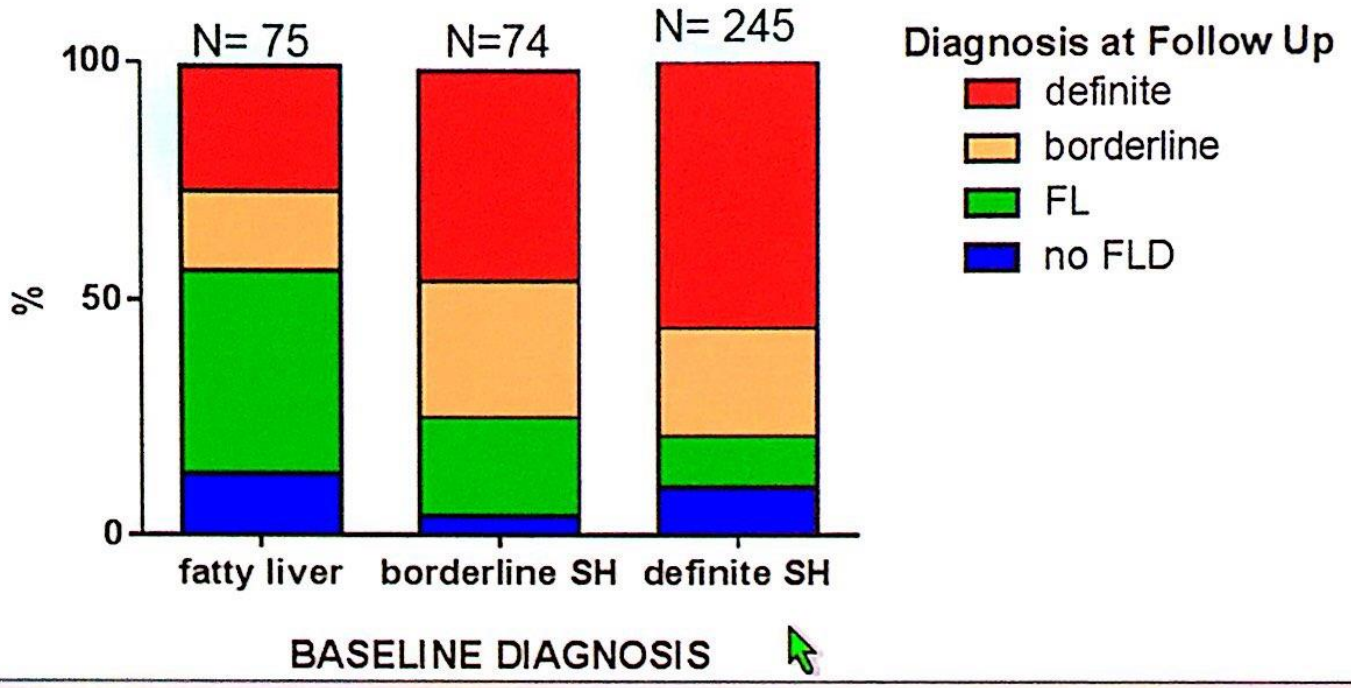
STEATOHEPATITIS (NASH) → **FIBROSIS**

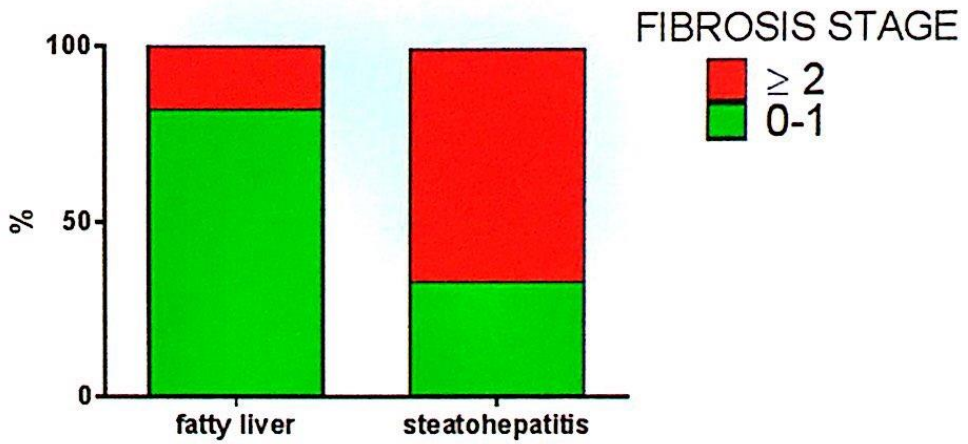
NAFLD diagnostic pattern changes bi-directionally over time



- NAFL progressed to borderline or definite NASH in 44% of cases
- Borderline SH is more likely to progress than regress (43% vs 22%)
- Definite SH regressed to borderline (20%), NAFL (11%) or normal in 11%

Sanyal, AASLD 2016

Fibrosis progression in those with NAFL was linked to evolution to NASH



HISTOLOGICAL PHENOTYPE ON BX # 2

	Odds ratio for fibrosis progression	95% CI	P*
NAFLD progression	7.2	2.4 – 21.5	<0.001
Years between Lbx	1.2	0.9 – 1.5	0.19

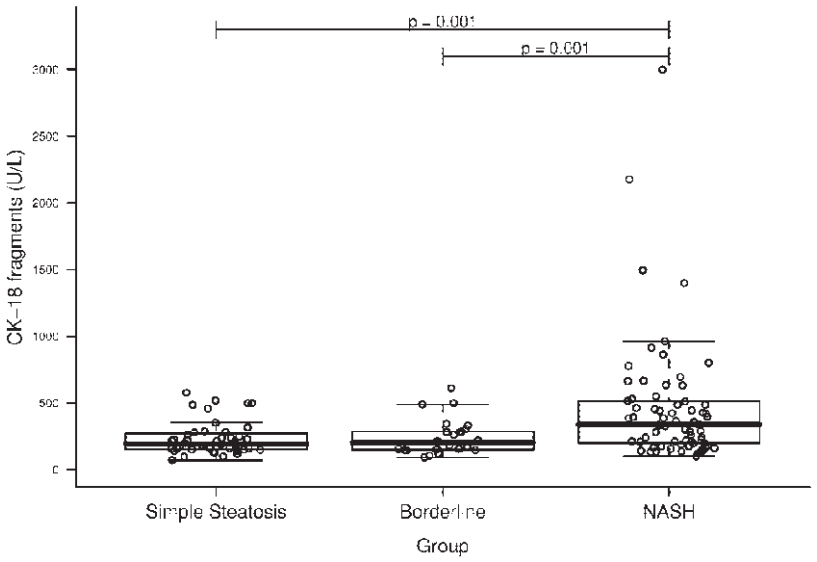
*NAFLD progression x years between bx interaction P=0.58

Sanyal, AASLD 2016

Non invasive diagnosis of NASH

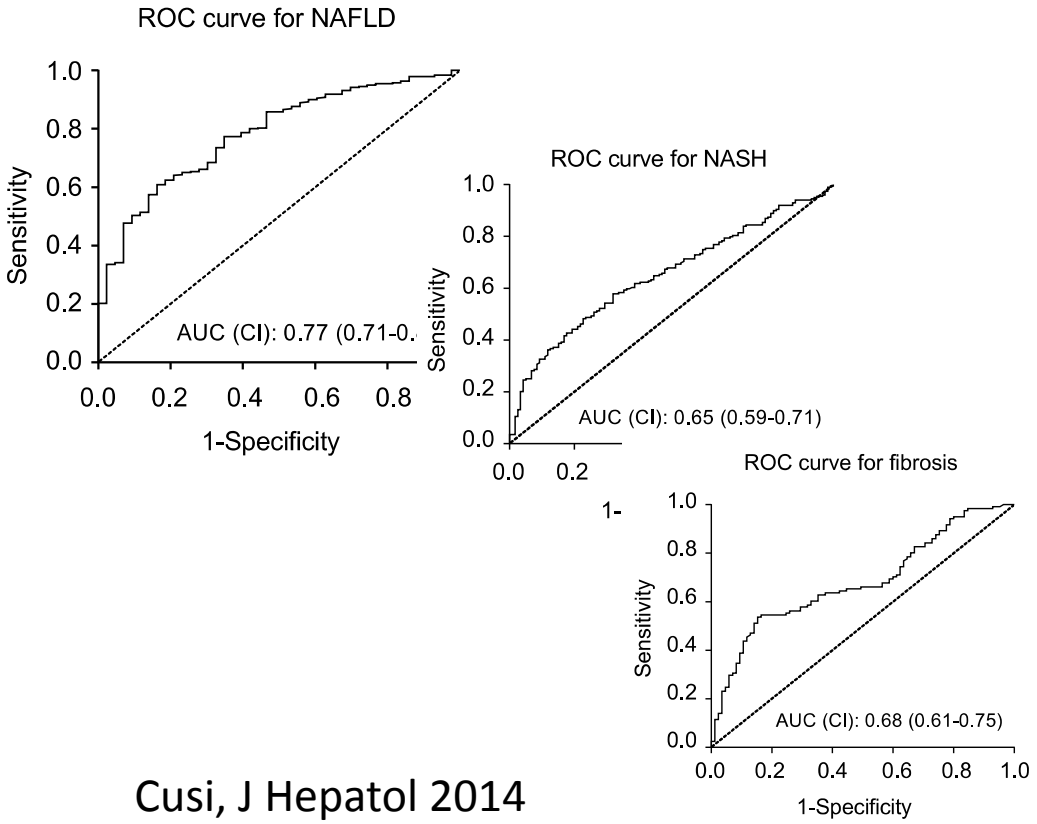
No non-invasive bio-marker for NASH validated for the moment

CK – 18: potential usefulness for dg of NASH



Feldstein, Hepatology 2009

Limited value of CK 18



Cusi, J Hepatol 2014

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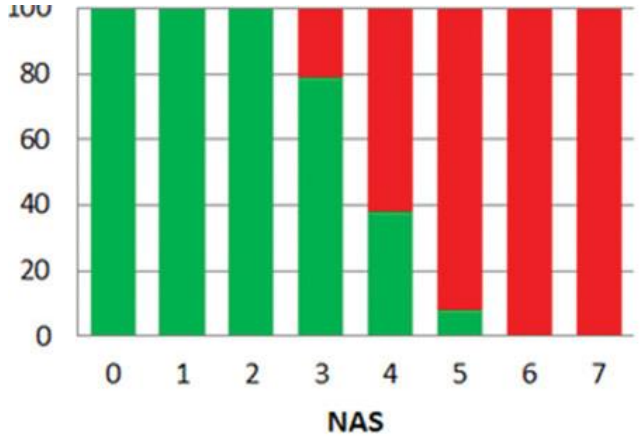
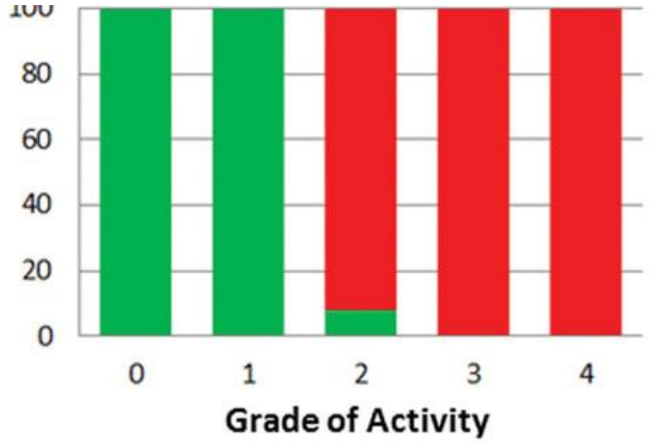
Liver Biopsy

NAS (NASH CRN)	SAF (FLIP Algorithm)
• Combines steatosis with components of activity; • Fibrosis not included	• Separately assess steatosis, activity and fibrosis
• Unequal weight of the 3 components with steatosis (0 – 3) having a large impact on the total score (0 – 8)	• Activity score defined by adding semiquantitative score of LI (0 – 2) and ballooning (0 – 2)
• Not intended for diagnosis purpose	• Improves inter/intra-observer variability (k = 0.8)





Bedossa, Hepatology 2012

C D

What do we want to diagnose and why?

STEATOSIS

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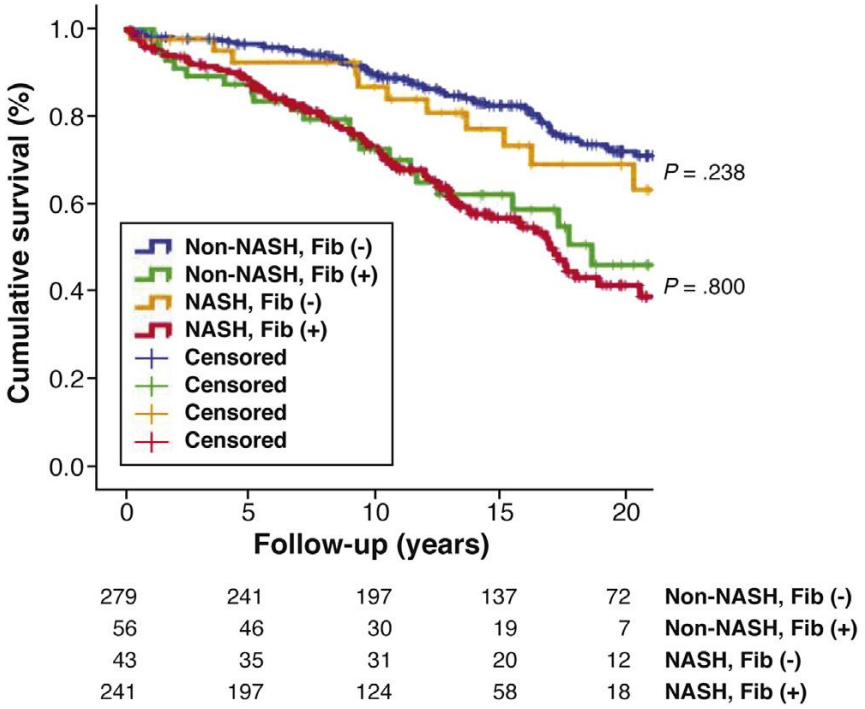
STEATOHEPATITIS (NASH) → **FIBROSIS**

↓

ESLD + COMPLICATIONS
HCC
OVERALL, LIVER RELATED MORTALITY

FIBROSIS – OVERALL, LIVER RELATED OUTCOMES

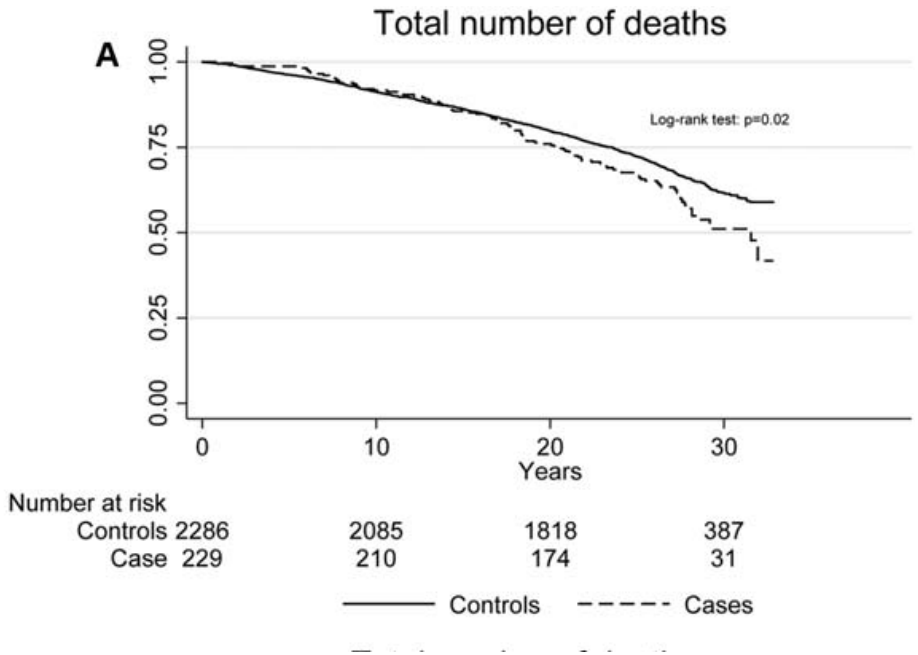
Mean FU = 12.6 yrs



279	241	197	137	72	Non-NASH, Fib (-)
56	46	30	19	7	Non-NASH, Fib (+)
43	35	31	20	12	NASH, Fib (-)
241	197	124	58	18	NASH, Fib (+)

Angulo, Gastroenterology 2015

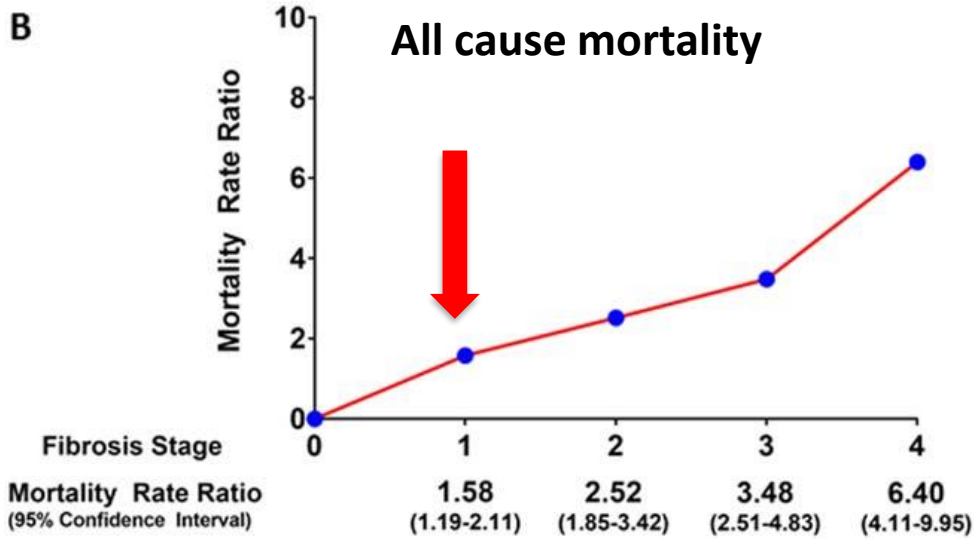
FU = 33 years

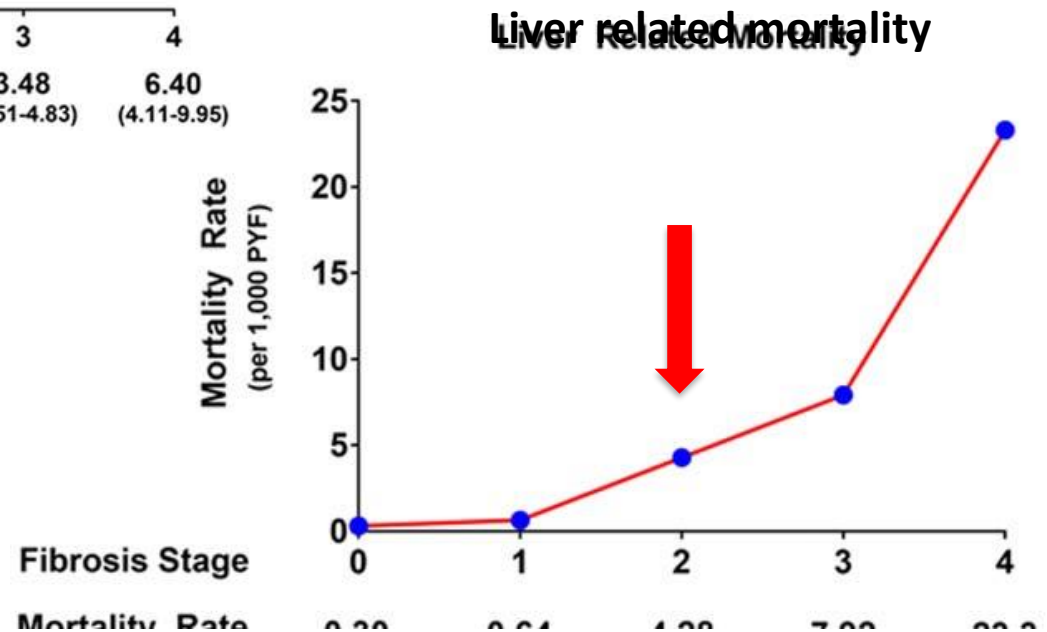


Ekstedt, Hepatology 2014

FIBROSIS – OVERALL, LIVER RELATED OUTCOMES

B





Dulai, Hepatology 2017

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DIAGNOSTIC NON INAVSIF DE LA FIBROSE

TESTS SANGUINS SIMPLES

- ✓ FIB4
- ✓ NFS Fibrosis Score
- ✓ APRI
- ✓ BARD

TESTS PATENTÉS

- ✓ FibroTest
- ✓ FibroMetre

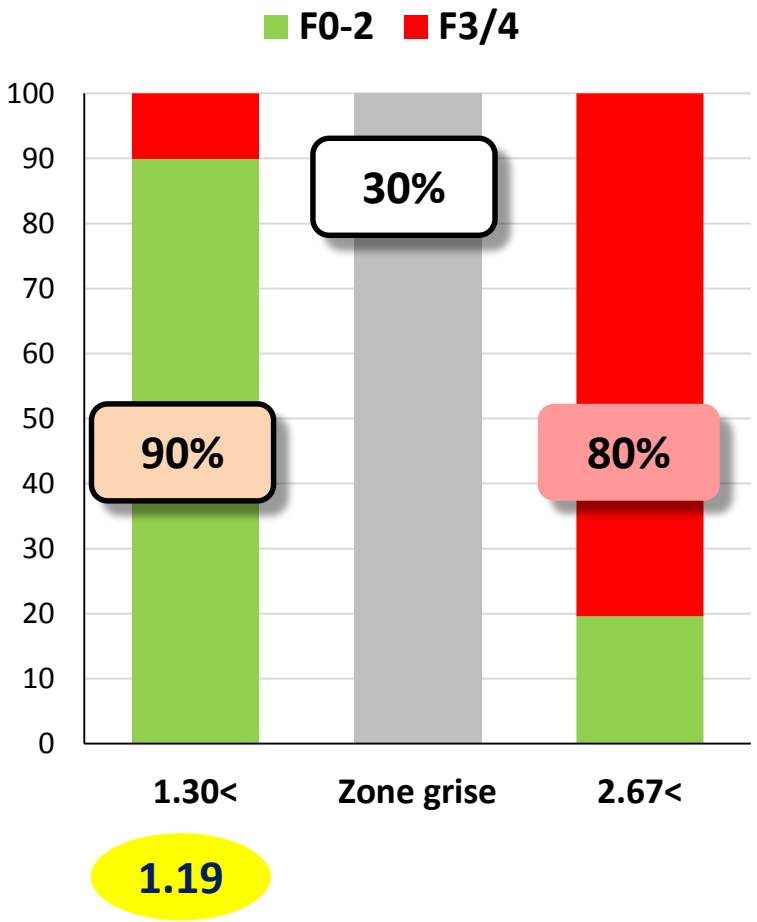
AUTRES

- ✓ FibroScan
- ✓ MRE

COMBINAISONS

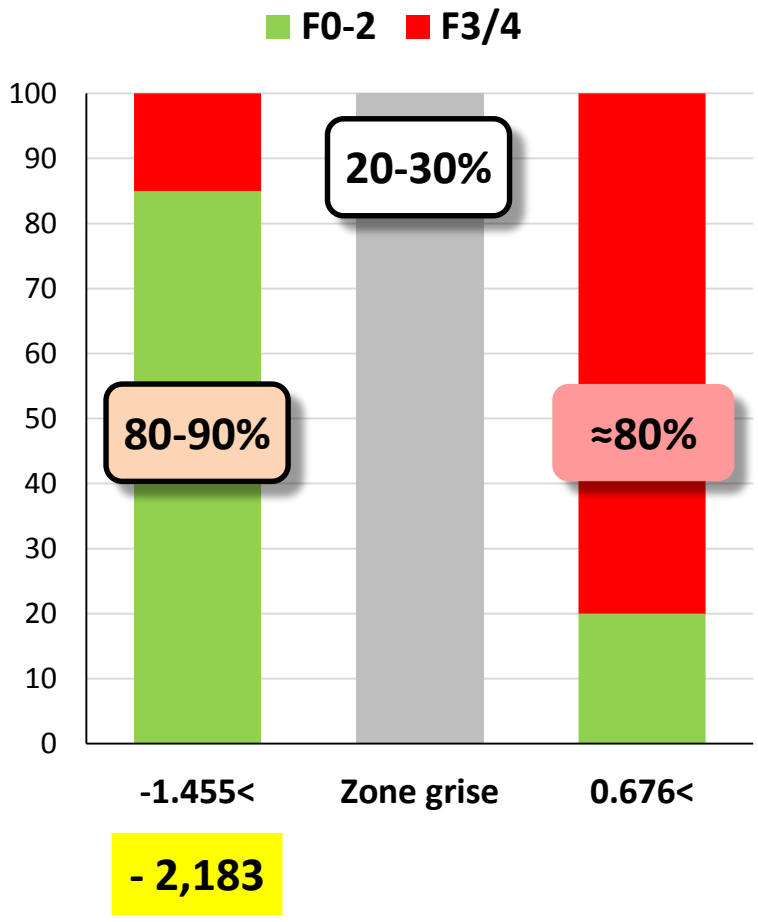
Tests simples : bonne valeur prédictive négative

FIB-4



Shah, Clin Gastroenterol Hepatol 2009

NAFLD Fibrosis Score



Angulo, Hepatology 2007
Boursier, Current Opin Med Diag 2012

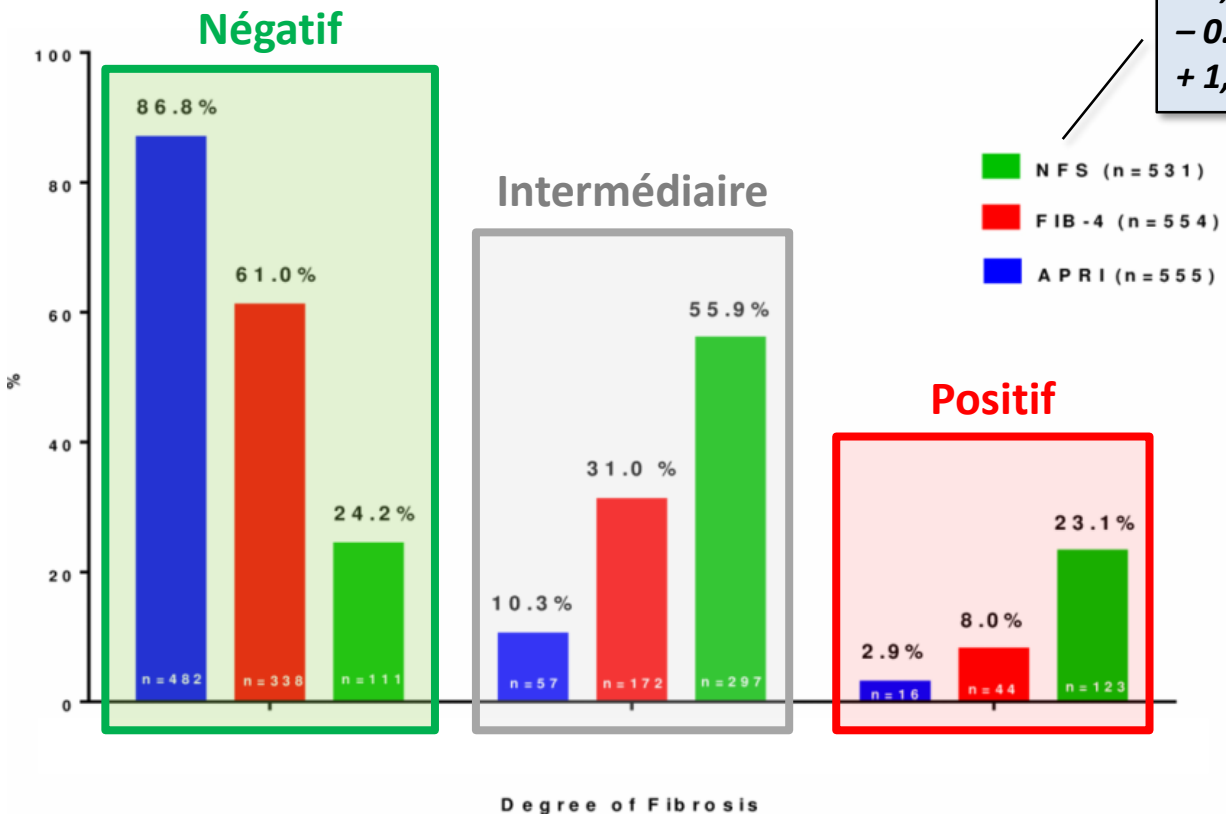
NFS: un bon test chez les diabétiques ?

1693 patients US diabétiques
(codage ICD-9 du 09/11 au 11/15)

1018 Sans NASH

675 probable NASH
(ASAT ou ALAT ≥30 (H) ou
DNID, pas autre cause, pa

0,037*âge
+ 0,094*BMI
+ 1,13*IFG/diabète
+ 0,99*ASAT/ALAT
– 0,013*plaquettes
– 0.66*albumine
+ 1,675



Joshi, ILC2016-RS-4095

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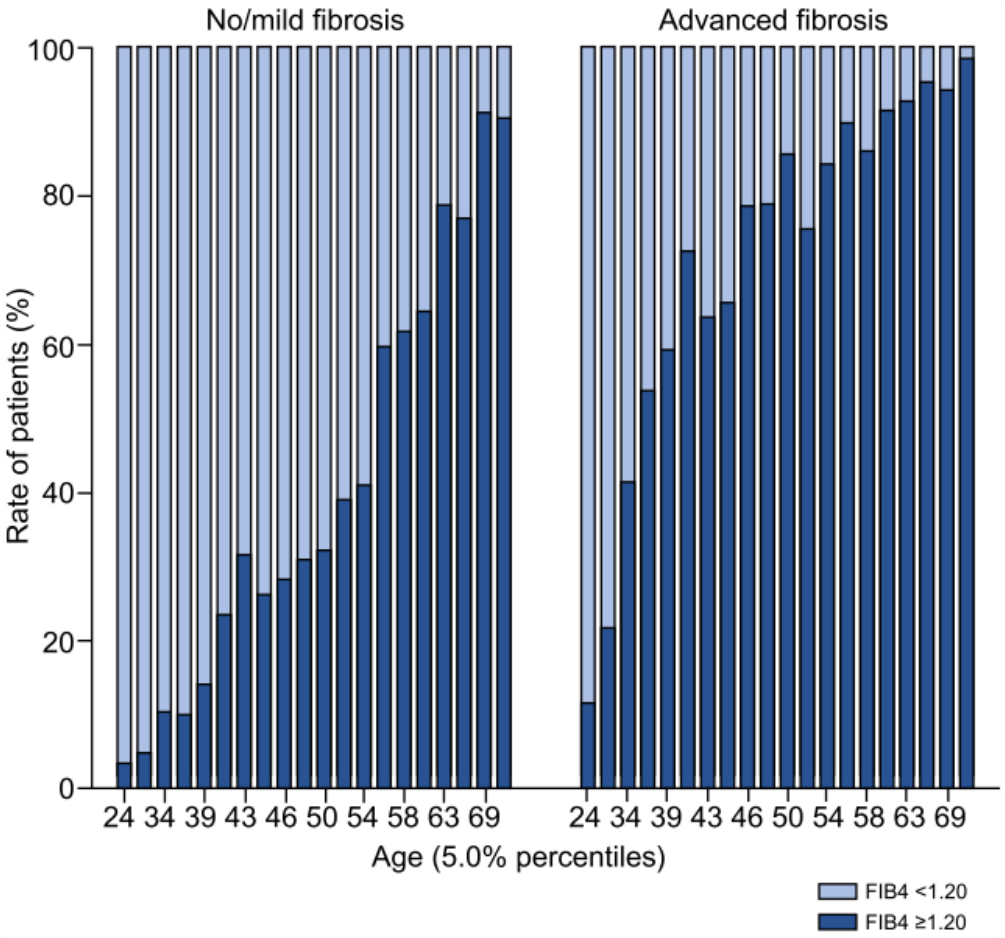
Tests sanguins de fibrose : attention à l'âge !

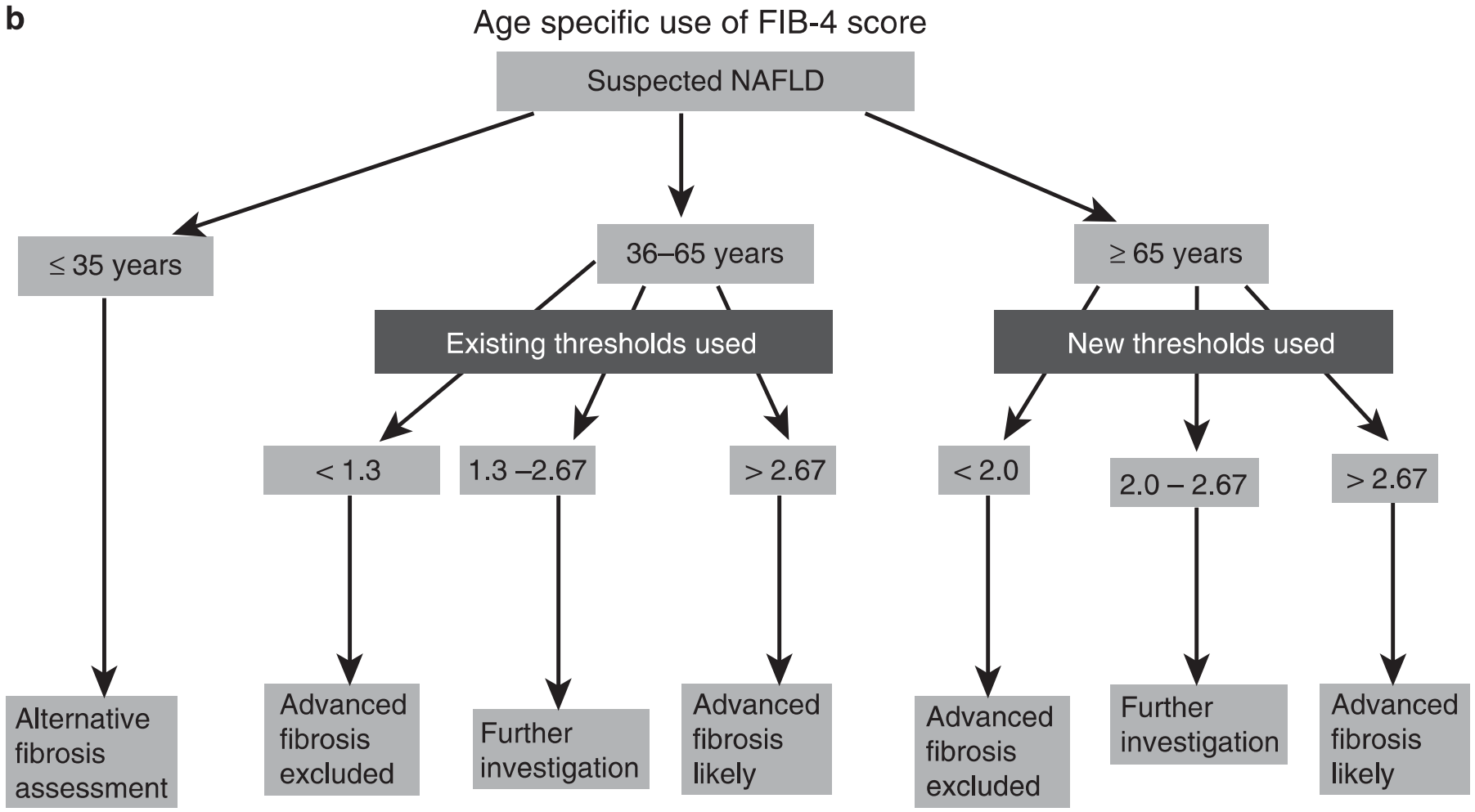


3754 patients,
hépatopathie chronique
prouvée histologiquement

Chez les patients ≥60 ans, le taux de faux positifs était de **82.0%**

Boursier, J Hepatol 2017

Tests sanguins de fibrose : attention à l'âge !



McPherson, Am J Hepatology 2017

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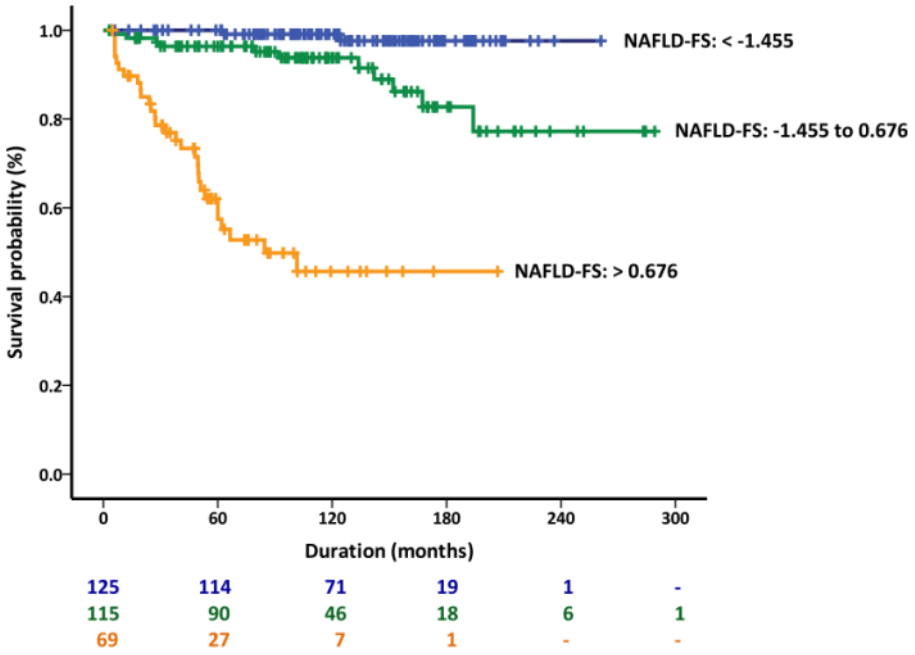
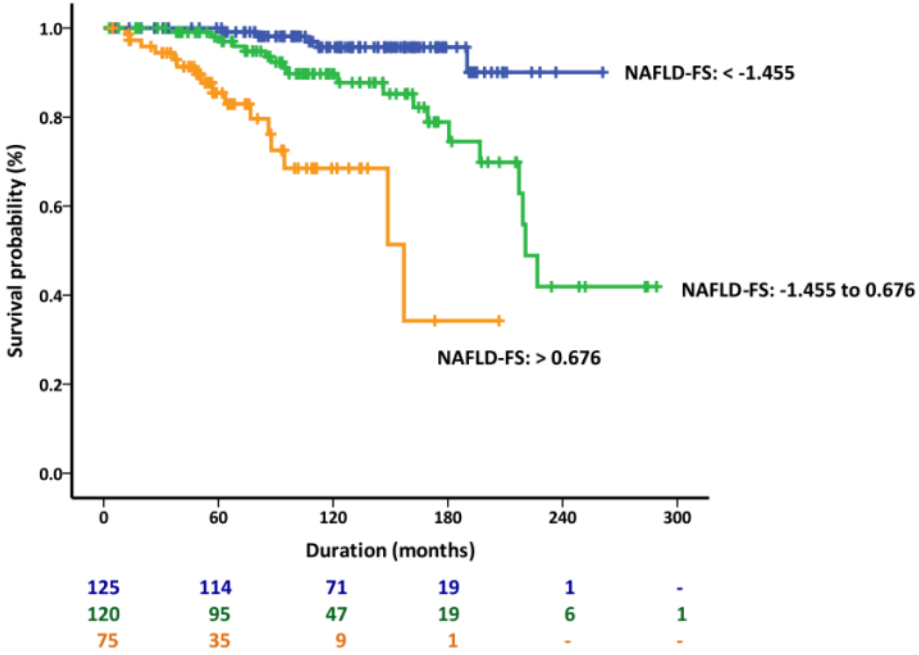
Valeur pronostique des tests sanguins

Complications hépatiques

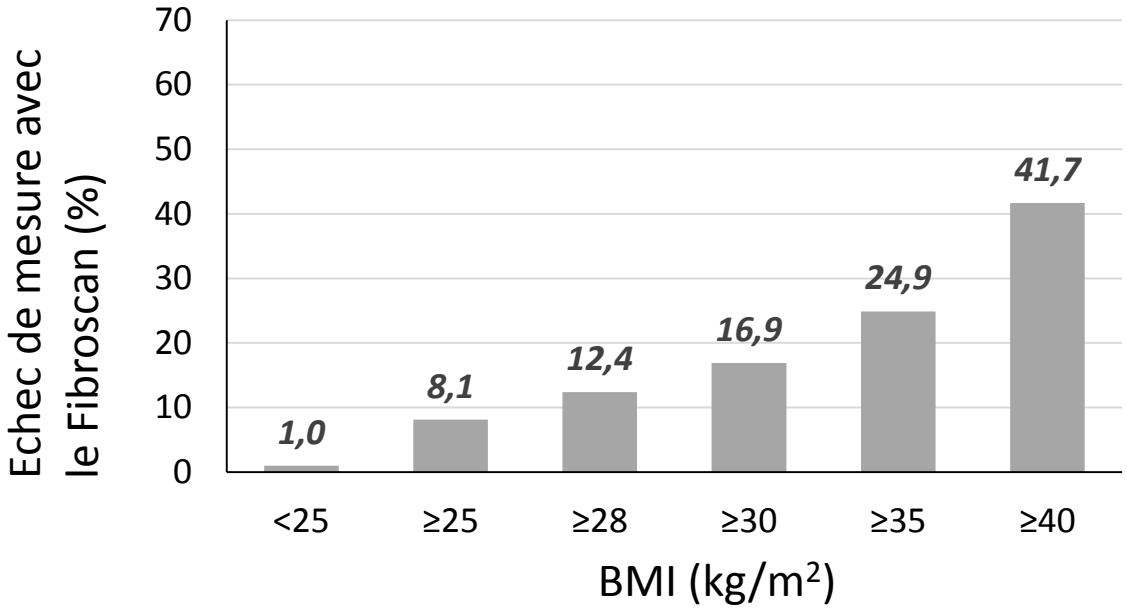


Décès hépatiques



Angulo, Gastroenterology 2013

Taux d'échec du Fibroscan



	OR	95% CI	P
BMI > 30	3.3	2.8 – 4	< 0.001
Operator experience	3.1	2.4 – 3.9	< 0.001
Age > 52 years	1.8	1.6 – 2.1	< 0.001
Female sex	1.4	1.2 – 1.6	< 0.001
High Blood Pressure	1.3	1.1 – 1.5	0.003
Type 2 diabetes	1.2	1 – 1.5	0.05

Castera, Hepatology 2010

< 2,5

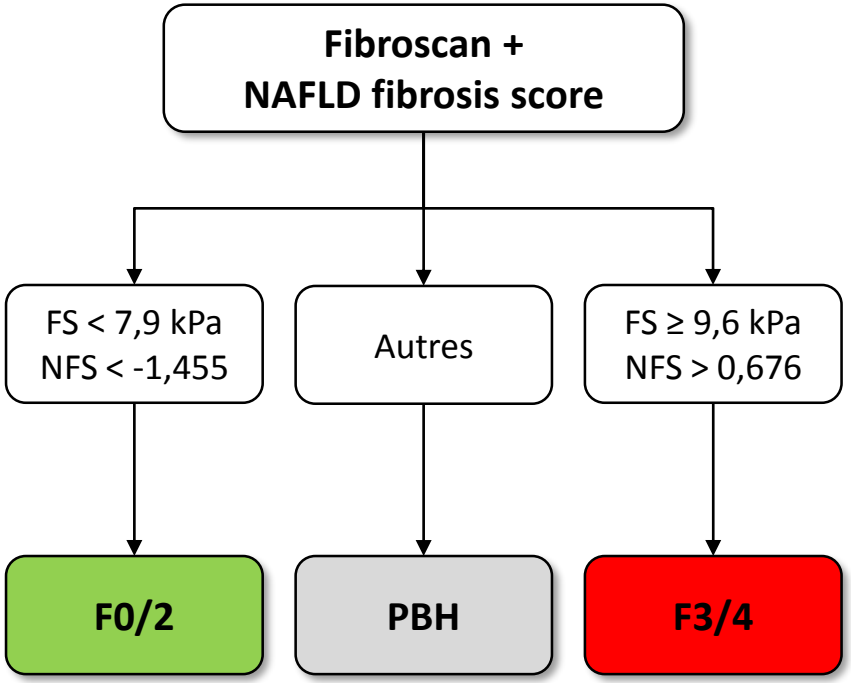
2,5 6,5

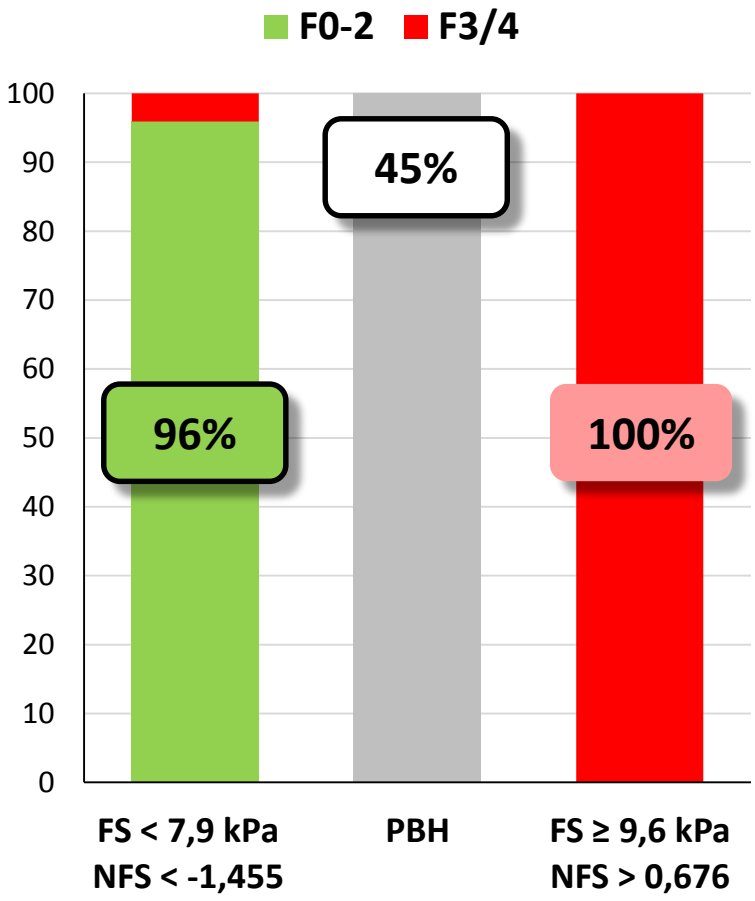
M

3,5 7,5

XL

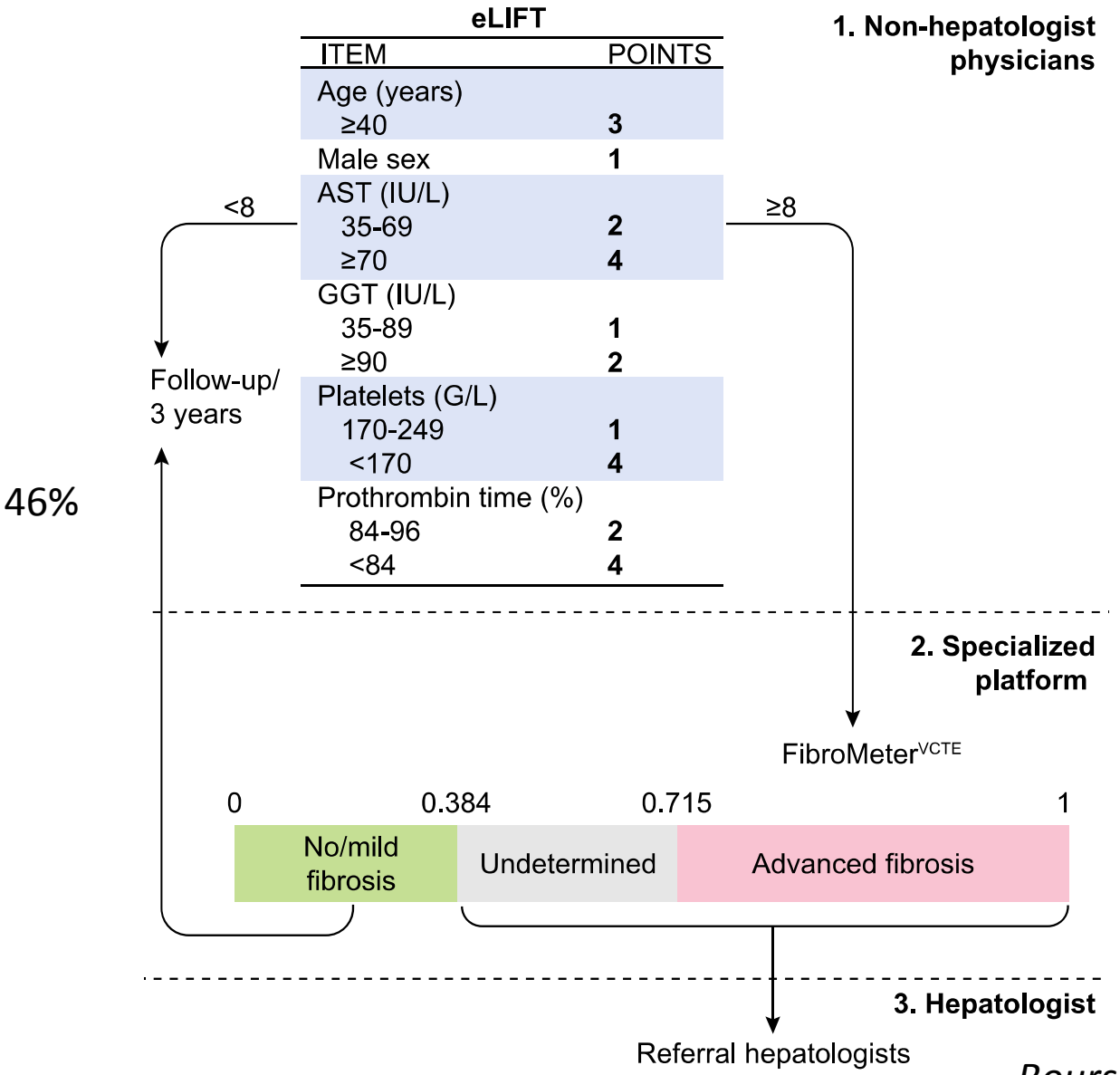
Combinaison tests sanguins + Fibroscan





Petta, Liver Int 2015

Les tests sanguins de 2nde génération en soin primaire ?



Boursier, J Hepatol 2017

Conclusion – diagnostic non invasif de la fibrose

- Pour interpréter les tests sanguins il faut regarder la concordance des paramètres qui le composent
- Tests simples : bonne valeur prédictive négative
- Fibroscan : attention aux critères de fiabilité et bien choisir la sonde
- L'association de tests non invasifs augmente la performance diagnostique

1. **Les tests non invasif ont une bonne valeur pronostique**
2. **Les tests non invasifs peuvent être utilisés pour dépister la fibrose dans les populations à risque**