1er Colloque Francophone-Méditerranée
VIH/Hépatites
Alger

Cas clinique

Évaluation de la fibrose hépatique au cours de l'hépatite virale B

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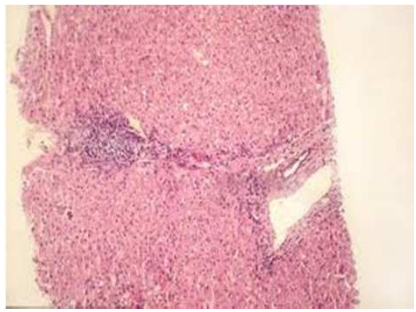
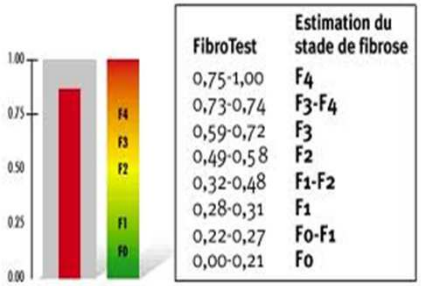
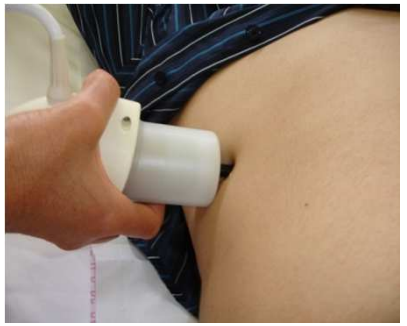
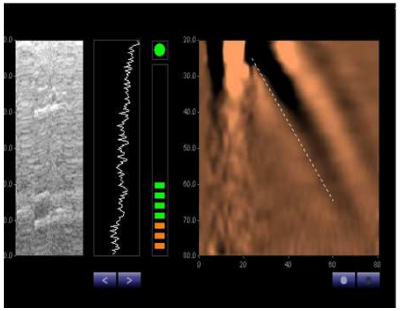
Introduction





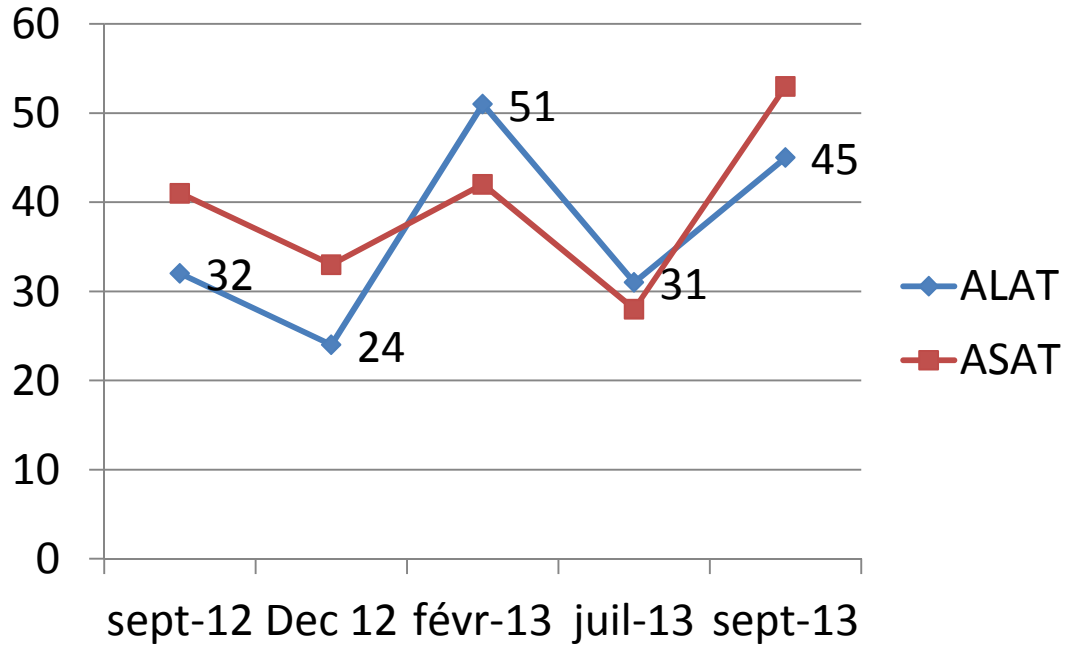




Évaluation de la fibrose hépatique VHB
1. Diagnostic, 2. décision thérapeutique, 3. pronostic

Patient

- S.A 51 ans
- ATCD:
  - portage familial VHB: non
  - Coïnfection virale: non
  - Médicaments au long cours, Alcool, tabac, cannabis: non
  - Contage viral: acupuncture, extraction dentaire
- Diagnostic infection VHB septembre 2012
  - Bilan d'une asthénie



- Septembre 2013: Examen sans anomalie, BMI 22 Kg/m^2
- Bilan
  - ALAT 45 U/ml, ASAT 53 U/ml (LSN 40)
  - Plaquettes 174.000/mm, TP 92%
  - BT N, Albumine N, bilan rénal N, bilan lipidique N
  - Ag Hbe (-)
  - DNA: 214.000 UI/ml (5.22 LOG)
  - Échographie hépatique est sans anomalies.

Que faut-il faire chez ce patient?

1. Surveillance trimestrielle des transaminases
2. Biopsie hépatique
3. Refaire la CV dans 6 mois
4. Traiter d'emblée le patient

DNA >20.000 UI/ml et TGP <2N

Biopsie hépatique

DNA viral UI/ml	ALAT UI/ml	PBH	Décision
2000-20.000	**N (>1an)**	**NON**	**Surv, Fibroscan***
2000-20.000	>2N	OUI	TRT si fibrose significative >A1/F1
> 20.000	**>2 N**	**NON ****	**TRT d'emblée**
> 20.000	≤ 2N	OUI	TRT si fibrose significative >A1/F1

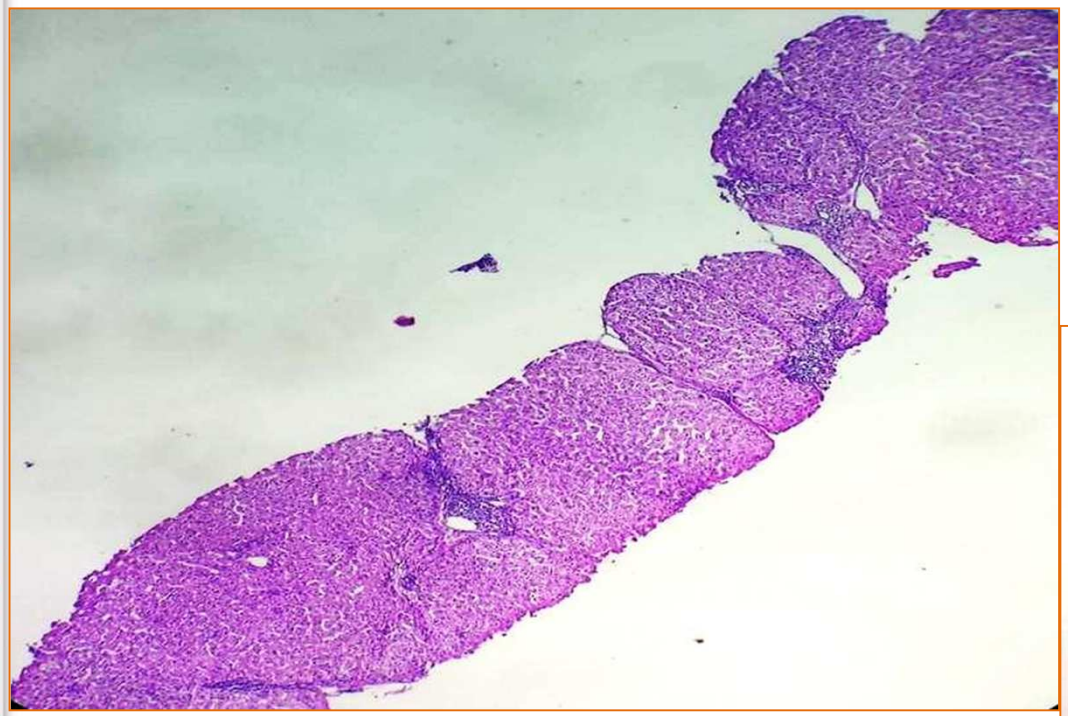
* Surveillance ALAT/ 3 mois, DNA / 6 mois, > 3 ans → suivi du portage inactif

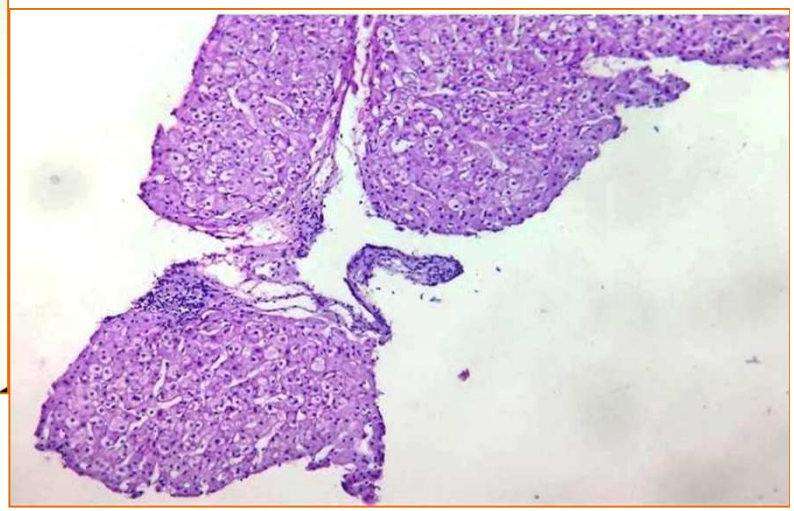
**PBH peut apporter des renseignements utiles. Si non méthode non invasive ++++

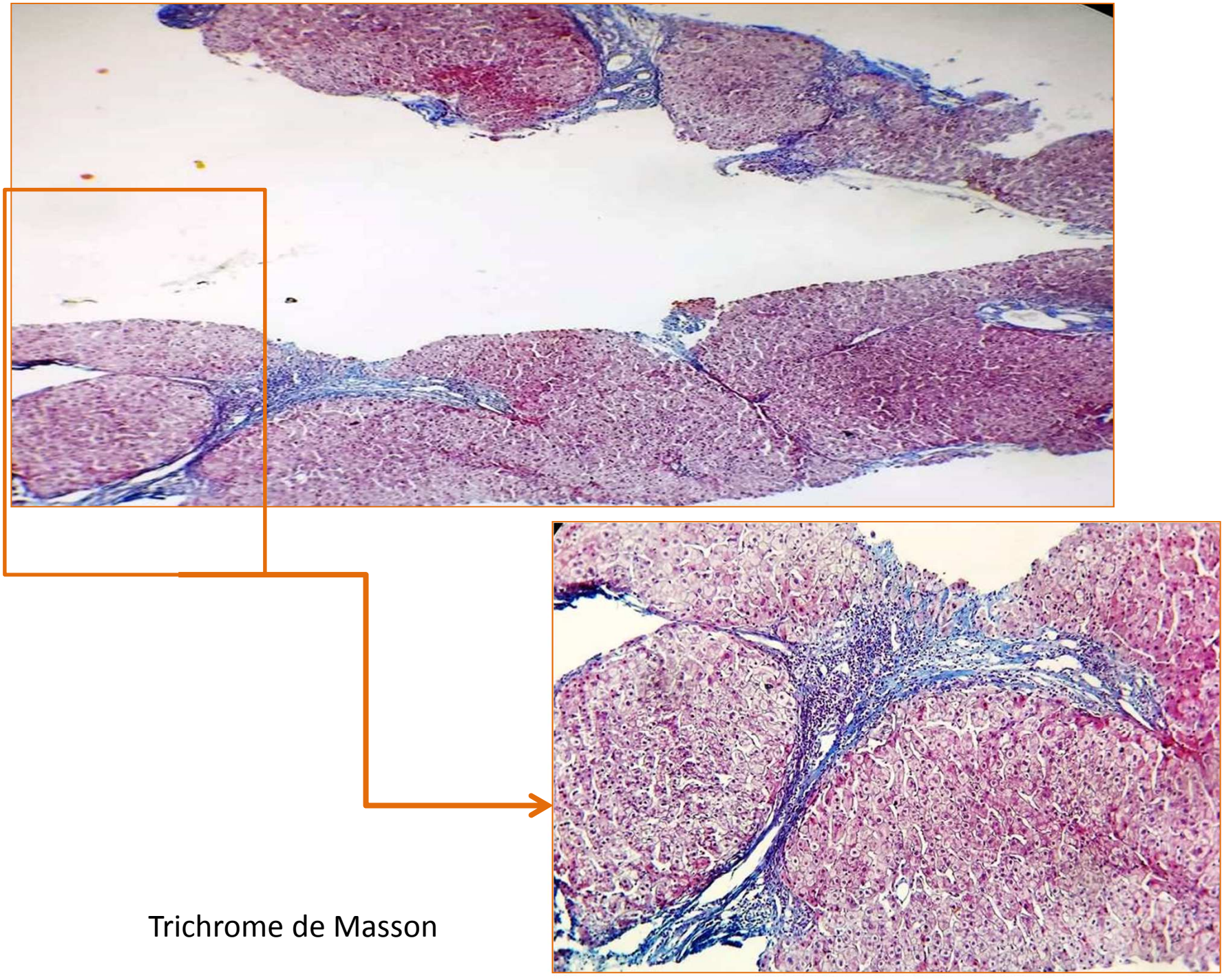
EASL Clinical practice guidelines. J Hepatol 2012;57:167-185

Biopsie hépatique

- 20 mm, EP: 13 METAVIR: **A2F4**

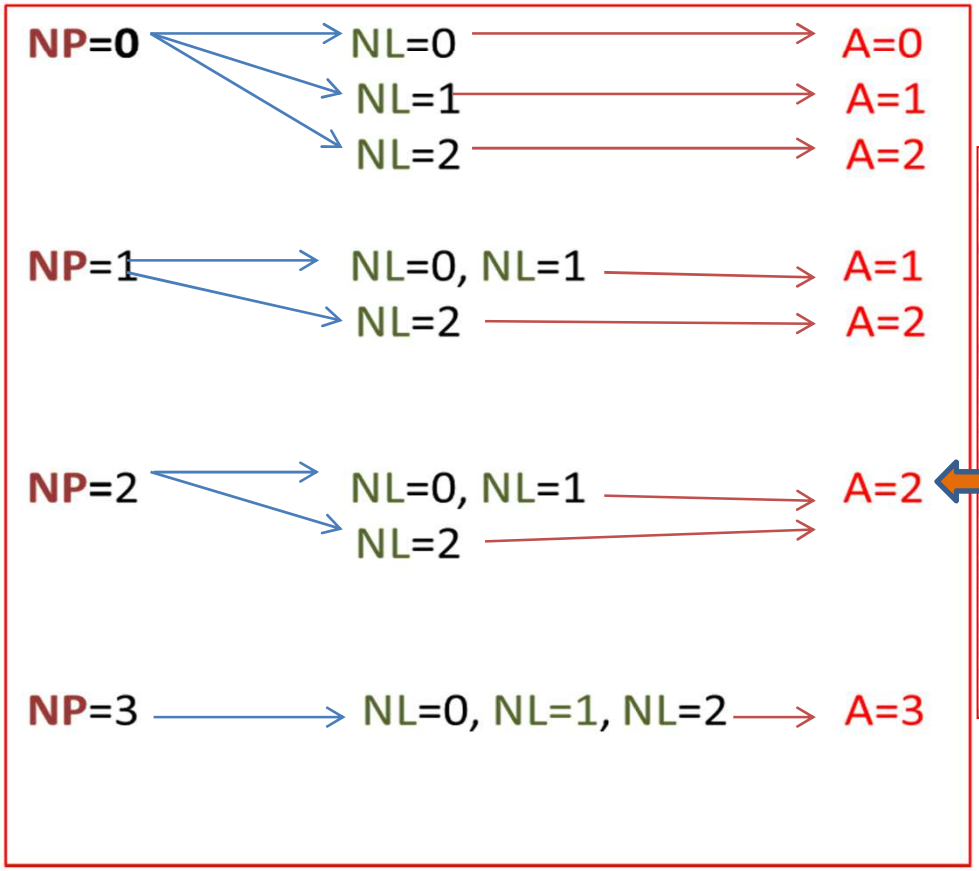


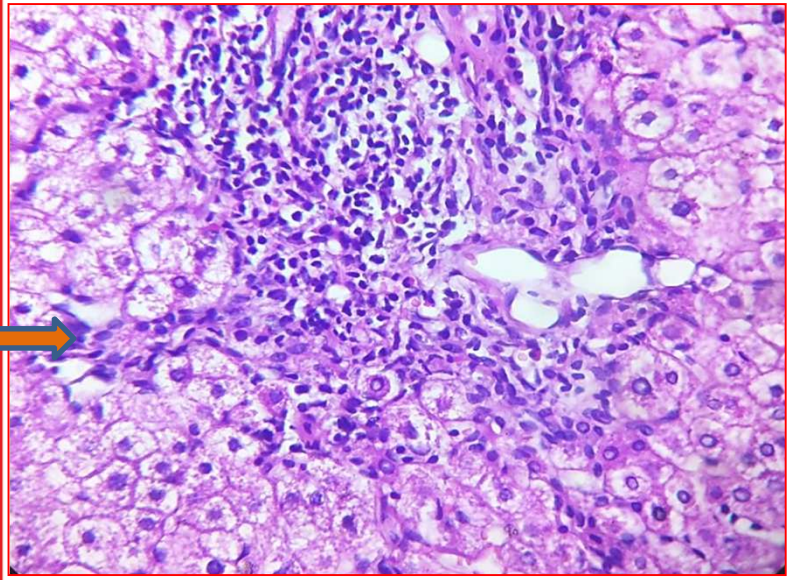




Trichrome de Masson

METAVIR/ ACTIVITE



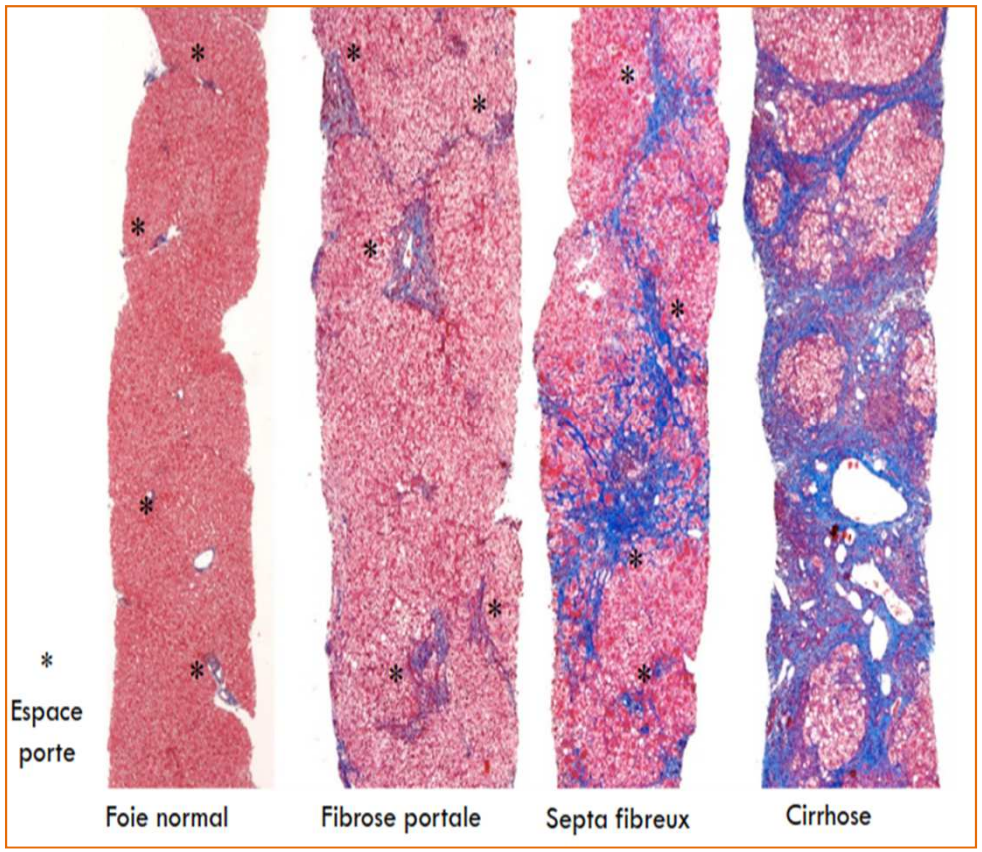


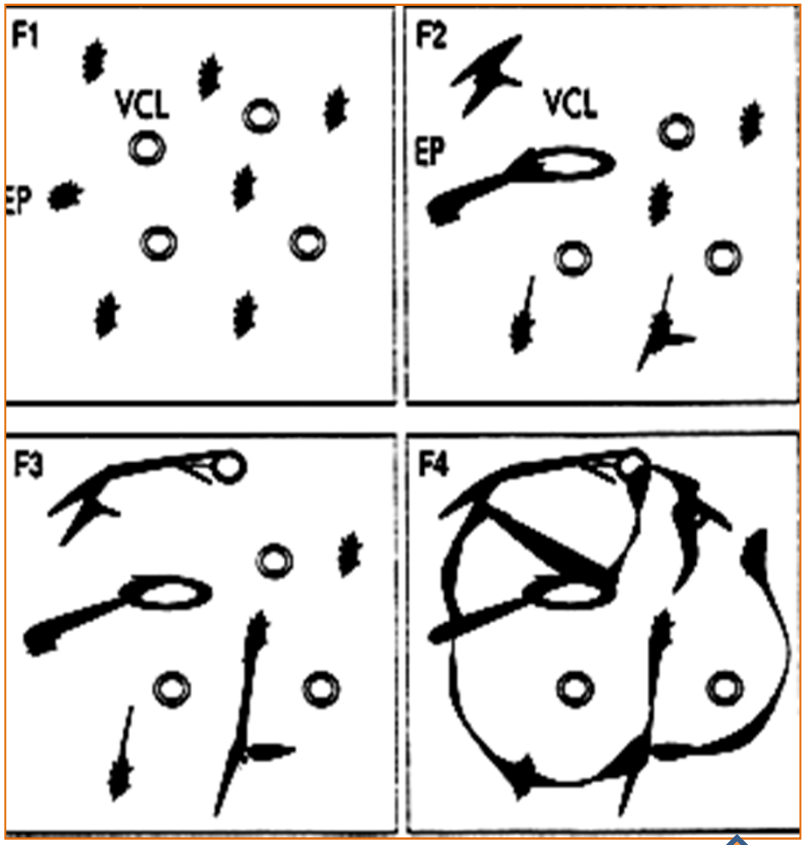
A2: Activité modérée

NP: Nécrose parcellaire

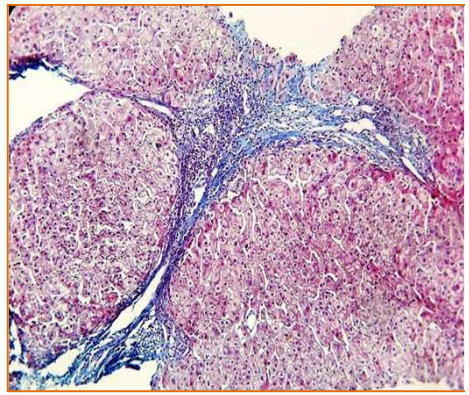
NL: Nécrose lobulaire

METAVIR/ FIBROSE





F4



Comment évaluer la fibrose hépatique au cours de l'infection chronique VHB?

1. PBH
2. Fibroscan
3. PBH + Fibroscan
4. PBH + Fibrotest
5. Fibrotest + Fibroscan

[44–51]. Transient elastography, which is a non-invasive method widely used in Europe, offers high diagnostic accuracy for the detection of cirrhosis,

Unresolved issues : Assess the role of non-invasive markers (serum and biophysical) for the evaluation of the severity of liver disease and for the follow-up of treated and untreated patients.

Journal of Hepatology **2012** vol. 57 | 167–185

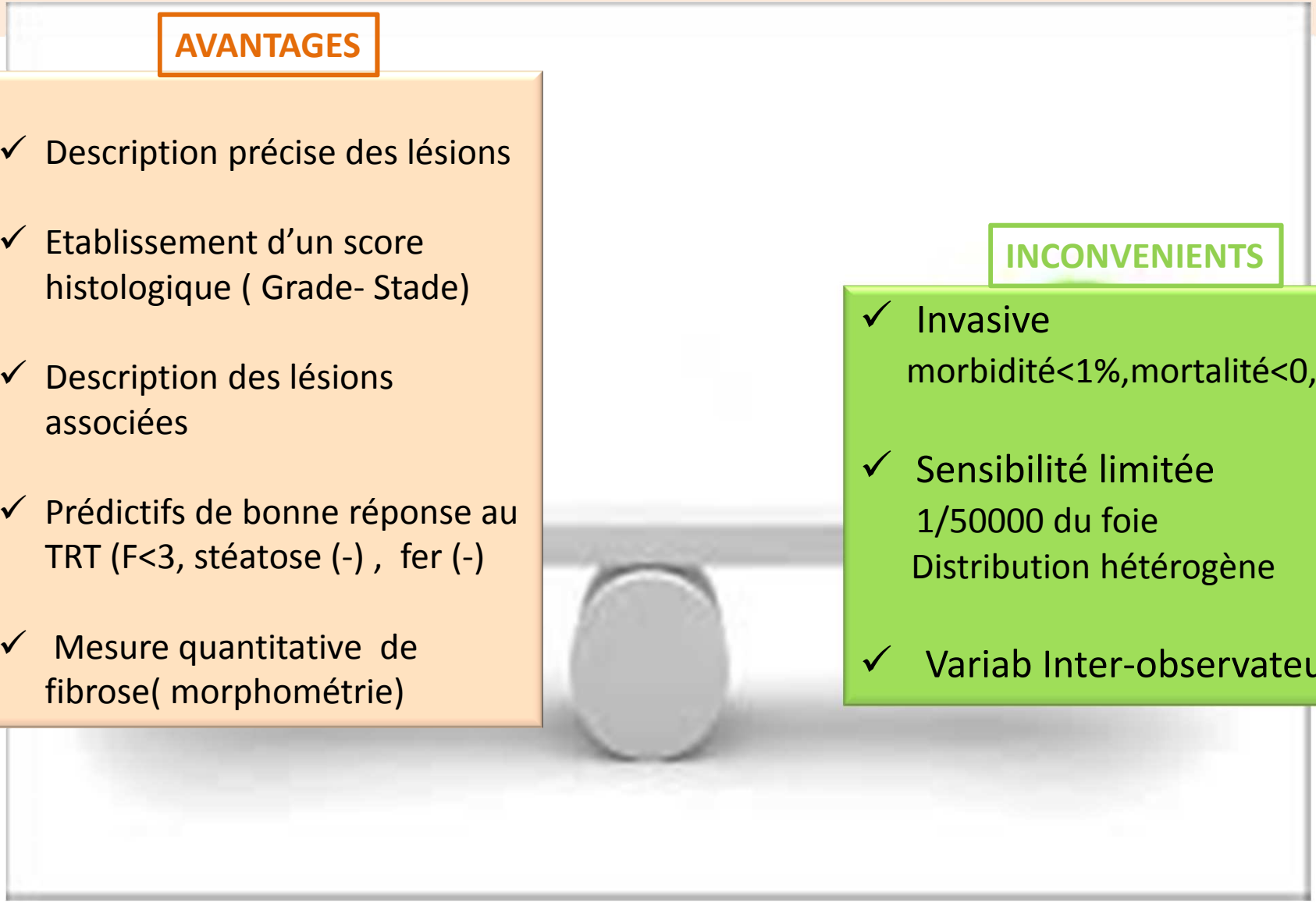
Place de la PBH

AVANTAGES

- ✓ Description précise des lésions
- ✓ Etablissement d'un score histologique (Grade- Stade)
- ✓ Description des lésions associées
- ✓ Prédictifs de bonne réponse au TRT (F<3, stéatose (-) , fer (-)
- ✓ Mesure quantitative de fibrose(morphométrie)

INCONVENIENTS

- ✓ Invasive
  morbidité<1%,mortalité<0,03%
- ✓ Sensibilité limitée
  1/50000 du foie
  Distribution hétérogène
- ✓ Variab Inter-observateurs

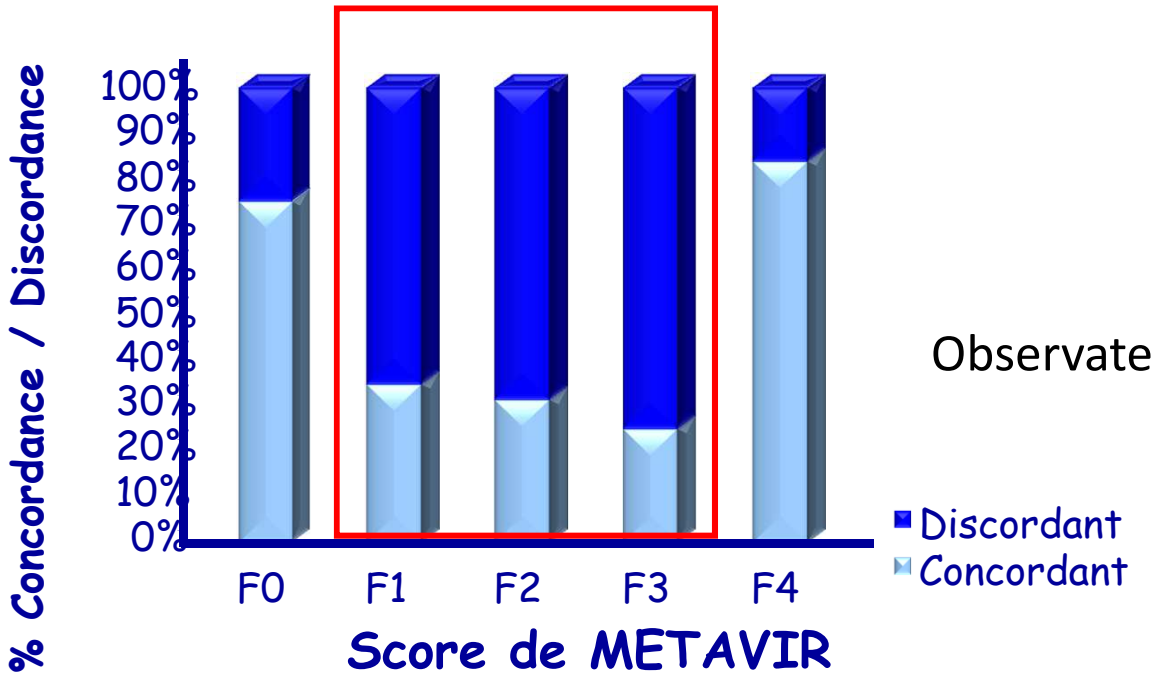


Bedossat P. J Hepatol 2009;50:1-3

Cadranel J et al. Hepathology 2000; 32; 477-481

Limites de la biopsie : Variations inter-observateurs

- Discordance Activité > Discordance Fibrose *
- Série personnelle: Discordance Activité: 19%
  Discordance Fibrose: 9%

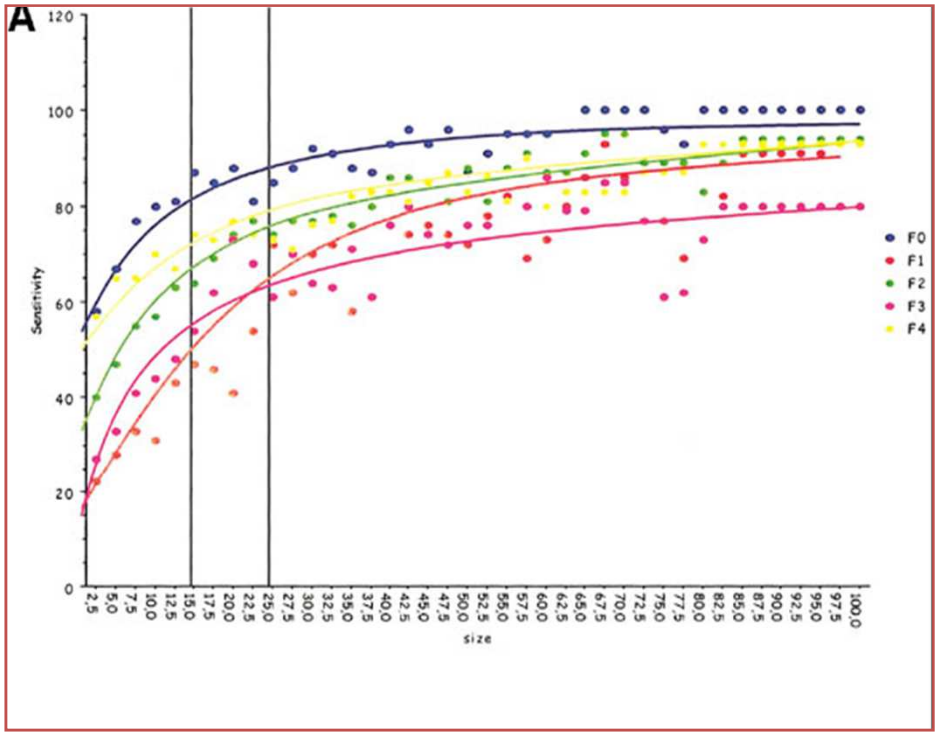


Observateurs n=3, PBH n=234

M. Pinzani, Florence

*R A Standish. An appraisal of the histopathological assessment of liver fibrosis. GUT 2006

- Optimiser les performances diagnostiques de la PBH:
  - Taille de la biopsie ≥2,5 cm*
  - Expérience du pathologiste**



*Bedossa et al, Hepatology 2003

** RA Standish..An appraisal of the histopathological assessment of liver Fibrosis. GUT 2006

Hepatology. 2003 Dec;38(6):1356-8.

Liver biopsy size matters in chronic hepatitis: bigger is better.

Scheuer PJ.

Performance diagnostique FS: F≥2, F4

Table 1 Transient elastography performance for the diagnosis of significant fibrosis (F ⩾ 2) in chronic hepatitis B

Ref.	Patients (*n*)	Cut-off (kPa)	Sn	Sp	LR^-	LR^+	AUROC (95%CI)
Oliveri *et al*[21]	188	7.5	93%	88%	0.07	8.2	0.96 (0.94-0.99)
Marcellin *et al*[89]	173	7.2	70%	83%	0.36	2.6	0.81 (0.73-0.86)
Chan *et al*[34]	161	8.4	84%	76%	0.20	3.5	0.87 (0.82-0.93)
Degos *et al*[90]	284	5.2	89%	38%	0.28	1.4	-
Viganò *et al*[25]	217	8.7	64%	92%	0.40	7.5	-
Verveer *et al*[27]	241	6.0	-	-	-	-	0.85
Cardoso *et al*[26]	202	7.2	74%	88%	0.30	6.2	0.86

Table 2 Transient elastography performance for the diagnosis of cirrhosis (F4) in chronic hepatitis B

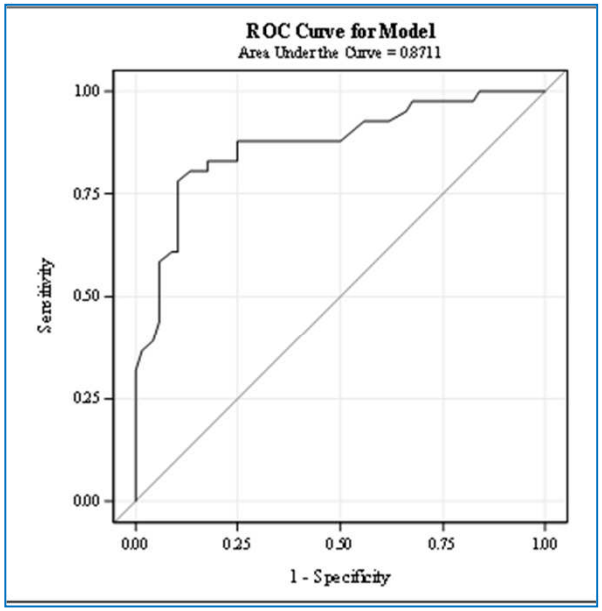
Ref.	Patients (*n*)	Cut-off (kPa)	Sn	Sp	LR^-	LR^+	AUROC (95%CI)
Oliveri *et al*[21]	188	11.8	93%	88%	0.07	8.2	0.97 (0.95-0.99)
Marcellin *et al*[89]	173	11.0	70%	83%	0.36	7.1	0.93 (0.82-0.98)
Chan *et al*[34]	161	13.4	79%	92%	0.20	9.8	0.93 (0.89-0.97)
Viganò *et al*[25]	217	9.4	100%	82%	0.01	5.5	-
Cardoso *et al*[26]	202	11.0	75%	90%	0.20	7.3	0.93

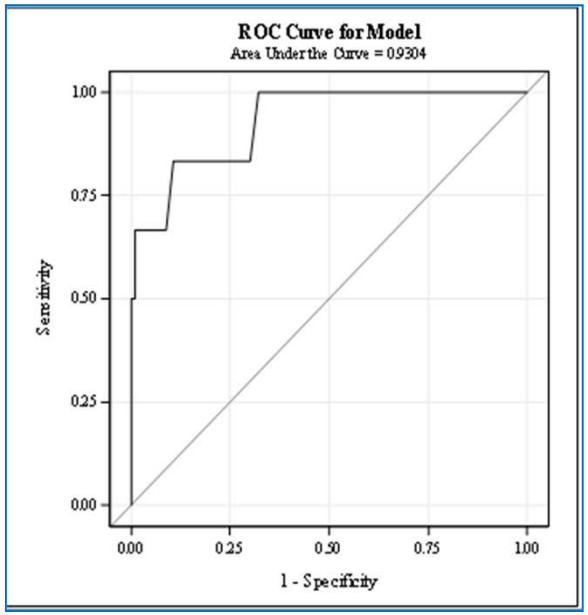
Oliveri F, *World J Gastroenterol 2008;* ***14: 6154-6162***
Chan HL. *J Viral Hepat 2009;* ***16: 36-44***
Vigano M. *Aliment Pharmacol Ther 2011*
Cardoso AC. *Liver Int 2012;* ***32: 612-621***
Marcellin P. *Liver Int 2009;* ***29: 242-247***
Degos F. *Hepatol 2010;* ***53: 1013-1021***
Verveer C. Liver Int 2012; ***32: 622-628***

Performance diagnostique FS: F≥2, F4

- Notre étude:
  - Evaluer la performance diagnostique du FibroScan / PBH
  - 135 patients porteurs chroniques du VHB (Janv11-Dec14)
  - Co-infection, TRT antiviral, CHC → exclus
  - Ag Hbe (-) 91%,DNA ≥20.000 UI/ml 71.5%, ALAT >2N 11%.
  - Taille moyenne PBH 26.4 mm (12-45)
  - Fibrose ≥ F2: 37.5%, stéatose >30%: 7.6%

N. Guessab. JFHOD 2015





F0F1vsF2F3F4
AUC = 0.87 [0.80-0.94] P<0.001
85% concordance

F0F1F2F3vs F4
AUC 0.93 [0.83;1] P<0.001
89% concordance

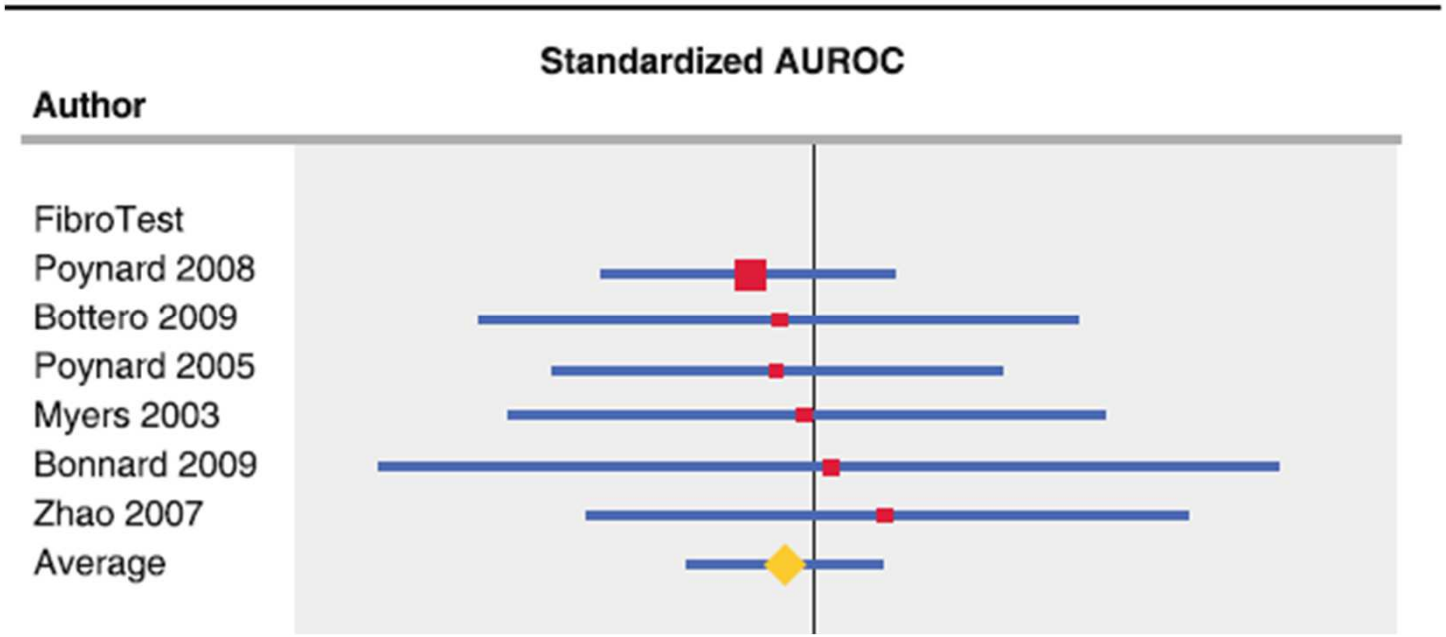
	F0F1Vs F2F3F4	F0F1F2 Vs F3F4	F0F1F2 F3 Vs F4
CUT OFF(KPa)	7.1	8.6	12
Sensibilité (%)	70	76	69
Spécificité (%)	90	93	99
VVP(%)	78	76	60
VPN(%)	90	94	98

Paramètres	LS Means 95%CI	P-value
Fibrose	F0: 6.9 [2.6; 11.1] F1: 8.6 [6.0; 11.3] F2: 9.9 [6.2; 13.6] F3: 8.7 [4.8; 12.6] F4: 20.1 [13.7; 26.6]	0.02
Activité	A0: 8.8 [4.2; 13.4] A1: 8.8 [6.2; 11.3] A2: 7.9 [5.1; 10.7] A3: 18.0 [12.0; 23.9]	0.03

Analyse multivariée

Performance des tests sanguins

- Méta-analyse 8 études, 1842 patients HCB. Fibrotest
- AUROC 0.84 (0.79–0.86) pour le diagnostic de fibrose significative, 0.87 pour le diagnostic de cirrhose



Poynard T. Curr Hepatitis Rep (2011) 10:87-97

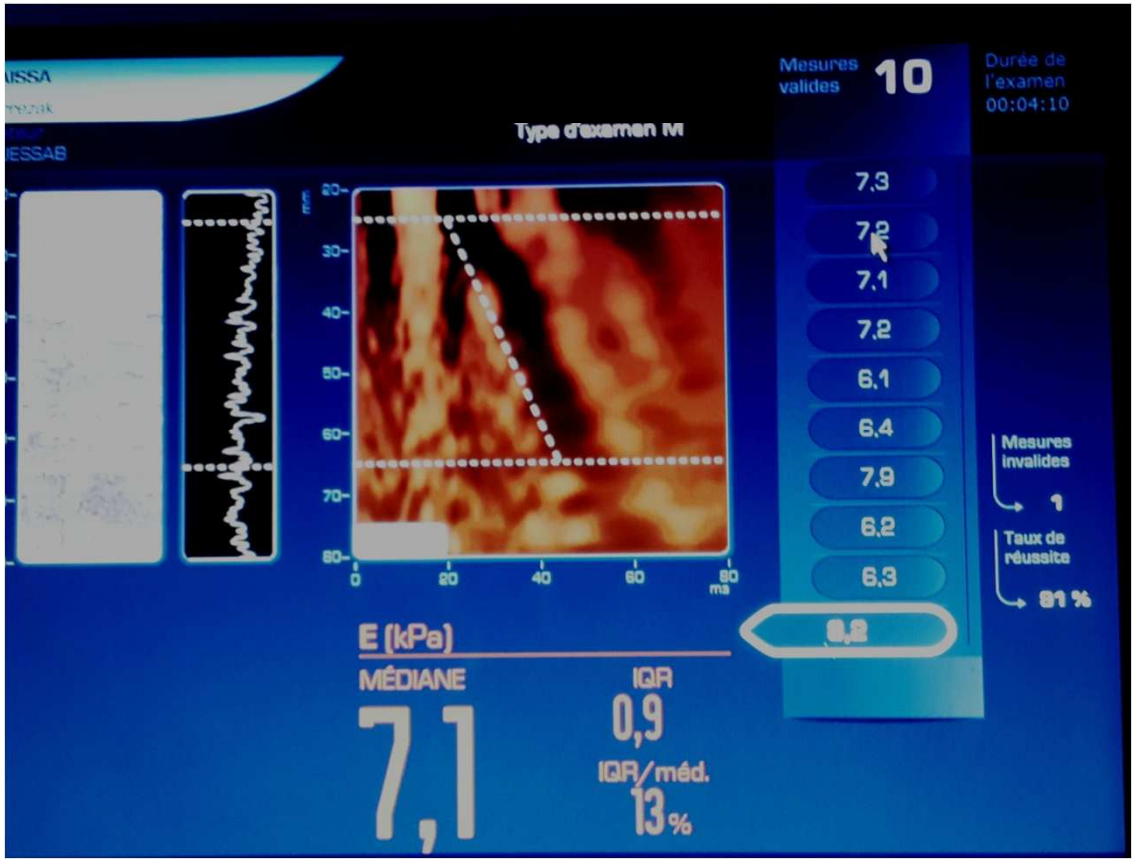
Performance des tests sanguins

		N	F2/F3/F4	Cirrhose
Myers	FibroTest	209	0,78	
Kim	FibroTest	194	0,90	0,87
Wu	Fibromètre	78	0,85	

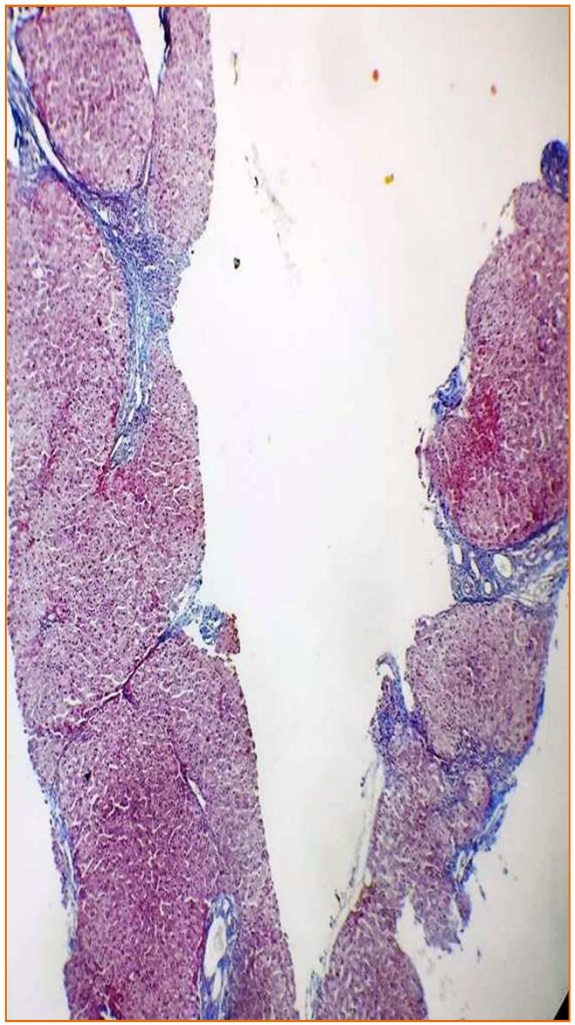
Muers RP et al. J Hepatol 2003; 39: 222-30
Kim BK et al. Plosone 212; 7e35825
Wu D et al. World J Gastroenterol 2010; 16: 501-7

Patient: Fibroscan

- 7.1 KPa
- IQR/med: 13%, mesures valides 10, TDR: 91%

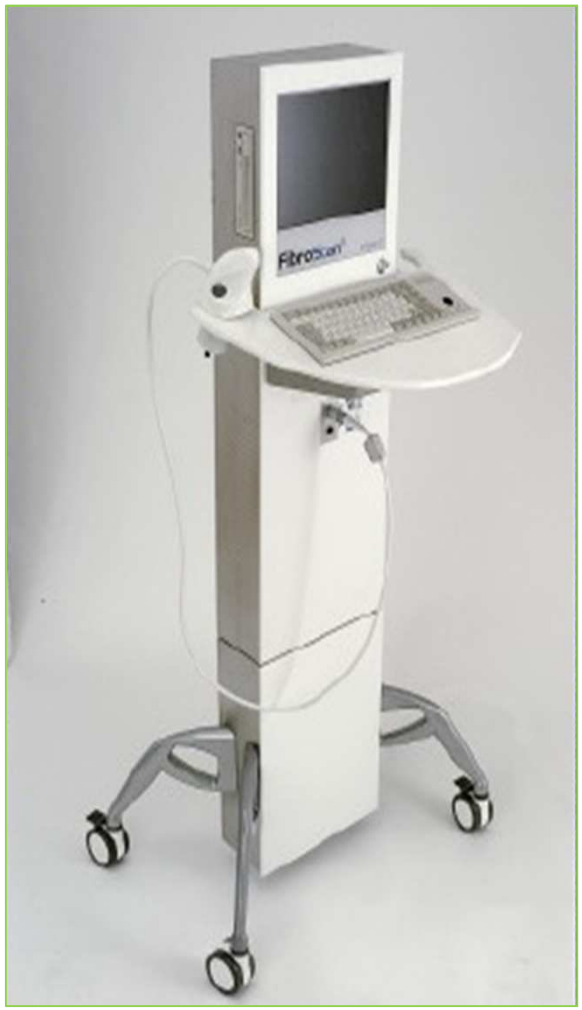


Que croire?

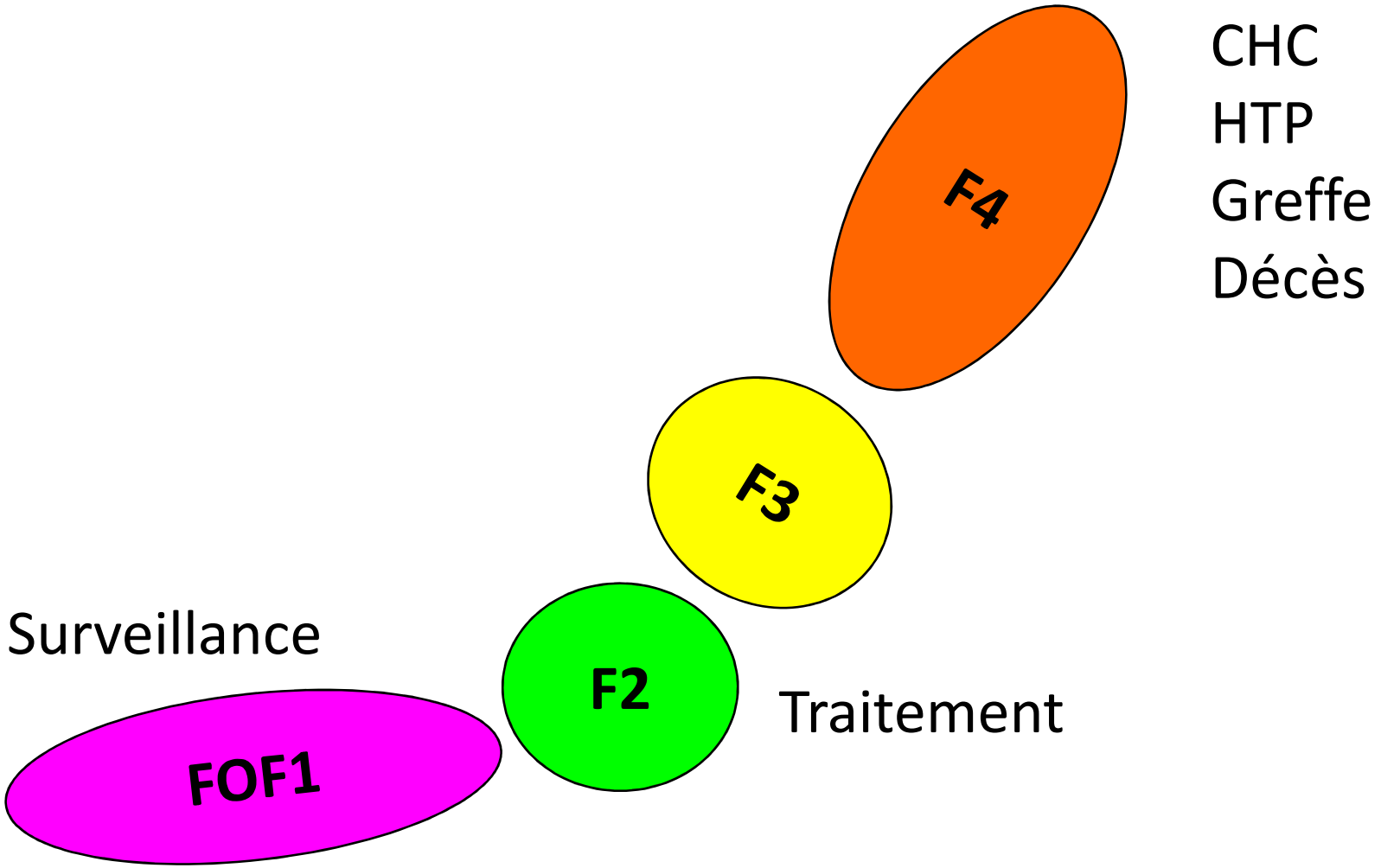


F4

≠



7.1 KPa (F2)


F4
F3
F2
FOF1
CHC
HTP
Greffe
Décès
Surveillance
Traitement

Quelles sont les causes de discordance entre la PBH et le Fibroscan?

1. Cytolyse hépatique
2. Activité necrotico-inflammatoire
3. Stéatose
4. La qualité de la biopsie
5. Expérience insuffisante de l'opérateur / Pathologiste

La PBH: Pièges diagnostiques

❑ Faux Positifs

- Biopsie sous capsulaire

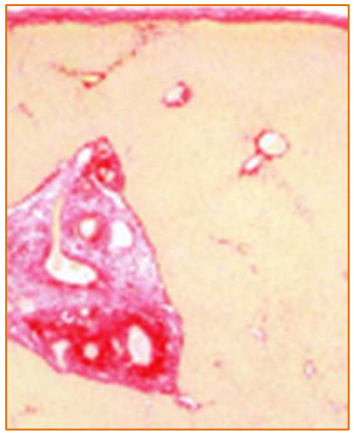
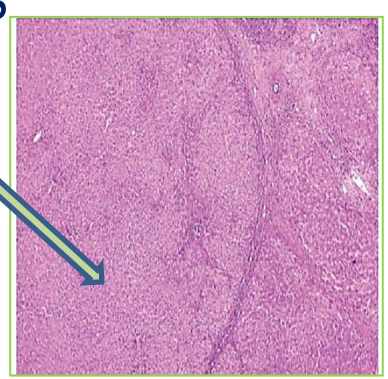


Table 3. Distribution of fibrosis stage based on LB and LSM in patients with discordance (n = 21).

	LB high group[a] (n = 2, 9.5%)	LSM high group[b] (n = 19, 90.5%)
Fibrosis stage		
F1	–	7
F2	–	12
F3	1	–
F4	1	–
LSM value, kPa		
F1 (<6.0 kPa)	2	–
F2 (≥6.0 kPa)	0	–
F3 (≥7.5 kPa)	–	4
F4 (≥9.4 kPa)	–	15

❑ Faux négatifs

- Hétérogénéité des lésions
- Cirrhose macronodulaire

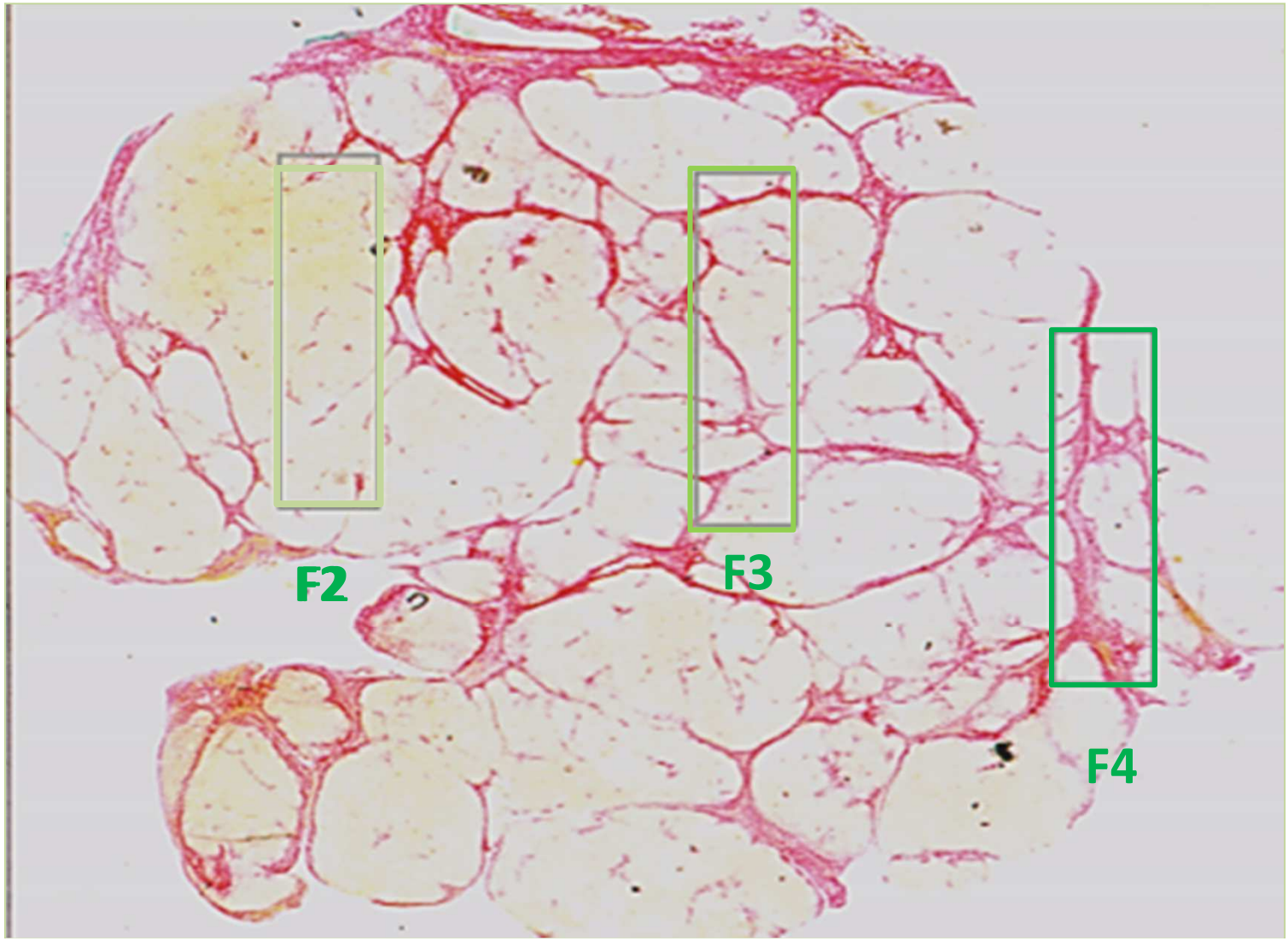


N=150, discordance:14% *
PBH:10% vs FS: 90%

*Seung Up Kim et al.Discordance between Liver Biopsy and FibroScanH inAssessing Liver Fibrosis in Chronic Hepatitis B: Risk Factors and Influence of Necroinflammation 2012

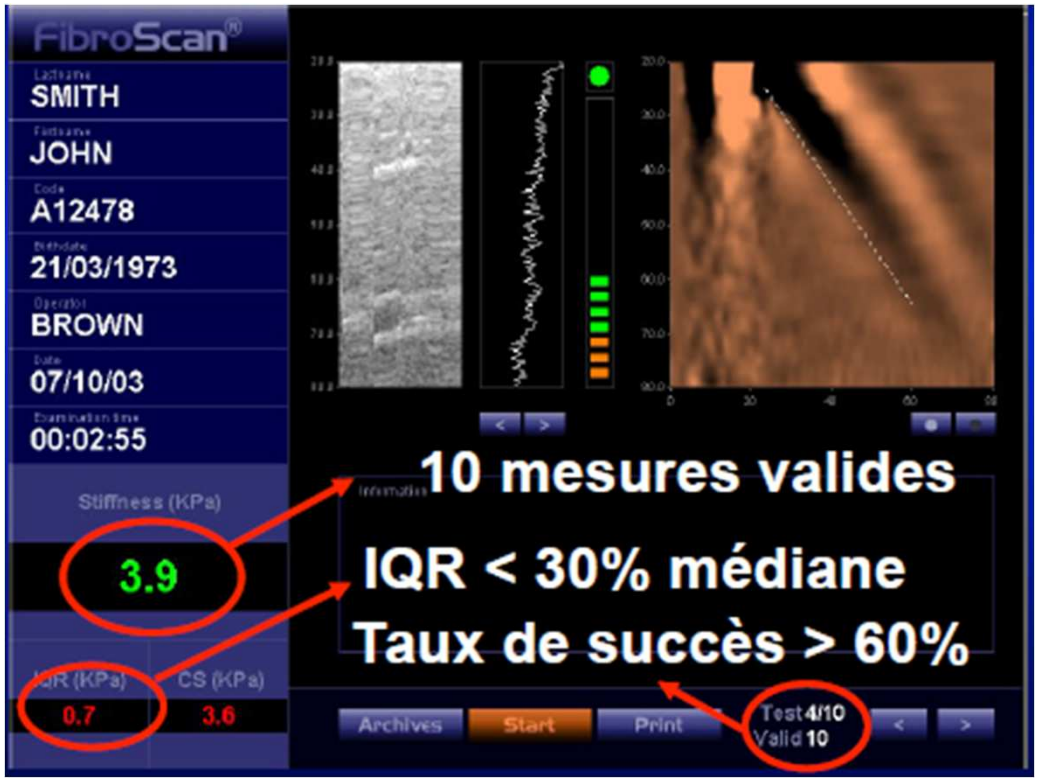
Faux négatifs

Hétérogénéité des lésions



Mesure de l'élasticité fiable?

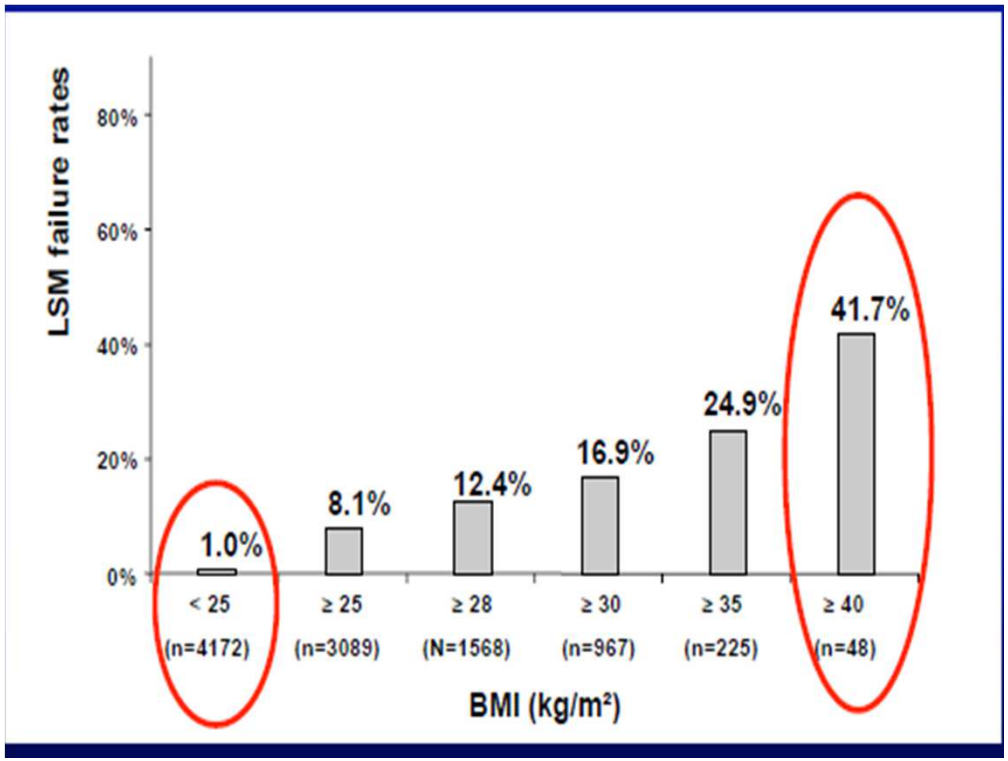
- Critères de fiabilité du Fibroscan non respectés +++
- 15.8%*



*Castera . Hepatology 2010; 51:828-35

Causes d'échec - discordance FS/PBH

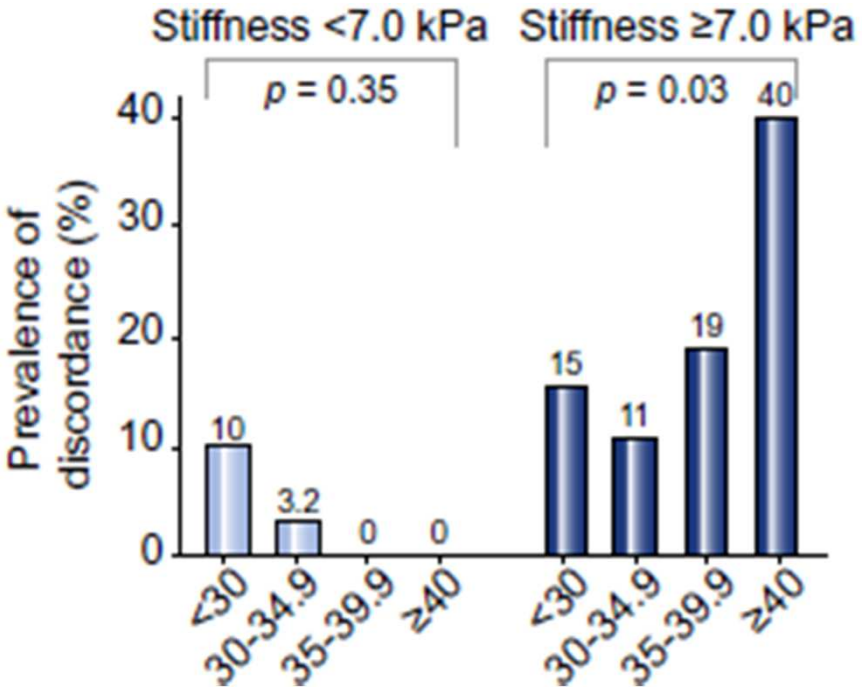
- Causes:
  - BMI > 28 (1, 2) Pannicule adipeux thoracique (3)
  - Expérience opérateur (1)
- N=13369 (2)
  - Echec 3%
  - 2.4 – 9.4% (1. 4)



1. **Foucher J**. *Eur JGastroenterol Hepatol 2006;* ***18: 411-412***
2. Castera . Hepatology 2010; 51:828-35.
3. Castera L, *J Hepatol 2008;* ***48:***835-847
4. **Fraquelli M**. *Gut 2007;* ***56: 968-973***

BMI ≥ 28 Kg/m2

- Sonde XL: la réponse ?
- 210 patients HC / BMI ≥28 kg/m2: PBH + FS (XL)
- Discordance (≥2 stades de fibrose) : 11% (surestimation élasticité 75%)

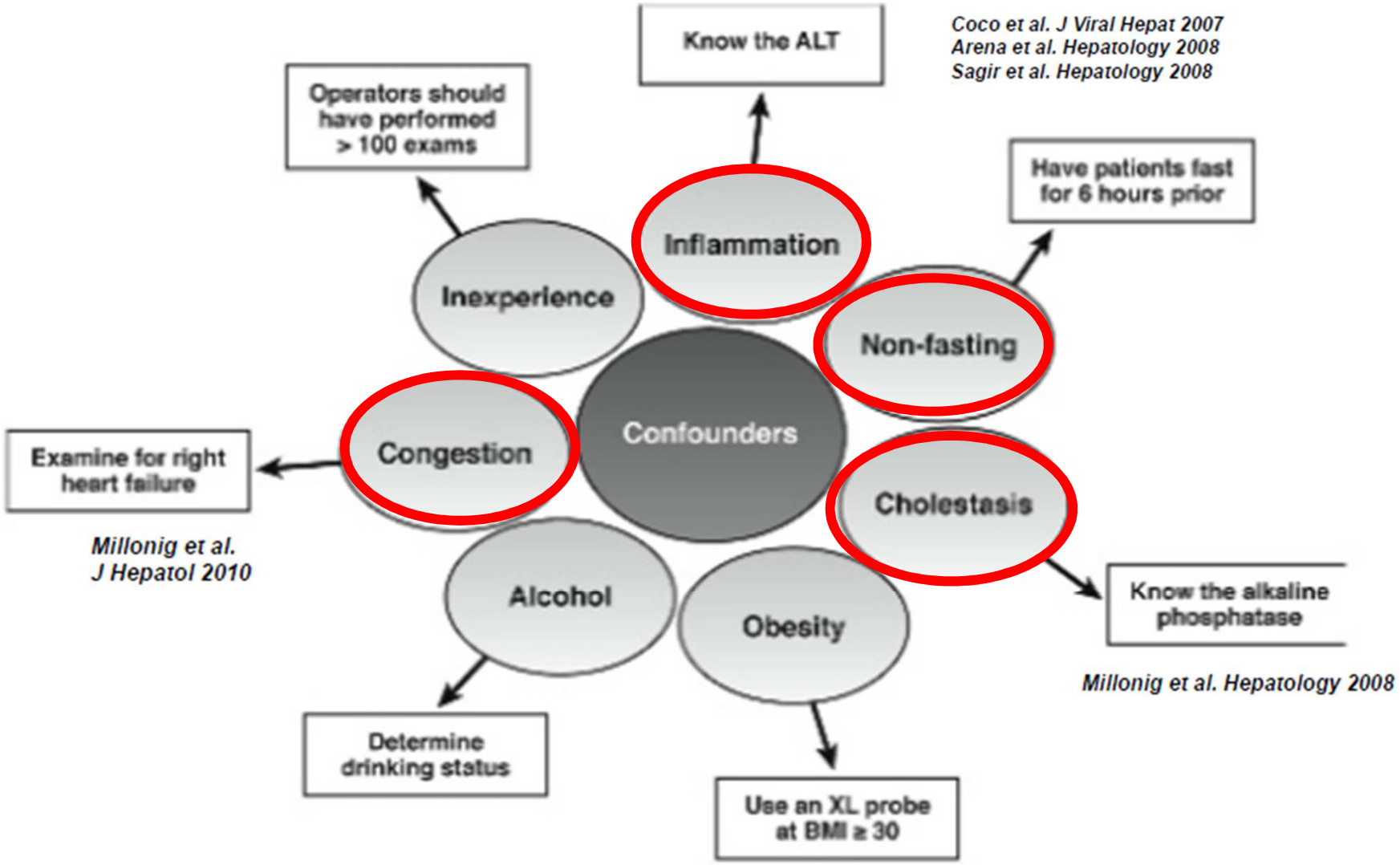


Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
BMI (per kg/m^2)	1.13 (1.06-1.21)	<0.0005	1.09 (1.01-1.18)	0.04
Skin-capsular distance ≥35 mm	10.0 (2.30-43.3)	0.002	3.33 (0.59-18.9)	0.17
Liver stiffness (log_{10}-transformed)	1.98 (1.18-3.31)	0.009	1.73 (0.95-3.18)	0.08
Unreliable LSM[#]	3.33 (1.39-7.94)	0.007	2.09 (0.75-5.82)	0.16

<10 valid shots, SR <60%, or IQR/M >30%.

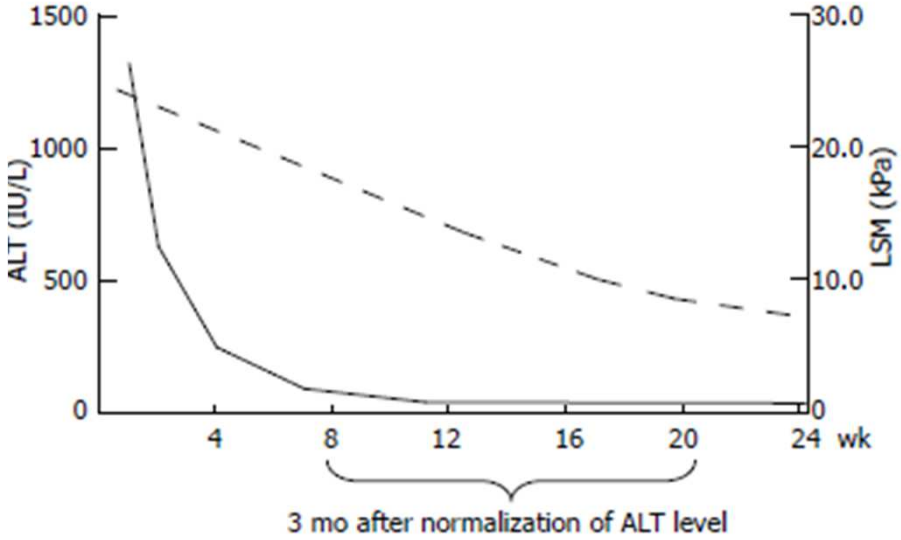
Myers RP. Journal of Hepatology 2012 vol. 56 j 564–570

Facteurs confondants



Transaminases

- Surestimation élasticité hépatique si cytolyse
- **Attendre au moins 3 mois après ALAT N / < 5N** [1, 2]



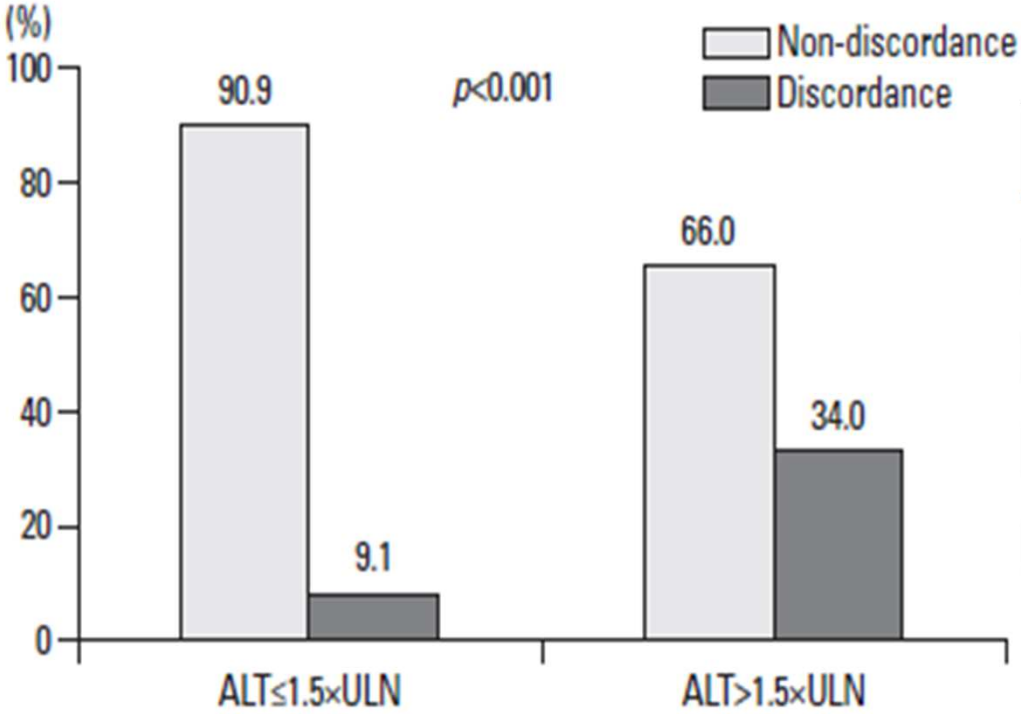
Falsely elevated liver stiffness measurement results in a patient with grossly elevated alanine aminotransferase levels [3]

1. **Chan HL**. *J Viral Hepat 2009;* ***16: 36-44***
2. ***3. Wong GL. B J Gastroenterol Hepatol 2009; 24: 1002-7***

2. Marcellin P. *Int 2009;* ***29: 242-247***

Transaminases

- 182 patients CHB, 68 patients CHC, PBH+FS

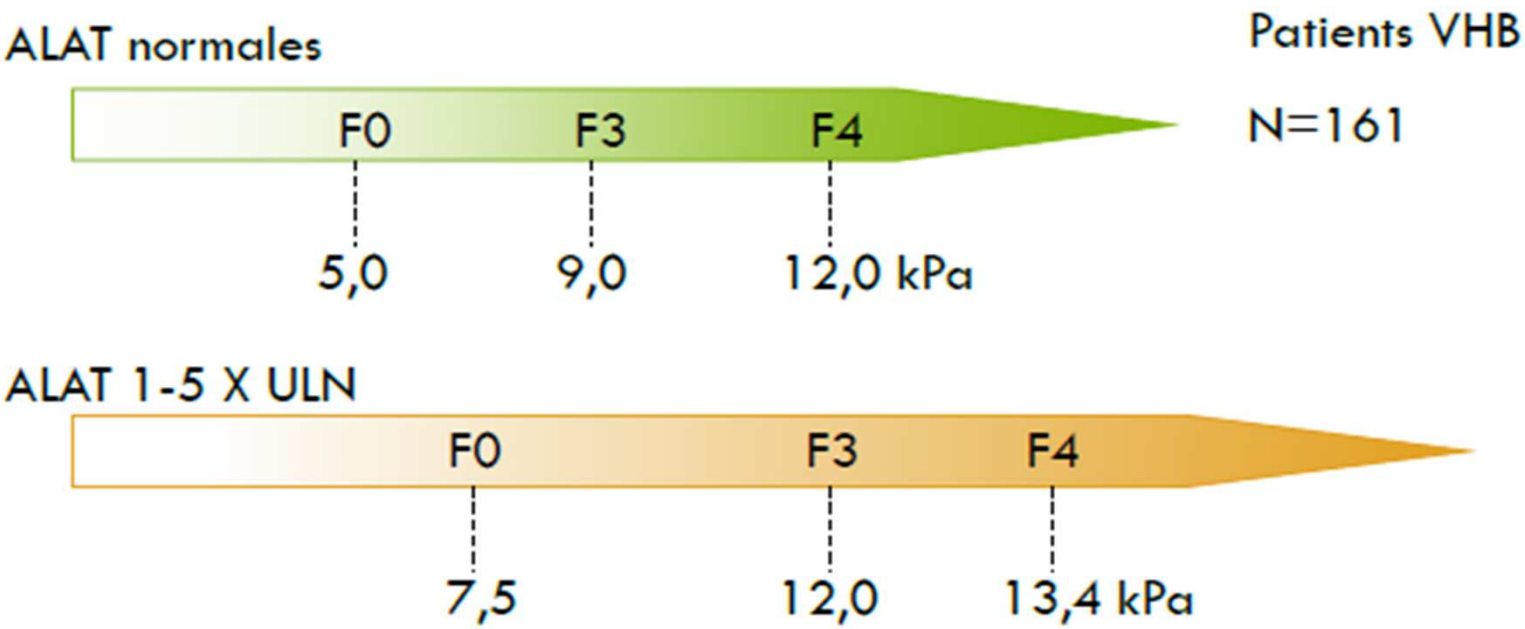


	Multivariate		
	HR	95% CI	*p* value
Chronic hepatitis B			
Age (yrs)	0.995	0.955-1.037	0.805
Male			
BMI (kg/m^2)			
Albumin (g/dL)	3.942	0.995-15.094	0.055
Total bilirubin (mg/dL)			
ALT (IU/L)	1.010	1.003-1.017	0.006
Platelet count (10^5/mm^3)	1.001	0.993-1.009	0.811
Prothrombin time (%)	1.072	0.983-1.168	0.115

ALT was the only predictor of discordance in fibrosis stage in patients with CHB, whereas no significant predictor was identified in those with CHC.

Hui Won Jang. Yonsei Med J 53(2):337-345, 2012

Élasticité variable selon le taux de transaminases

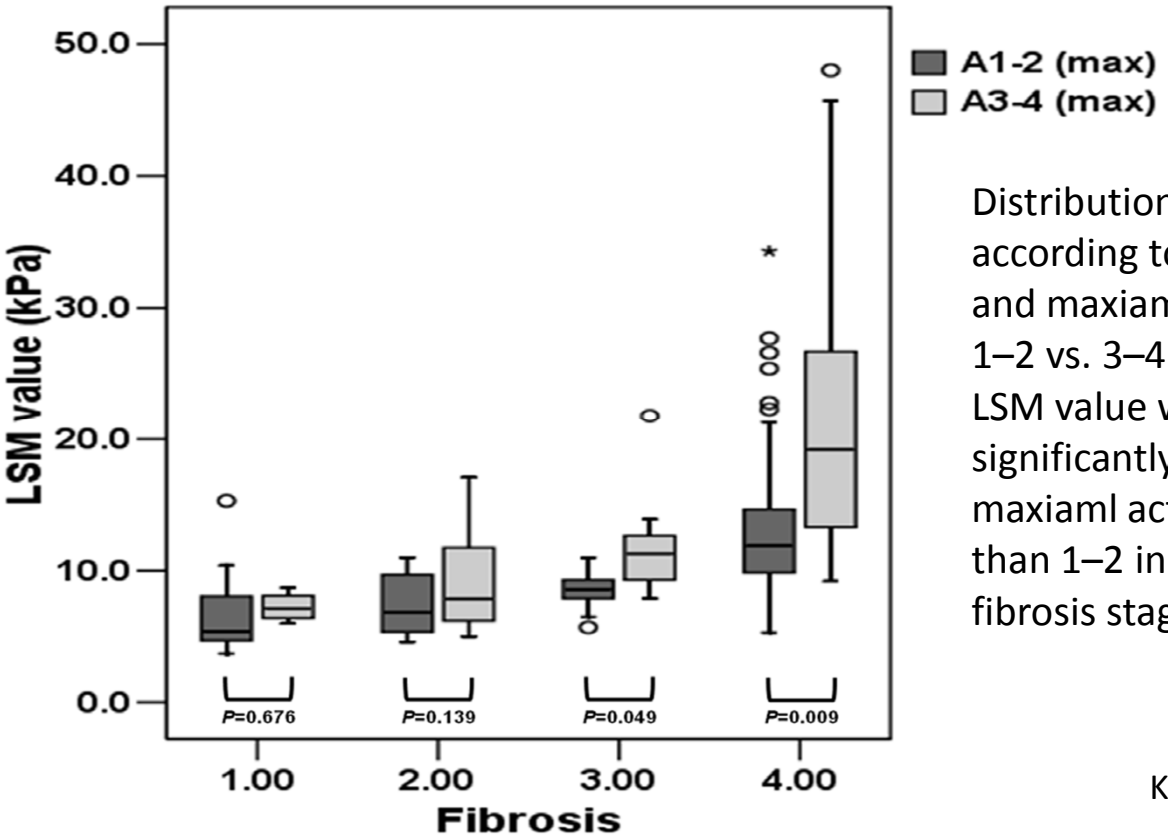


Chan et al. J Virol 2009;16:36-44

Activité nécrotico-inflammatoire

Discordance between Liver Biopsy and FibroScan® in Assessing Liver Fibrosis in Chronic Hepatitis B: Risk Factors and Influence of Necroinflammation

Seung Up Kim[1,2,5], Ja Kyung Kim[1,2,5], Young Nyun Park[3,4,5,6*], Kwang-Hyub Han[1,2,5,6*]



Distribution of LSM values according to fibrosis stage and maxiaml activity grade 1–2 vs. 3–4. The median LSM value was significantly higher in maxiaml activity grade 3–4 than 1–2 in F3 and F4 fibrosis stage

Kim SU. Plosone 2012;vol 7:issue 2

Stéatose

Etiology-related determinants of liver stiffness values in chronic viral hepatitis B or C

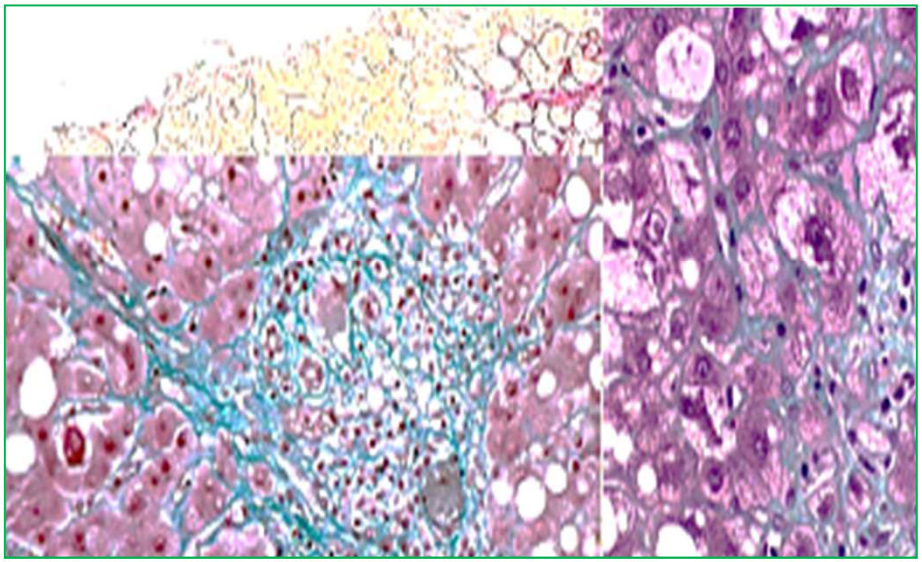
Mirella Fraquelli[1,*], Cristina Rigamonti[2], Giovanni Casazza[3], Maria Francesca Donato[2], Guido Ronchi[2], Dario Conte[1], Mariagrazia Rumi[2], Pietro Lampertico[2], Massimo Colombo[2]

Patients with chronic hepatitis-B (HBV, n = 104) or -C (HCV, n = 453) underwent percutaneous LB concomitantly with TE (FibroScan;
Fibrosis ($p < 0.0001$) and liver cell necroinflammatory activity ($p < 0.0001$) were independently associated with TE results in both HBV and HCV patients, whereas steatosis ($p < 0.0001$) was independently associated with TE in HCV only

Fraquelli M. Journal of Hepatology 2011 vol. 54 j 621–628

Stéatose

- La stéatose VHC > VHC
- n'affecte pas l'elasticité hépatique [1, 2]
- Hépatite + Sd métabolique
- Fibrotest:F4
- Fibroscan: 11KpA
- METAVIR: A1F1



1. Wong GLH. Am J Gastroenterol. 2008;103:3071-3081
2. Wong GLH. W J Hepatol 2013;27(5à:é-'6ééè'.

Notre patient

- BMI: 22 Kg/m^2
- À jeûn
- Critères de fiabilité +
- Ascite (-)
- Cholestase (-)
- Cytolyse < 1.5N
- Insuffisance cardiaque (-)
- Taille PBH 20mm
- 2 pathologistes expérimentés
- Stéatose PBH -
- Activité necrotico-inflammatoire A2

F4 → dépistage HTP / CHC

- Écho-doppler: absence d'HTP
- FOGD: absence d'HTP
- Traitement
  - Interféron peg → échec
  - Candidat TRT par analogues
- Suivi:
  - Fibroscan de contôle: 7.5 KPa !!

Conclusions

ELSEVIER

Journal of Hepatology 50 (2009) 1–3

Journal of Hepatology

www.elsevier.com/locate/jhep

Editorial

Liver biopsy: The best, not the gold standard ☆

Pierre Bedossa[1,*], Fabrice Carrat[2]

- **PBH:**
  - Indiquée HCB
  - sauf cirrhose évidente
  - essentielle avant TRT
- **Marqueurs non invasifs :**
  - cirrhose, suivi des patients
  - ↓ le recours de la PBH.
  - Interpretation prudente