WORKSHOP

How to manage patients with NASH?

Pr Jérôme Boursier – Angers, France

11th Paris Hepatology Conference

January 16th, 2018

Clinical case

Man 63 years old, referred by his diabetologist for high NAFLD fibrosis score (1,37)

Medical history :

- Arterial hypertension
- Dyslipidemia
- T2DM at 46 years old
- Alcohol : one bottle of wine /day, stopped since T2DM diagnosis

Treatment: valsartan, amlodipine, pravastatine, metformine, insulin

Weight 99 kg, height 163 cm, BMI 37
Waist circumference 128 cm
Arterial pressure 130/70 mm Hg

Clinical examination : nothing relevant

ALT : 29 IU/L, AST : 41 IU/L
GGT: 139 IU/L, ALP: 123 IU/L
Negative HCV and HBV antibodies
Ferritin: 452 µg/L, transferrin sat: 27%

Glycemia: 6,9 mmol/l, HbA1c: 6,4%
HDL chol: 1,18 mmol/L (46 mg/dL)
Triglycerides: 1,10 mmol/L (96 mg/dL)

Prothrombin time: 80%
Platelets: 190 G/L
Albumin: 42,8 g/L

Doppler-US:

- Bright liver
- Spleen diameter 112 mm

Question #1

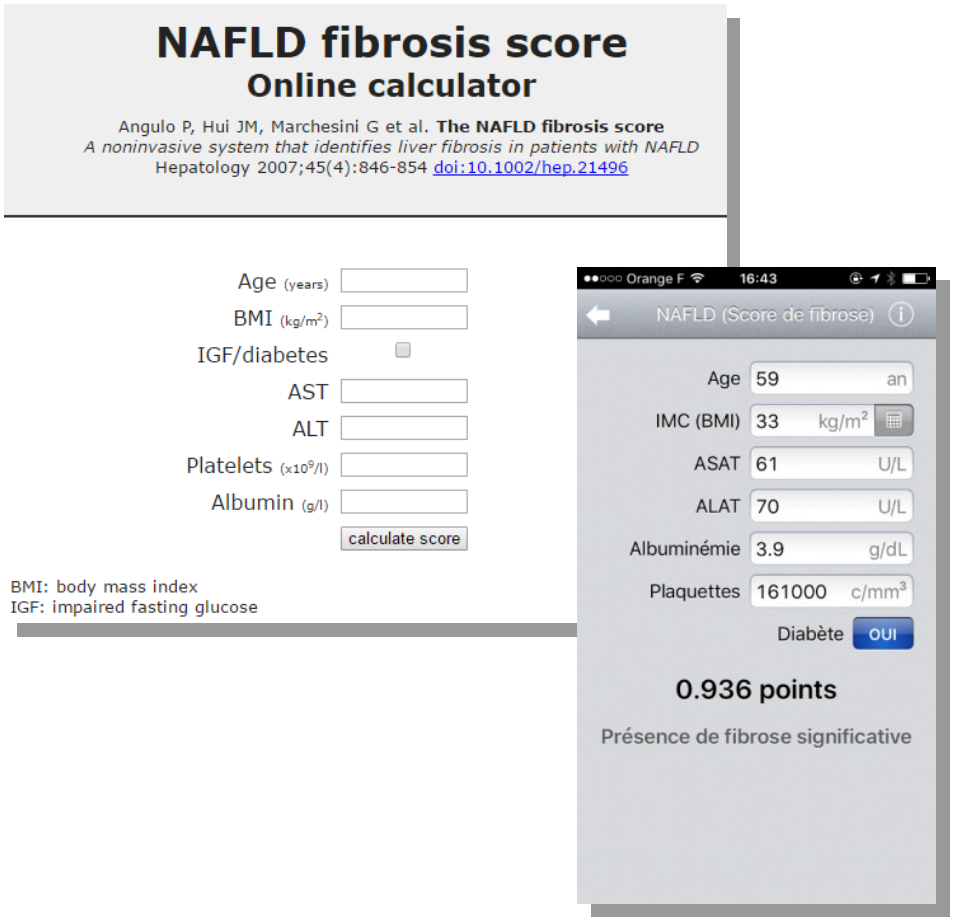
At first sight, what would be your diagnosis of liver fibrosis ?

1. No-mild (F0-1)
2. Significant (F ≥2)
3. Advanced (F ≥3)
4. Cirrhosis (F4)
5. Unknown

NAFLD fibrosis score

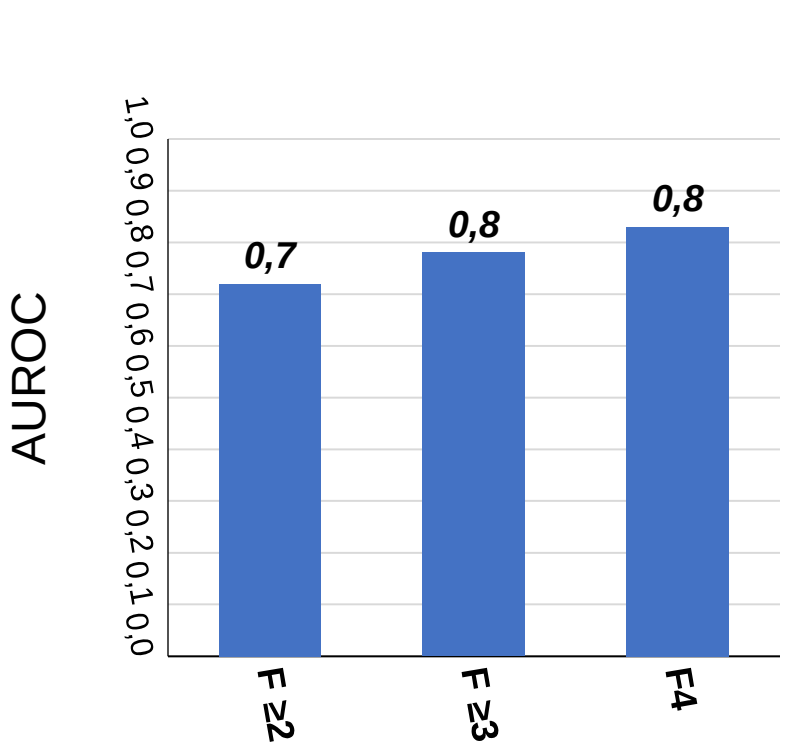
NAFLD fibrosis score

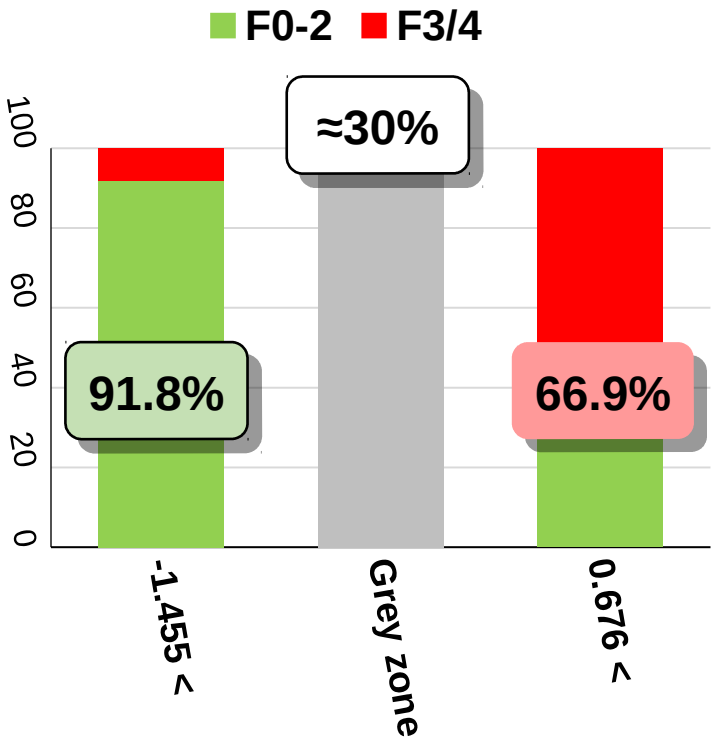
*0,037 * **age***
*+ 0,094 * **BMI***
*+ 1,13 * **IFG/diabetes***
*+ 0,99 * **AST/ALT***
*– 0,013 * **platelets***
*– 0.66 * **albumin***
+ 1,675



Angulo, Hepatology 2007; Boursier, Current Opin Med Diag 2012; Shah, Clin Gastroenterol Hepatol 200

NAFLD fibrosis score





Xiao, Hepatology 2017

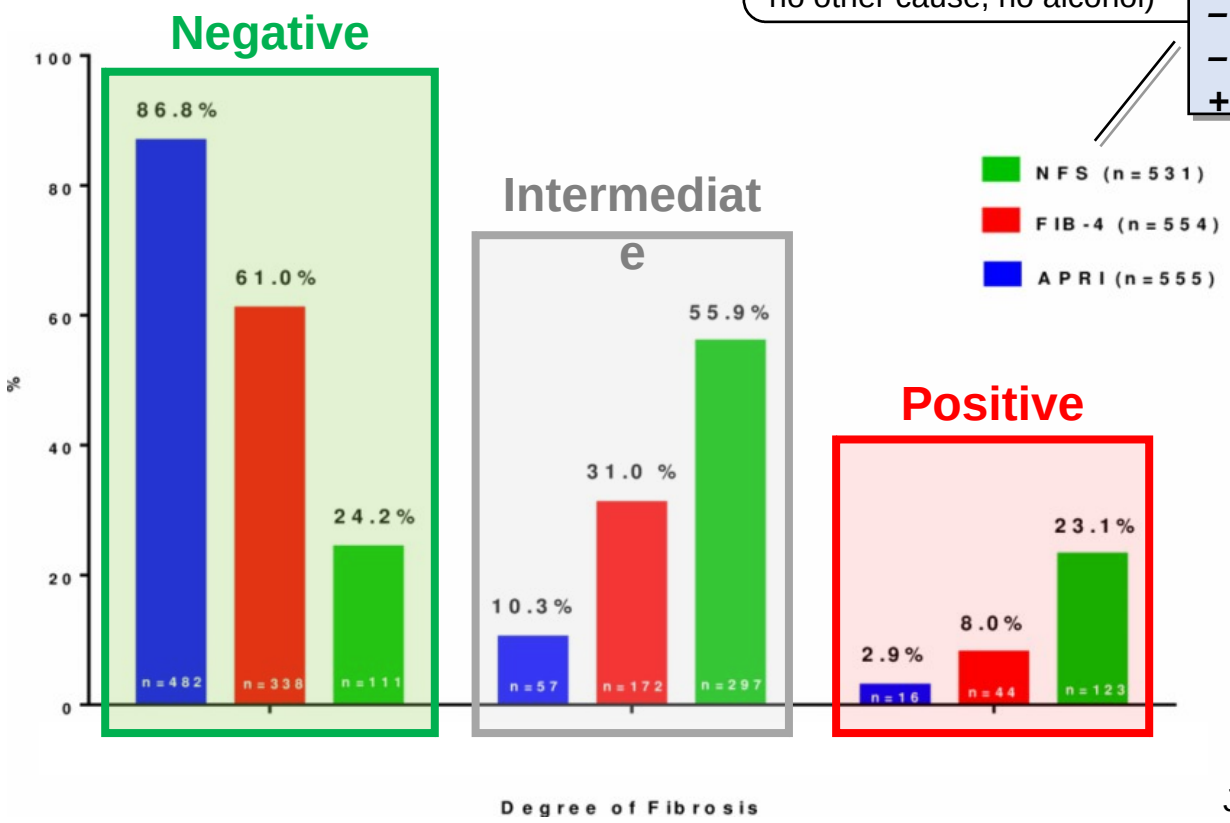
NFS: a good fibrosis test in diabetics?

1693 US diabetics
(code ICD-9 from 09/11 to 11/15)

1018 without NASH

675 probable NASH
(AST or ALT ≥30 (M) ou 19 (W
no other cause, no alcohol)

0,037*age
+ 0,094*BMI
+
1,13*IFG/diabete
+ 0,99*AST/ALT
– 0,013*platelets
– 0.66*albumin
+ 1,675



Joshi, ILC2016-RS-4095

Question #2

Which method would you use in you daily clinical practice to evaluate liver fibrosis in this patient ?

1. FIB4
2. Fibrotest / FibroMeter / ELF
3. Fibroscan
4. ARFI / SSI / ElastPQ
5. MRE
6. Liver biopsy

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- CAP: 289 dB/m (IQR 35)

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Question #3

What is your diagnosis of liver fibrosis ?

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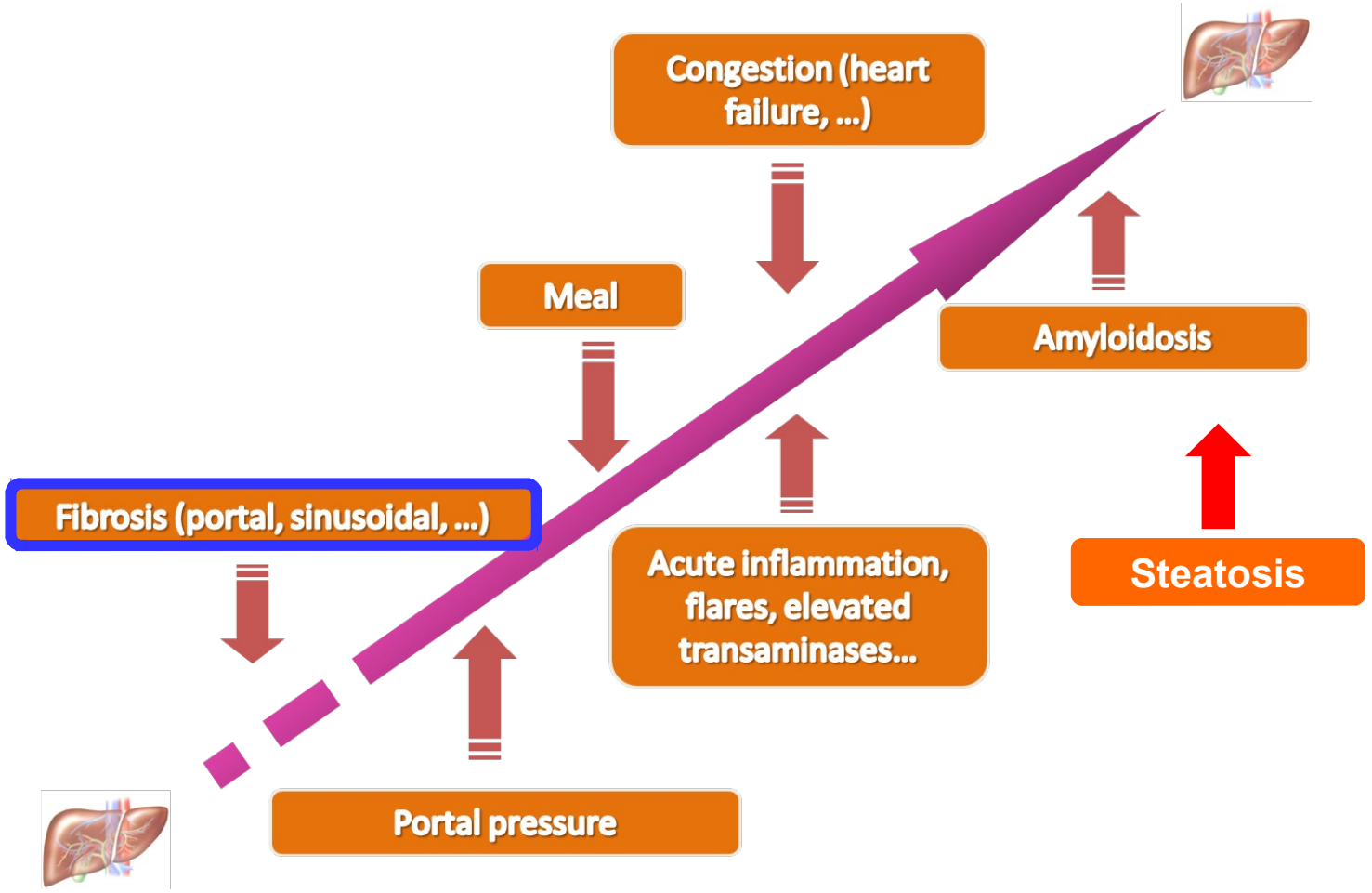
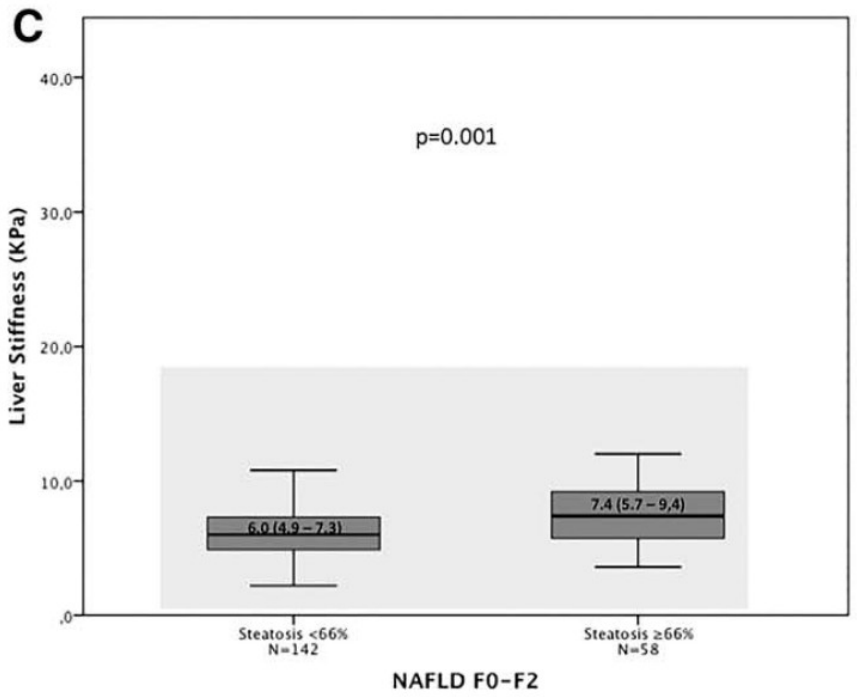
4. Cirrhosis (F4)
5. Unknown

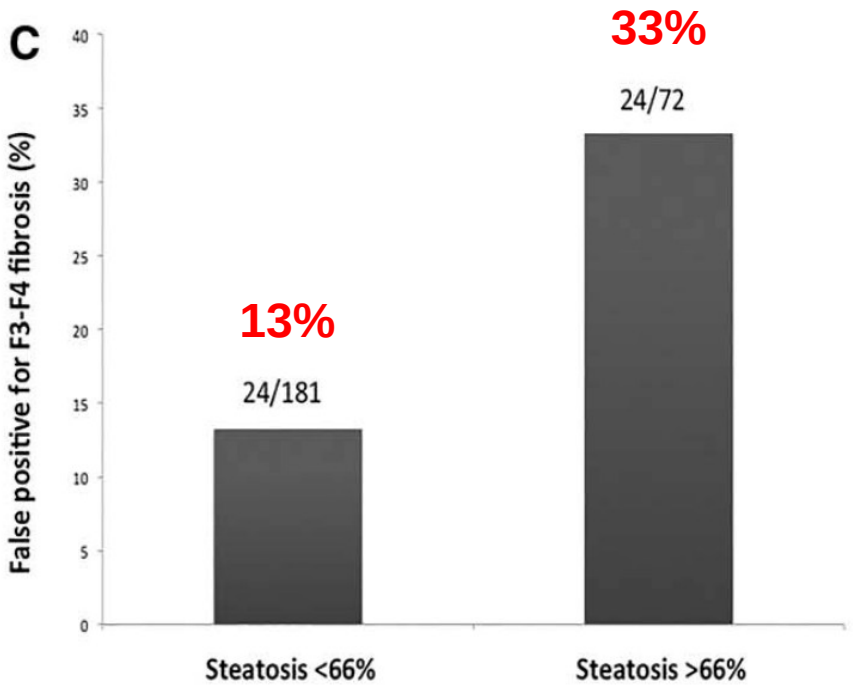
Factors influencing liver stiffness



De Ledinghen, Expert Med Rev Devices 2010
Boursier, J Gastroenterol 2014

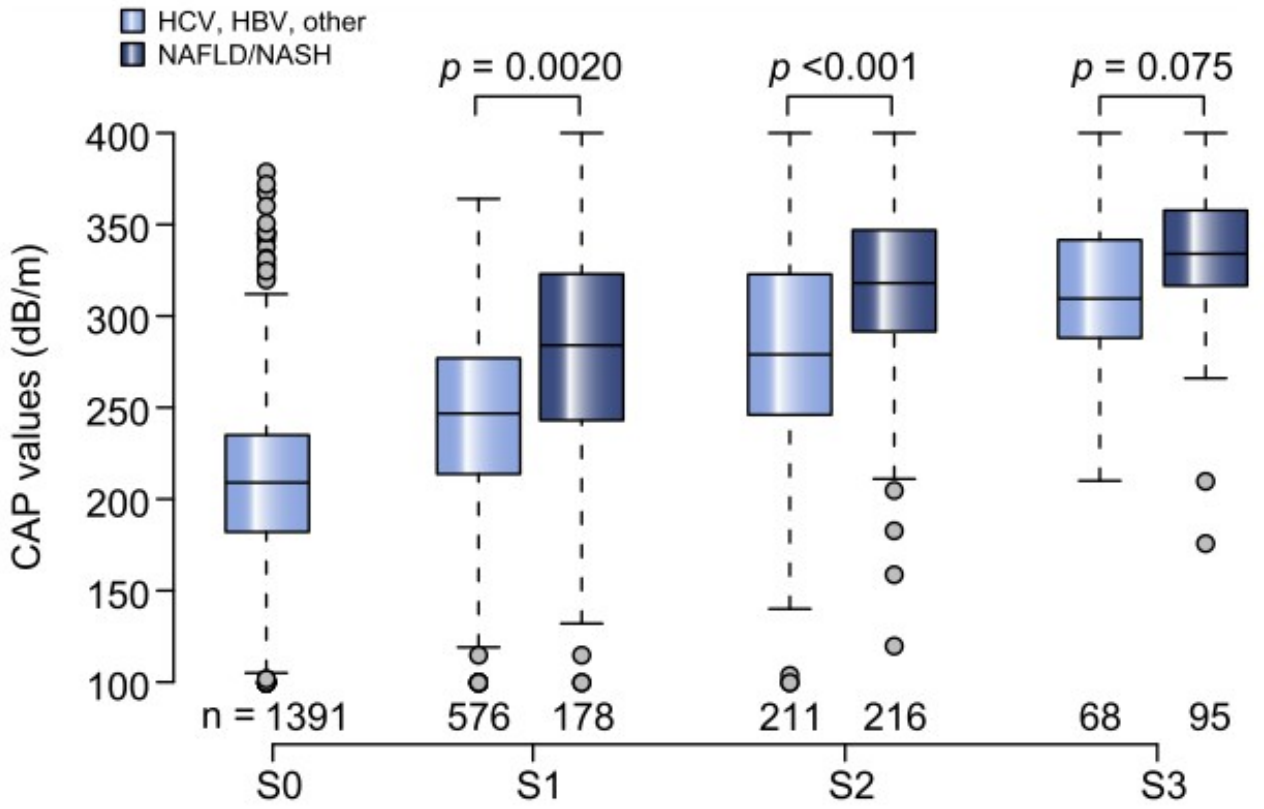
Steatosis increases liver stiffness in NAFLD





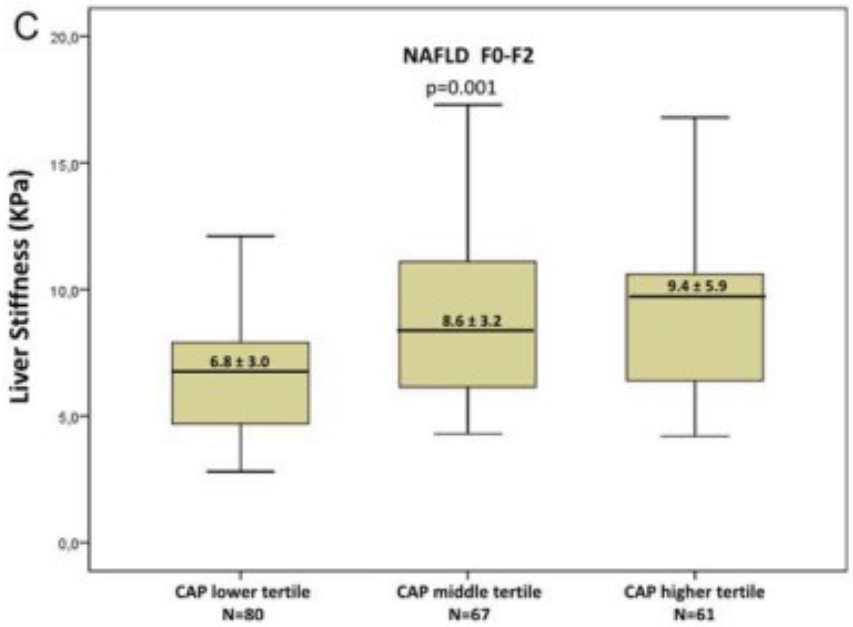
Petta, Hepatology 2016

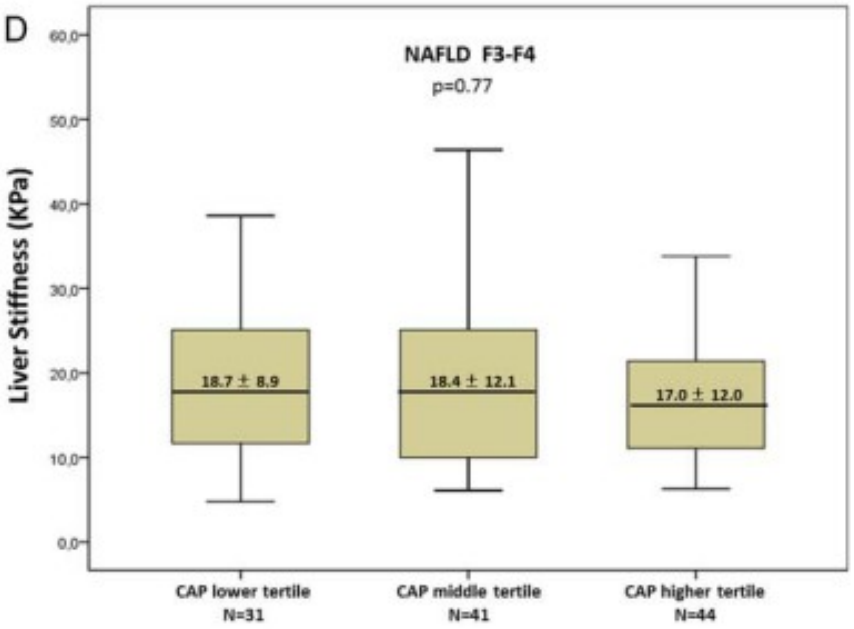
Controlled Attenuation Parameter (CAP)



Karlas, J Hepatol 2017

CAP to refine Fibroscan result in NAFLD





CAP: <300 300-340 >340 <300 300-340 >340

Petta, Hepatology 2016

Clinical case

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M probe

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- 16,2 kPa **(IQR: 8,0)**
- CAP: 289 dB/m (IQR 35)

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Doppler-US:

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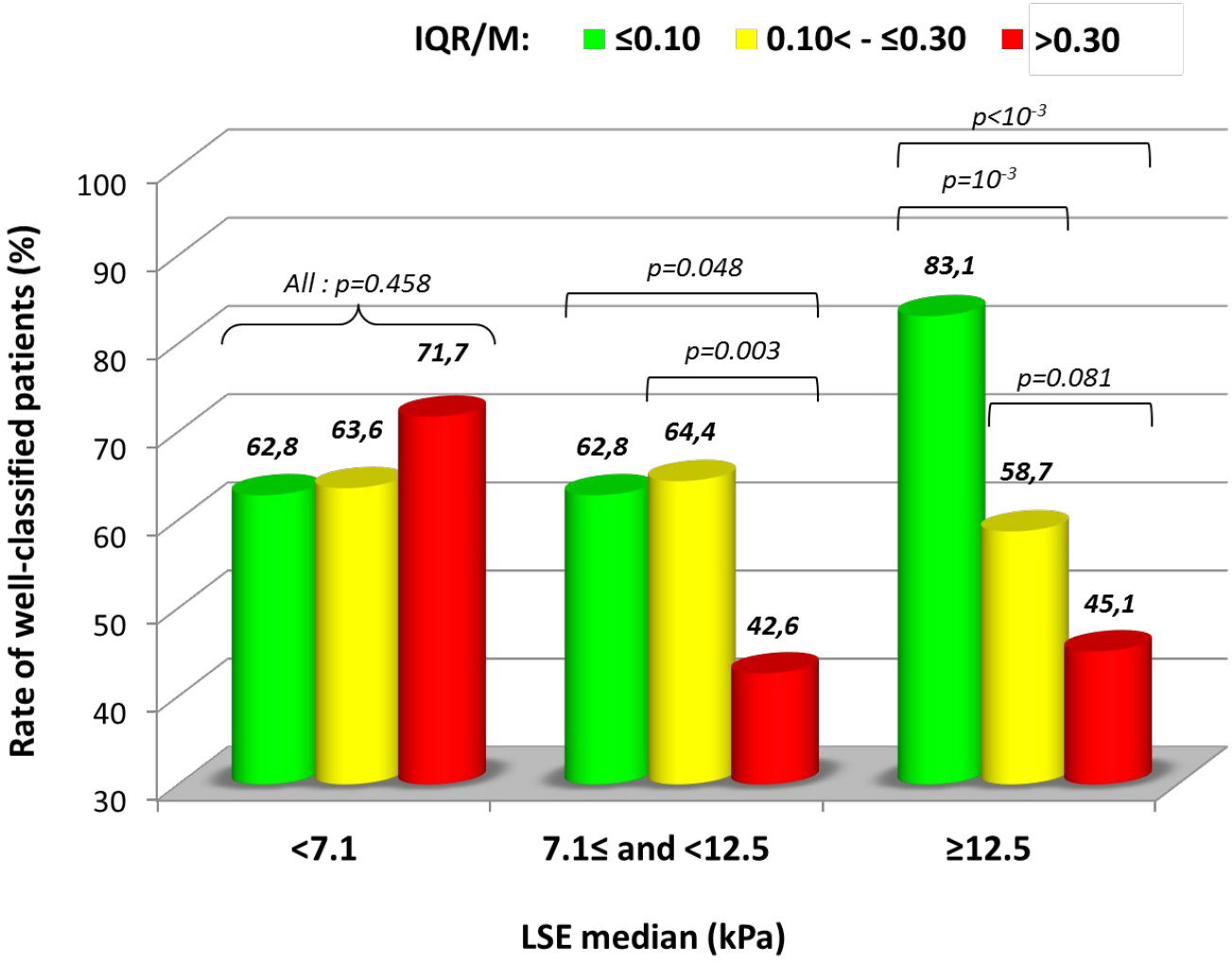
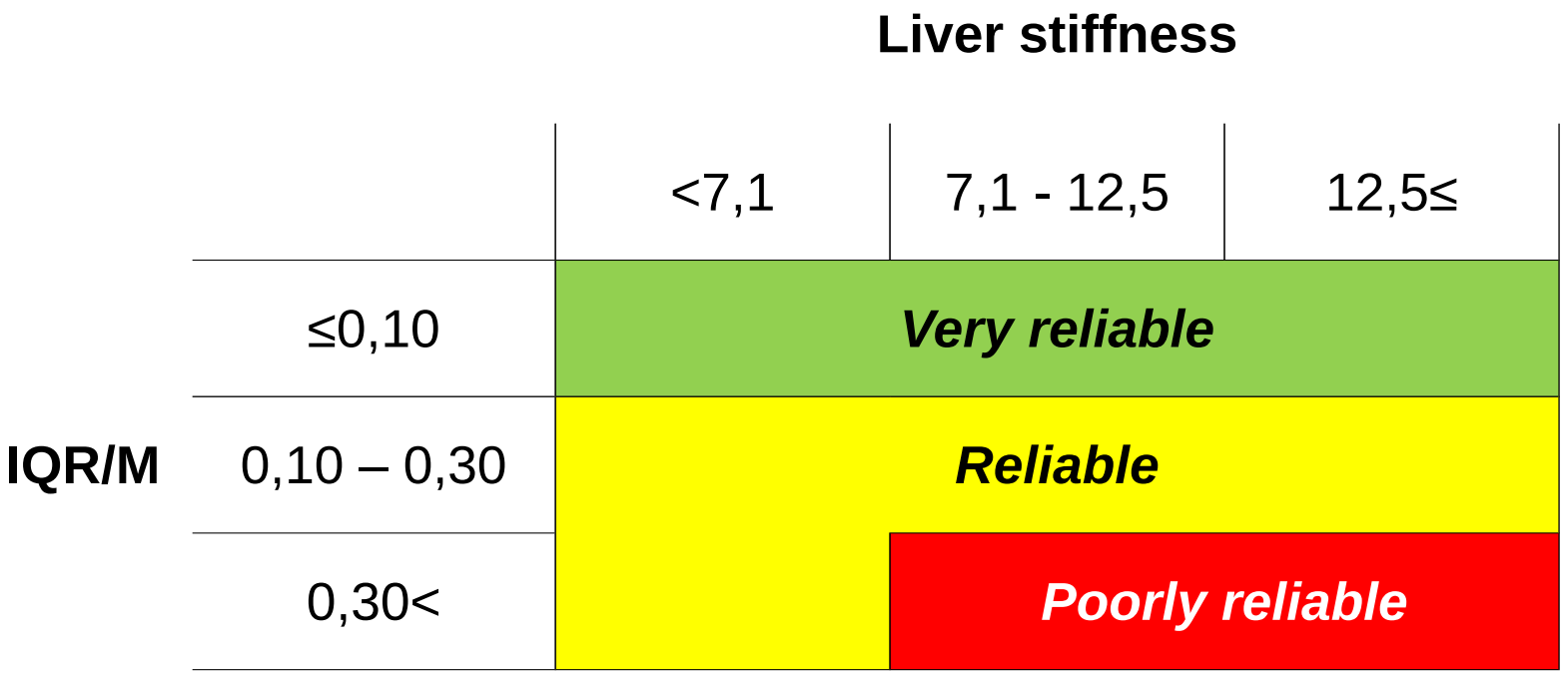
Fibroscan reliability criteria



Boursier, Heaptology 2013

Fibroscan reliability criteria



Boursier, Heaptology 2013

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Indication of XL probe
- 10/10 valid measures
- 14,5 kPa (IQR: 3 kPa)
- CAP: 275 dB/m (IQR 38)

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Doppler-US:
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Question #4

What is your diagnosis of liver fibrosis ?

1. No-mild (F0-1)
2. Significant (F ≥2)
3. Advanced (F ≥3)
4. Cirrhosis (F4)
5. Unknown

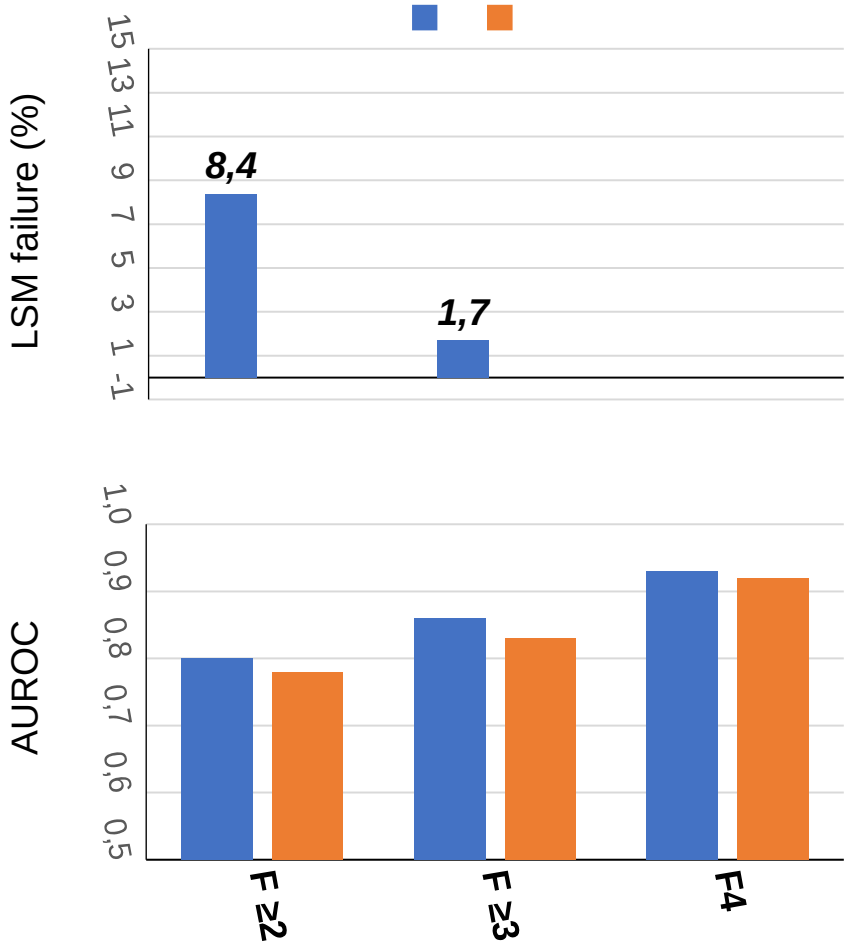
Fibroscan XL probe

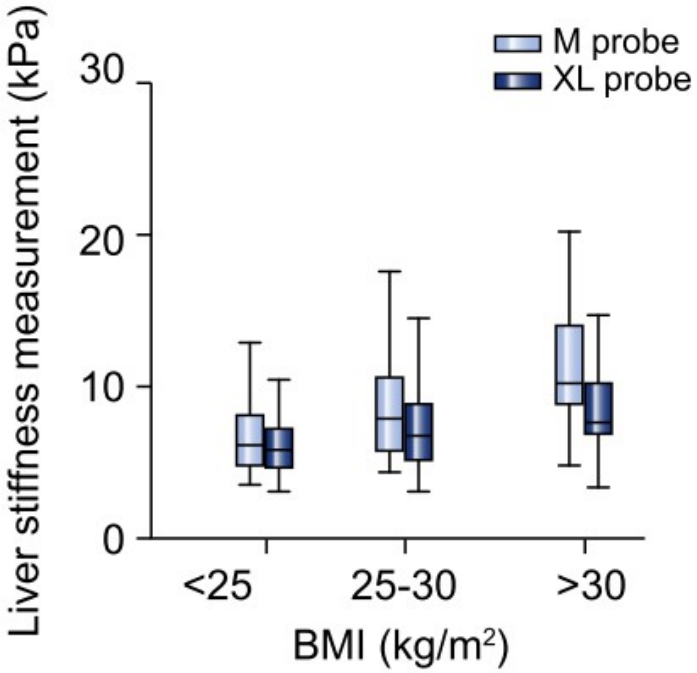
Each probe is specifically designed according to the patient body type

Characteristics	M Probe	XL Probe
US central frequency	3.5 MHz	2.5 MHz
Tip diameter	9 mm	12 mm
Measurement depths (below skin surface)	2.5 – 6.5 cm	3.5 – 7.5 cm
Criteria of use	SCD* < 2.5 cm	2.5 cm< SCD*< 3.5 cm


WITTGENSTEIN - PICASSO
Théodore
Né le 01.02.03
Code : 012547898388
Examen FibroScan M
05.01.10
Durée de l'examen
08 : 12
Taux de réussite
100 %
Mesures invalides
2
Mesures Valides
15
19.4 kPa
19.4 kPa
19.4 kPa
19.4 kPa
19.4 kPa
19.4 kPa
19.4 kPa
19.4 kPa
19.4 kPa
19.4 kPa
5.4 kPa
348
5.4
CAP (dB/m)
IQR
330
IQR/méd.
10 %
MÉDIANE
350
E (kPa)
MÉDIANE
5.6
IQR
3.9
IQR/méd.
18 %
Note
Note sur un détail éventuel intéressant à garder en mémoire
S1
S2
m
XL
Type d'examen

Fibroscan XL probe

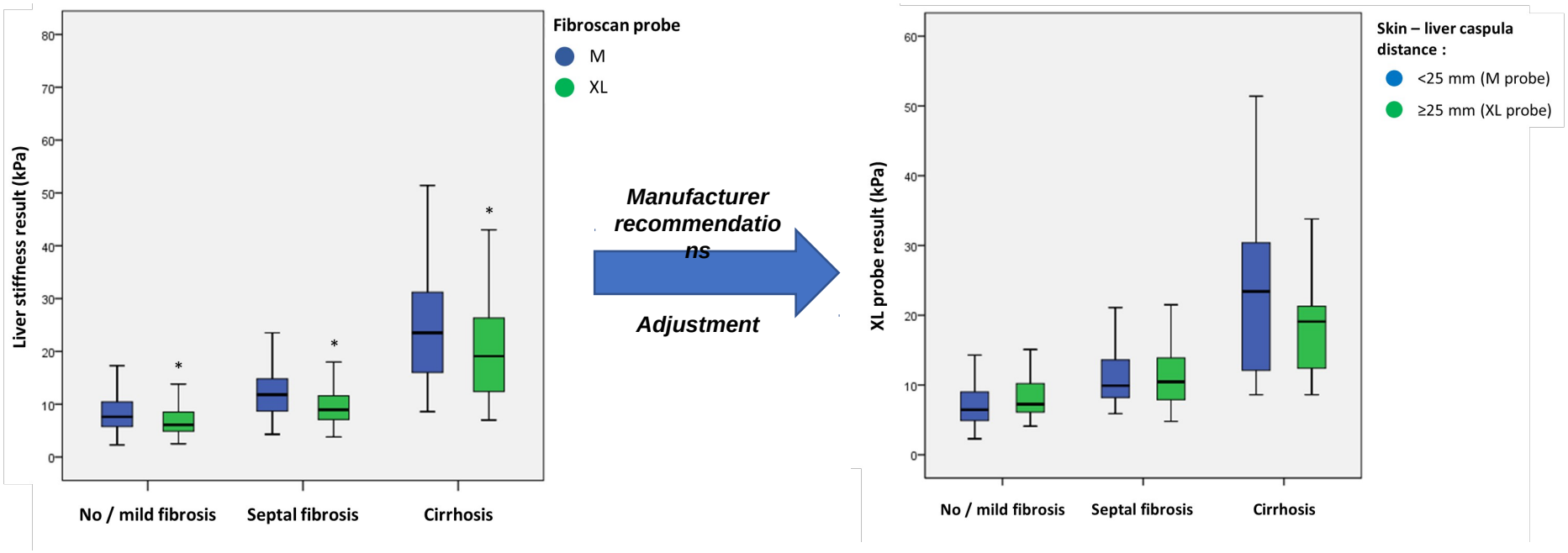




De Ledinghen, J Hepatol 2012

Fibroscan manufacturer recommendations

M probe if skin – liver distance capsula <25mm, XL probe if ≥ 25mm



Boursier, AASLD 2017

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

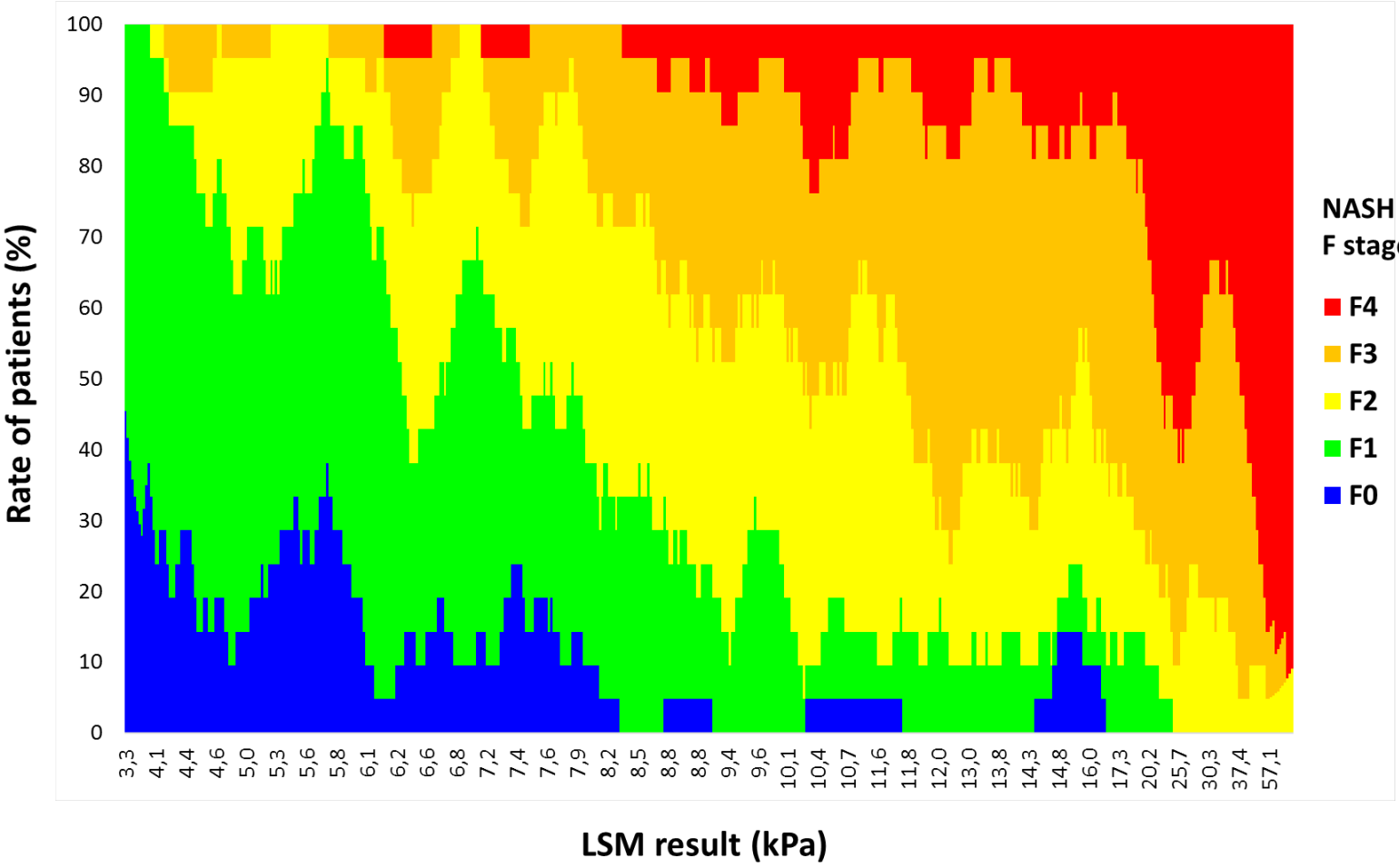
HEPATOLOGY, VOL. 66, NO. 5, 2017

Comparison of Laboratory Tests, Ultrasound, or Magnetic Resonance Elastography to Detect Fibrosis in Patients With Nonalcoholic Fatty Liver Disease: A Meta-Analysis

Guangqin Xiao,[1] Sixian Zhu,[2] Xiao Xiao,[3] Lunan Yan,[4] Jiayin Yang,[4] and Gang Wu[1]

Diagnostic target	Cut-off value	Studies (patients)	Summary Se	Summary Spe	Summary PPV	Summary NPV
Significant fibrosis	4,8 – 8,2	4 (654)	75,8	64,8	65,5	78,8
Advanced fibrosis	5,7 – 9,3	3 (579)	75,3	74,0	58,7	88,7
Cirrhosis	7,2 – 16,0	4 (654)	87,8	82,0	39,8	97,8

Fibrosis stage probability as a function of liver stiffness



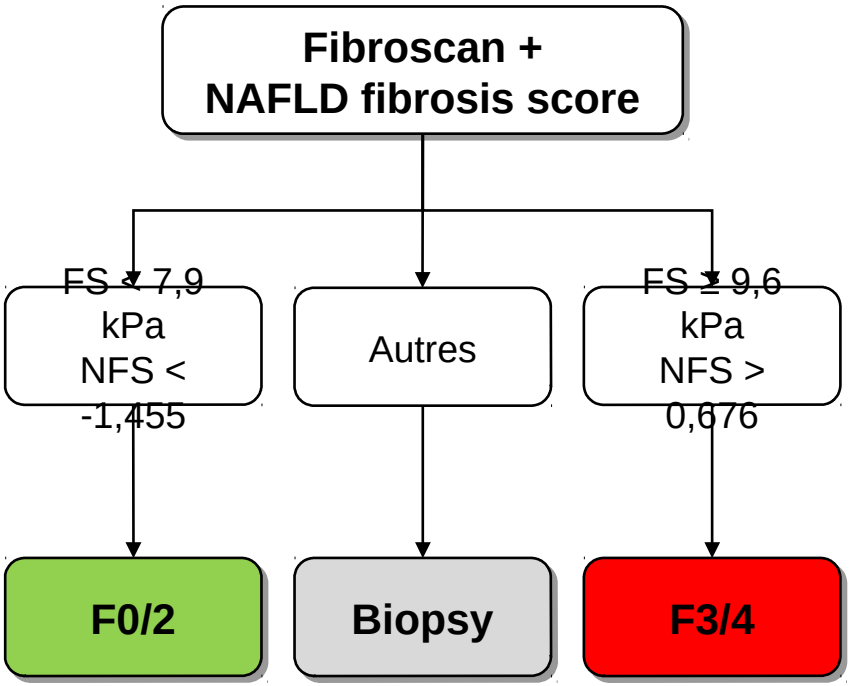
Boursier, J Hepatol 2016

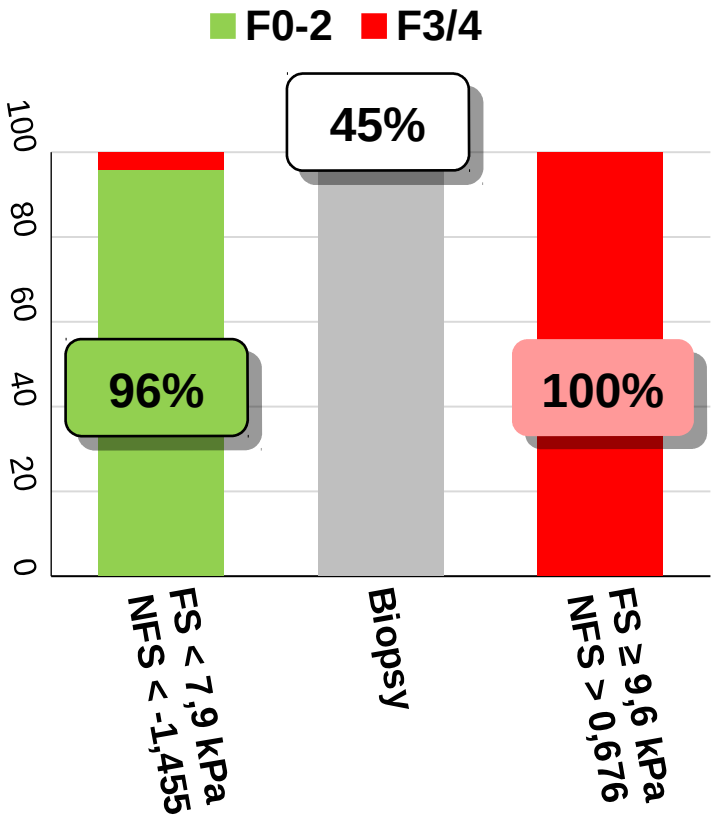
Question #5

Would you use another method for liver fibrosis evaluation ?

1. No
2. Fibrotest / FibroMeter / ELF
3. ARFI / SSI / ElastPQ
4. Elasto-MRE
5. Liver biopsy

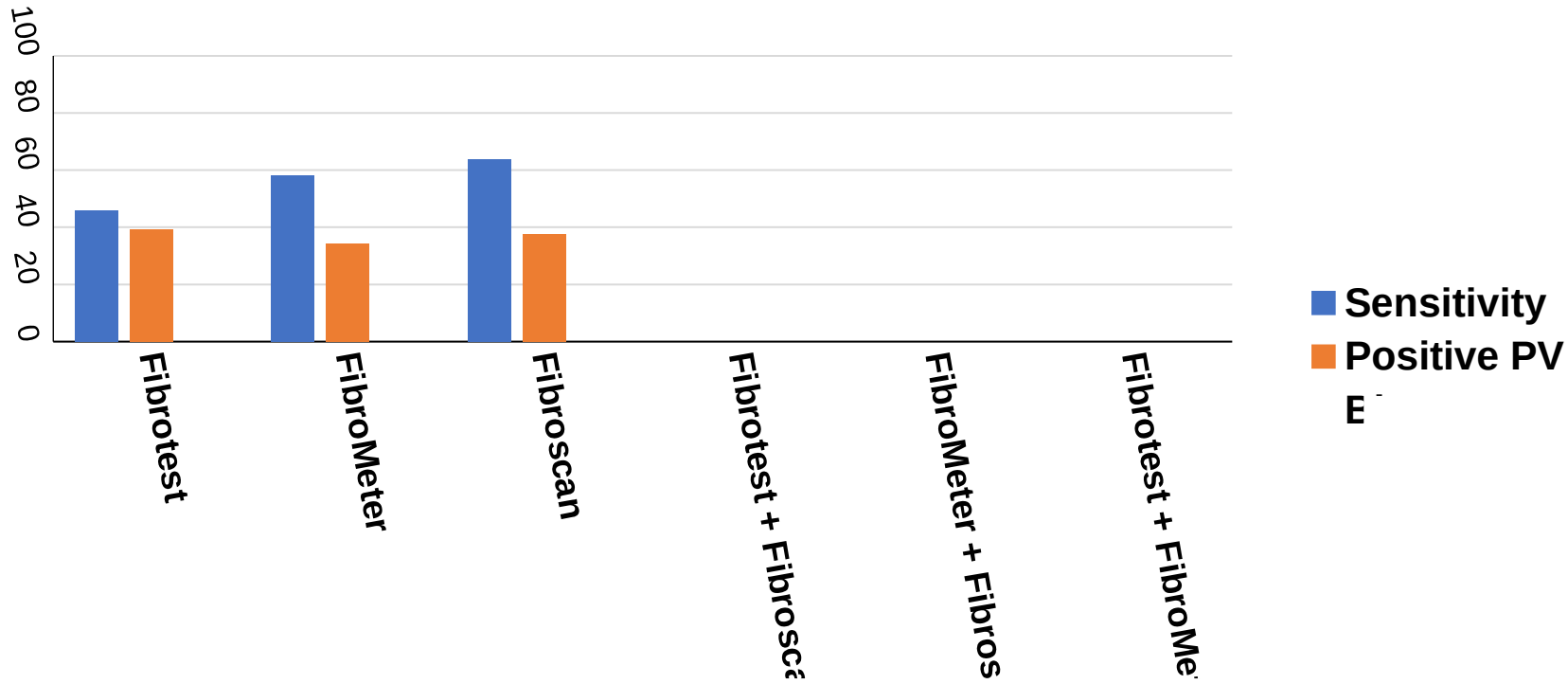
Combination blood tests + Fibroscan





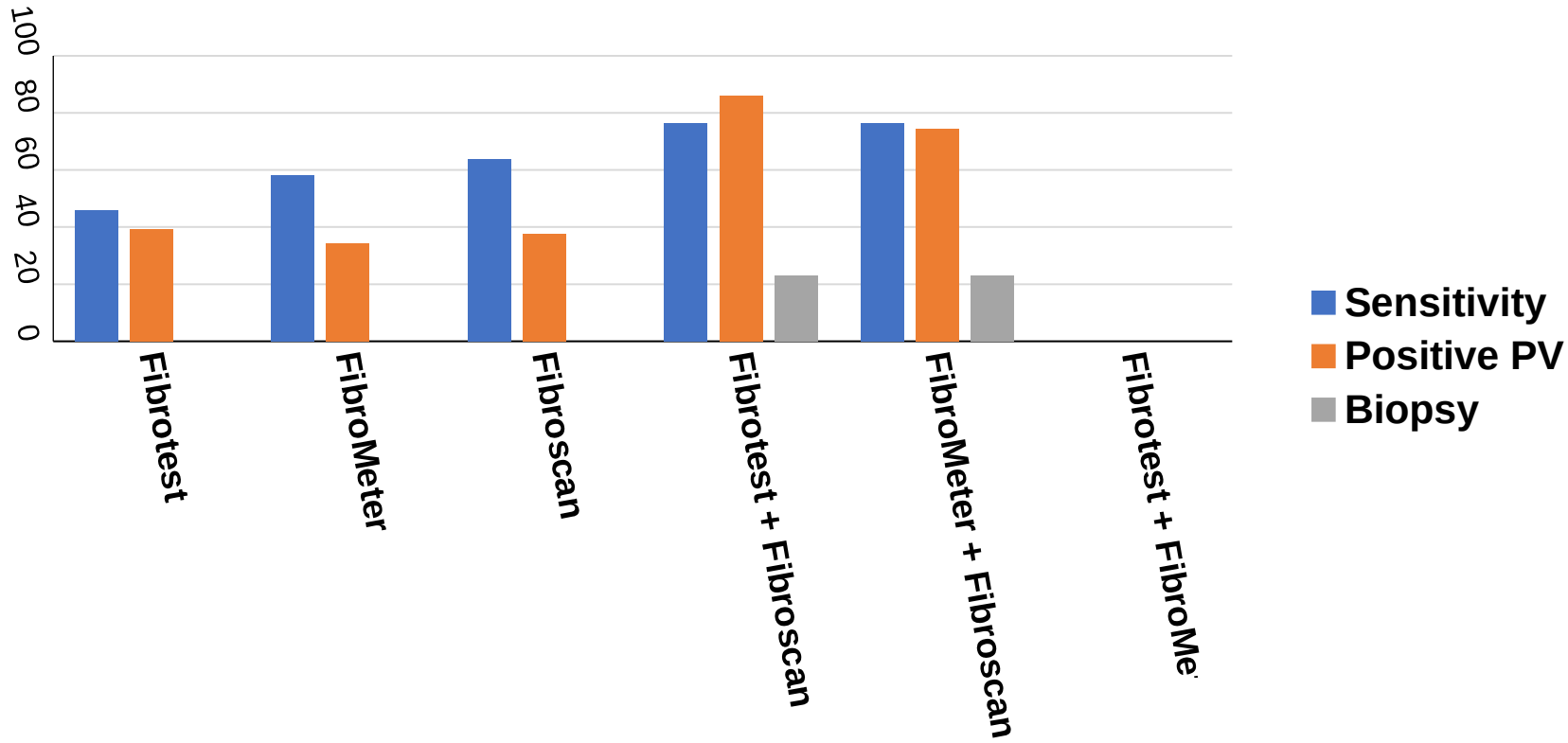
Petta, Liver Int 2015

Combination blood tests + Fibroscan



Boursier, EASL 2017

Combination blood tests + Fibroscan



Boursier, EASL 2017

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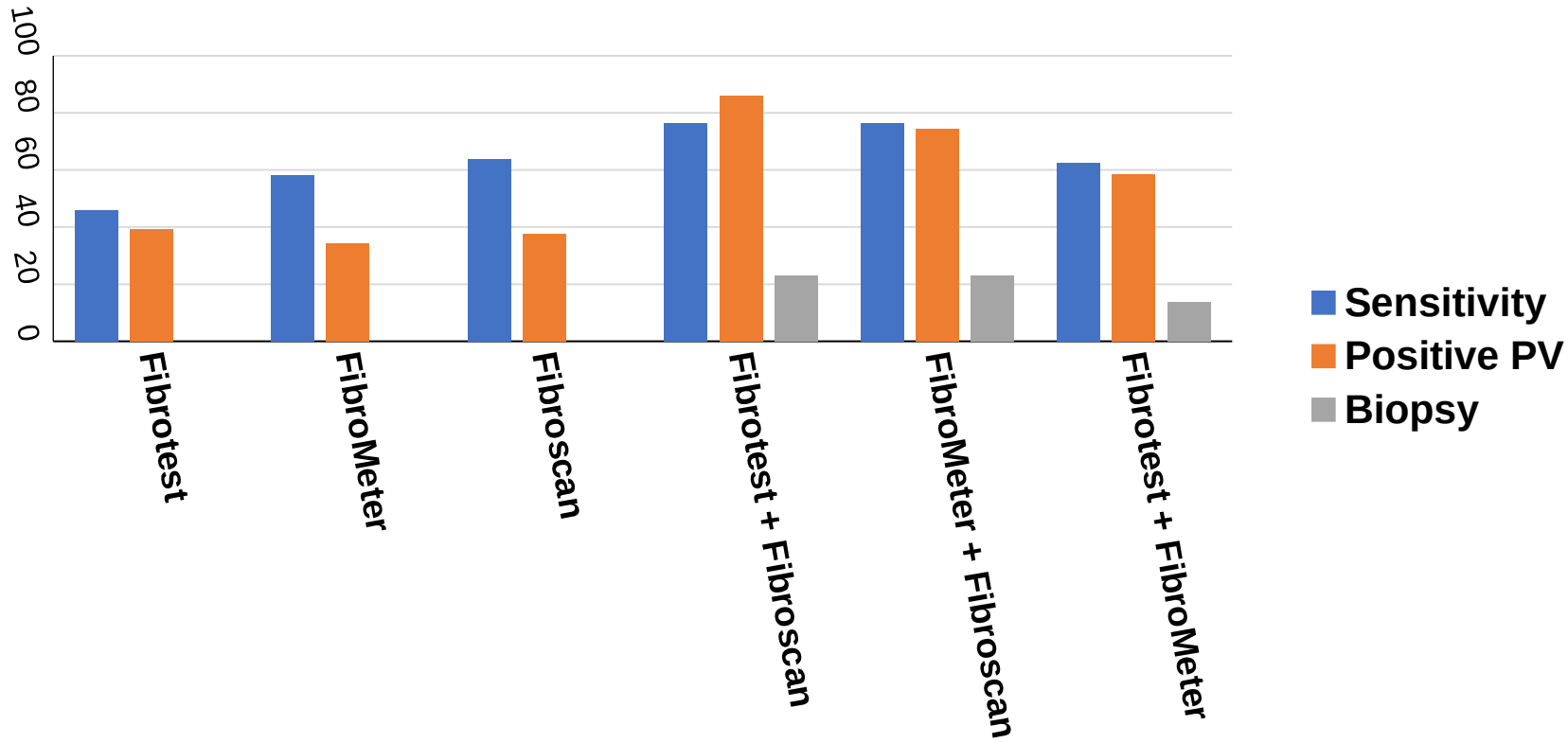

Boursier, EASL 2017

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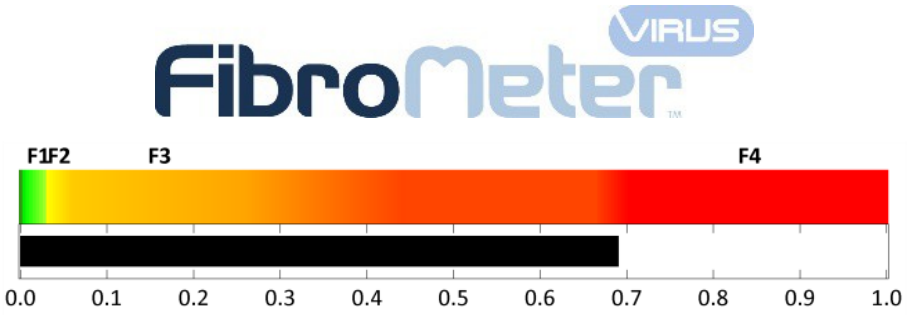

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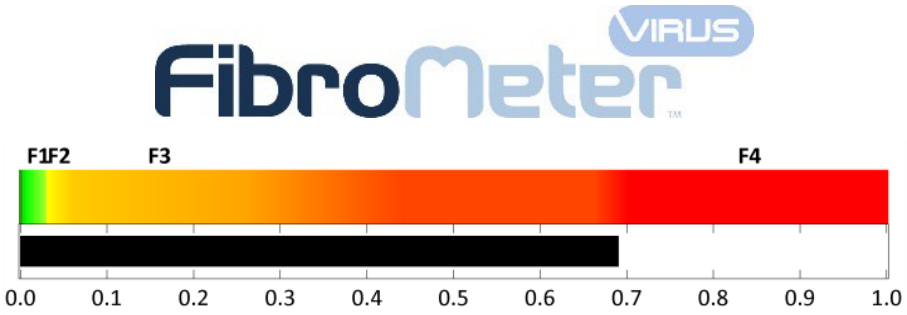
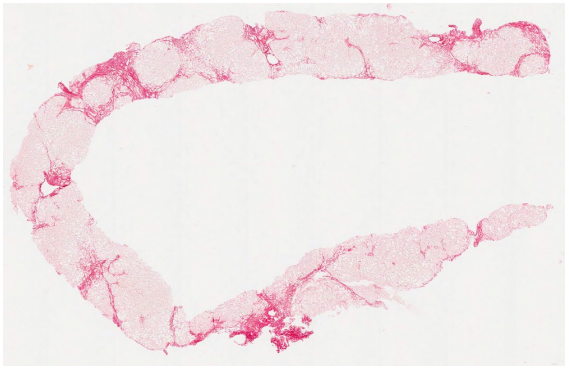


Liver biopsy
(NASH CRN system)

- Steatosis : <10% of hepatocytes
- Lobular inflammation : 1
- Ballooning : 0
- Portal inflammation : 0
- Fibrosis : 4



Question #6

What is your final diagnosis ?

1. NASH cirrhosis
2. Cryptogenic cirrhosis
3. Other

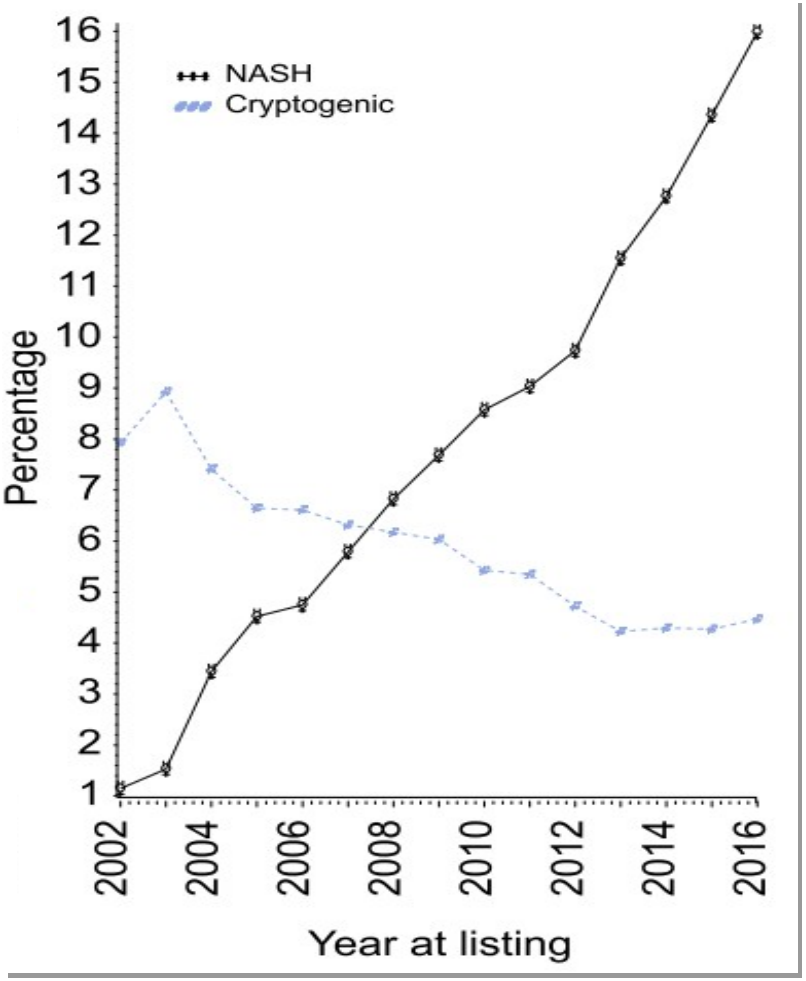
Cirrhosis: cryptogenic or not?

UNOS data base, 2002-2016

- 7 999 cryptogenic cirrhosis
- 11 302 NASH cirrhosis
- 27 714 alcoholic cirrhosis
- 3 447 auto-immune cirrhosis

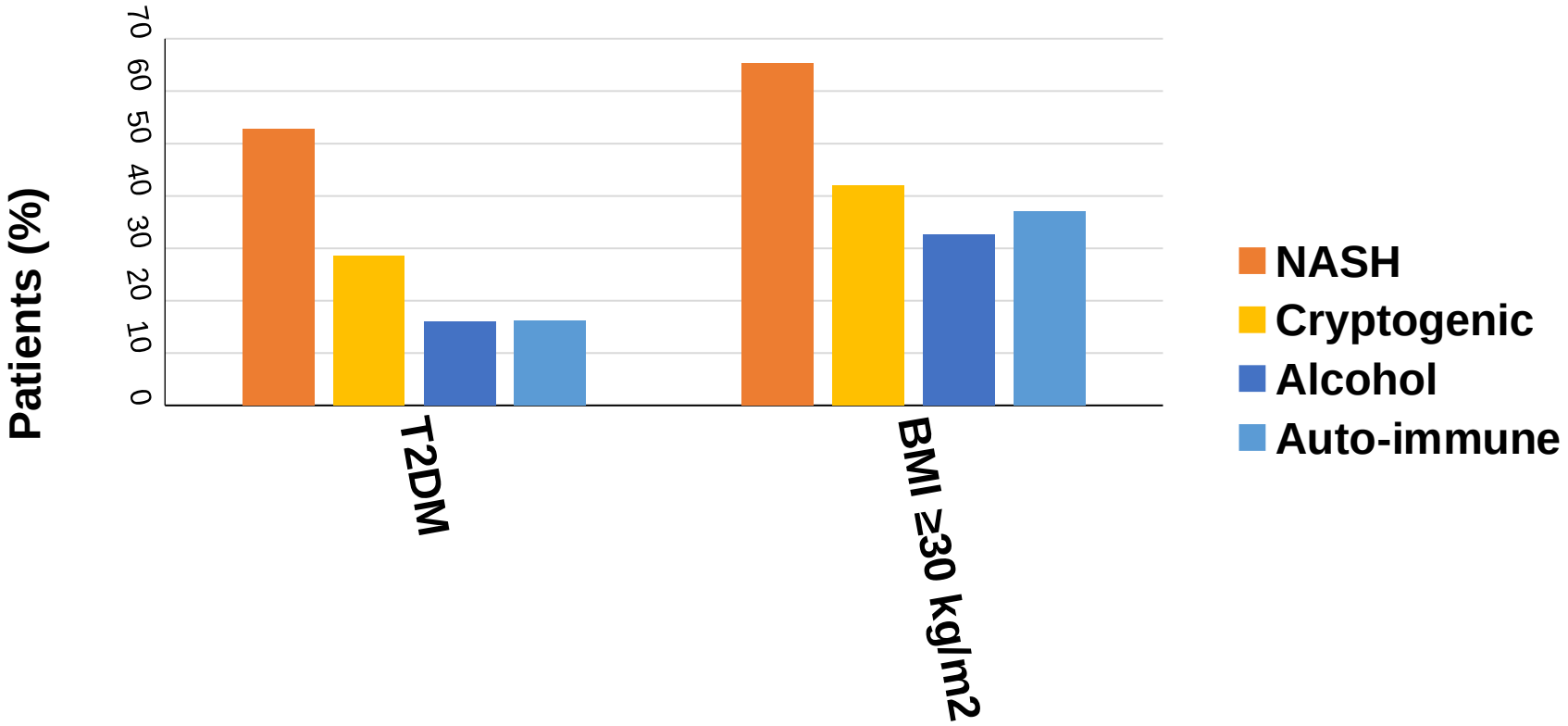
Factors associated with NASH-cirrhosis

- T2DM
- Obesity
- Age >60
- Sex
- Caucasian



Thuluvath, J Hepatol 2017

Cirrhosis: cryptogenic or not?



Thuluvath, J Hepatol 2017

Question #7

Would you perform an oesogastroduodenal endoscopy to screen for large oesophageal varices?

1. No
2. Yes

Position Paper

CrossMark

EASL JOURNAL OF HEPATOLOGY

Expanding consensus in portal hypertension
Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension

Roberto de Franchis*, on behalf of the Baveno VI Faculty†

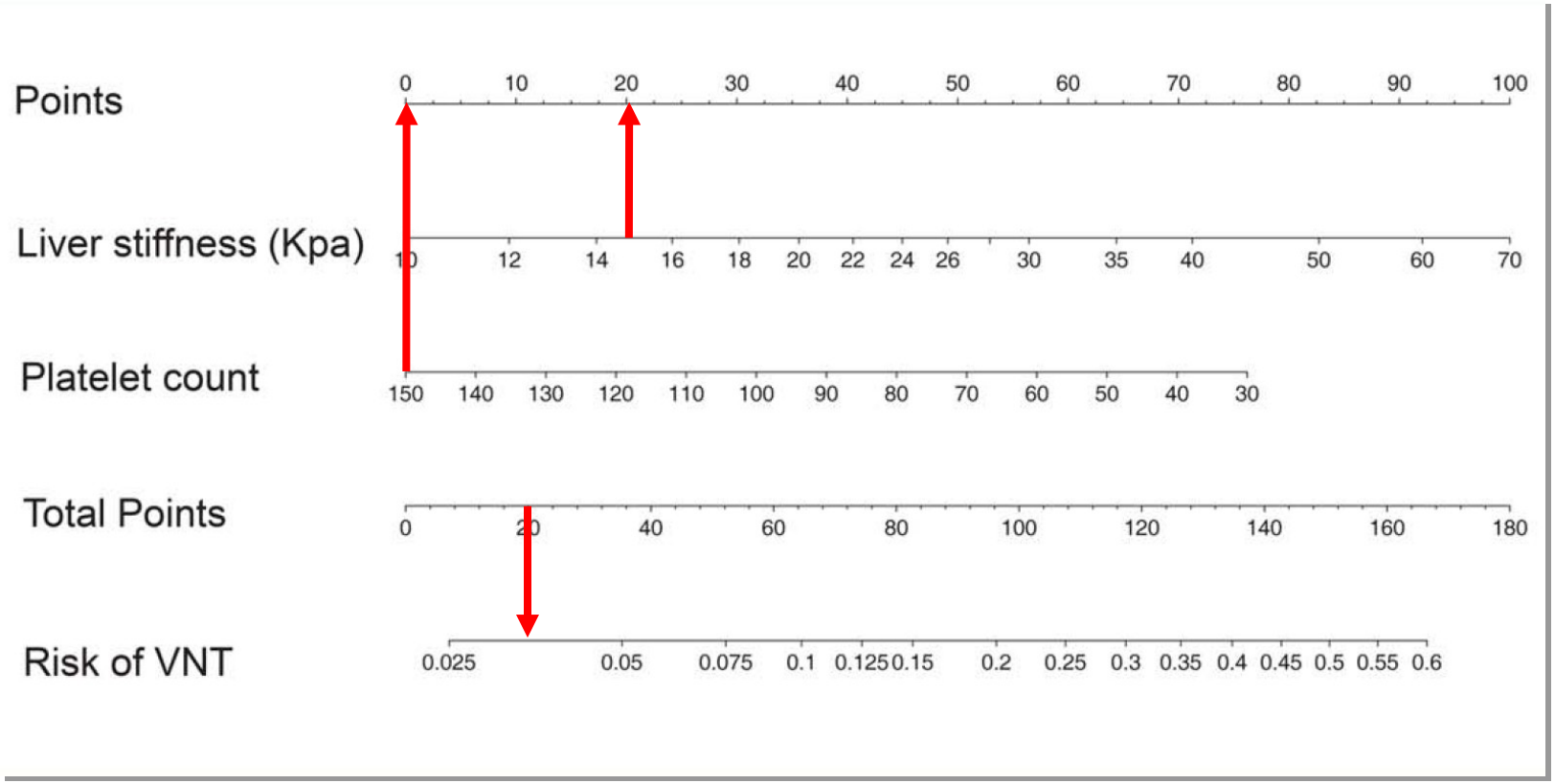
Department of Biomedical and Clinical Sciences, University of Milan, Gastroenterology Unit, Luigi Sacco University Hospital, Milan, Italy

LSM <20 kPa

and

Platelets >150 G/l

« Anticipate » normograms



Albraldes, Hepatology 2016

Expanded Baveno criteria

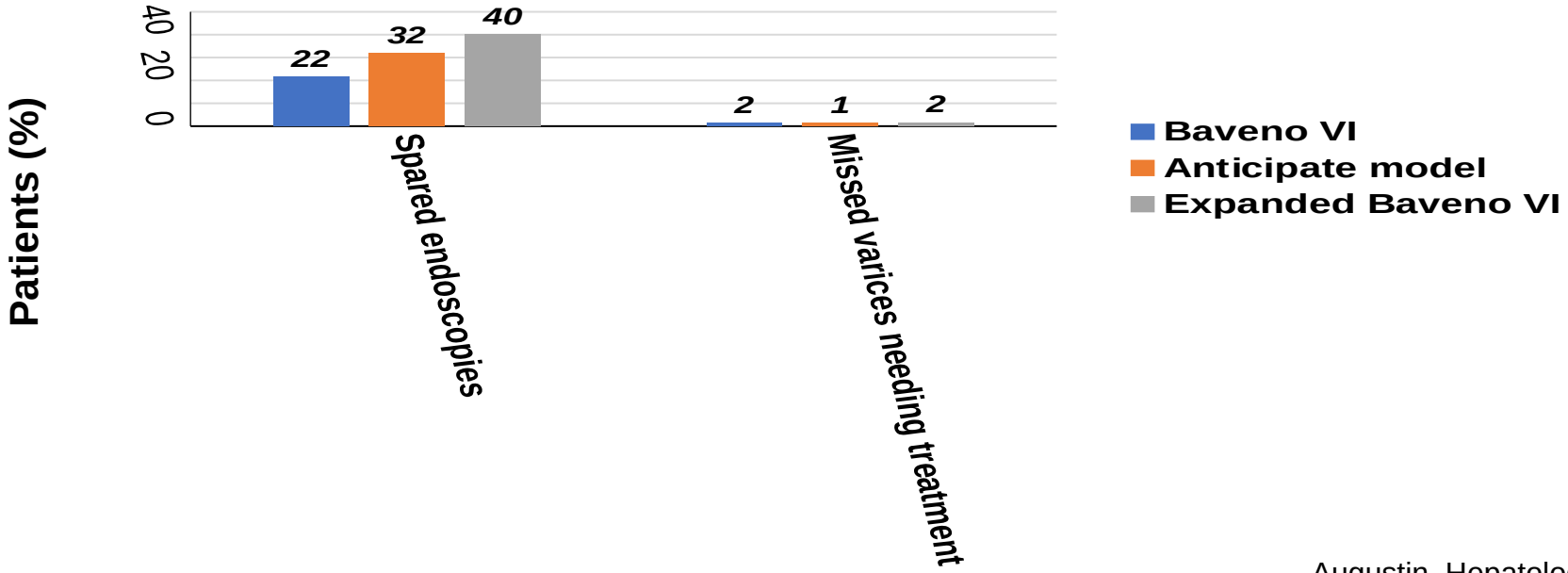
3 cohorts

925 patients

Baveno VI : LSM <20 kPa + platelets >150 G/l

Anticipate Model : LSM + platelets (risk <5%)

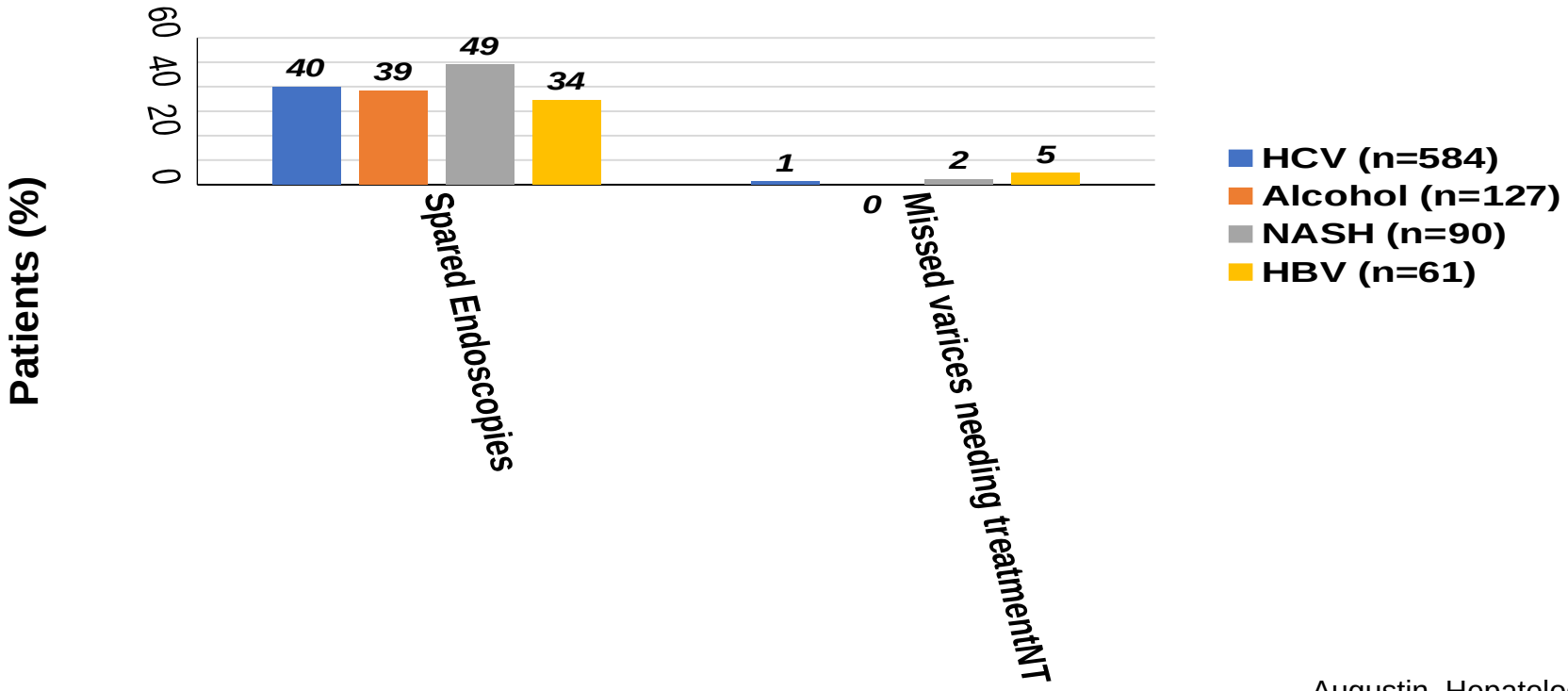
Expanded Baveno VI : LSM <25 kPa + platelets >110 G/l



Augustin, Hepatology 2017

Expanded Baveno criteria

Expanded criteria : LSM <25 kPa and platelets >110 G/L



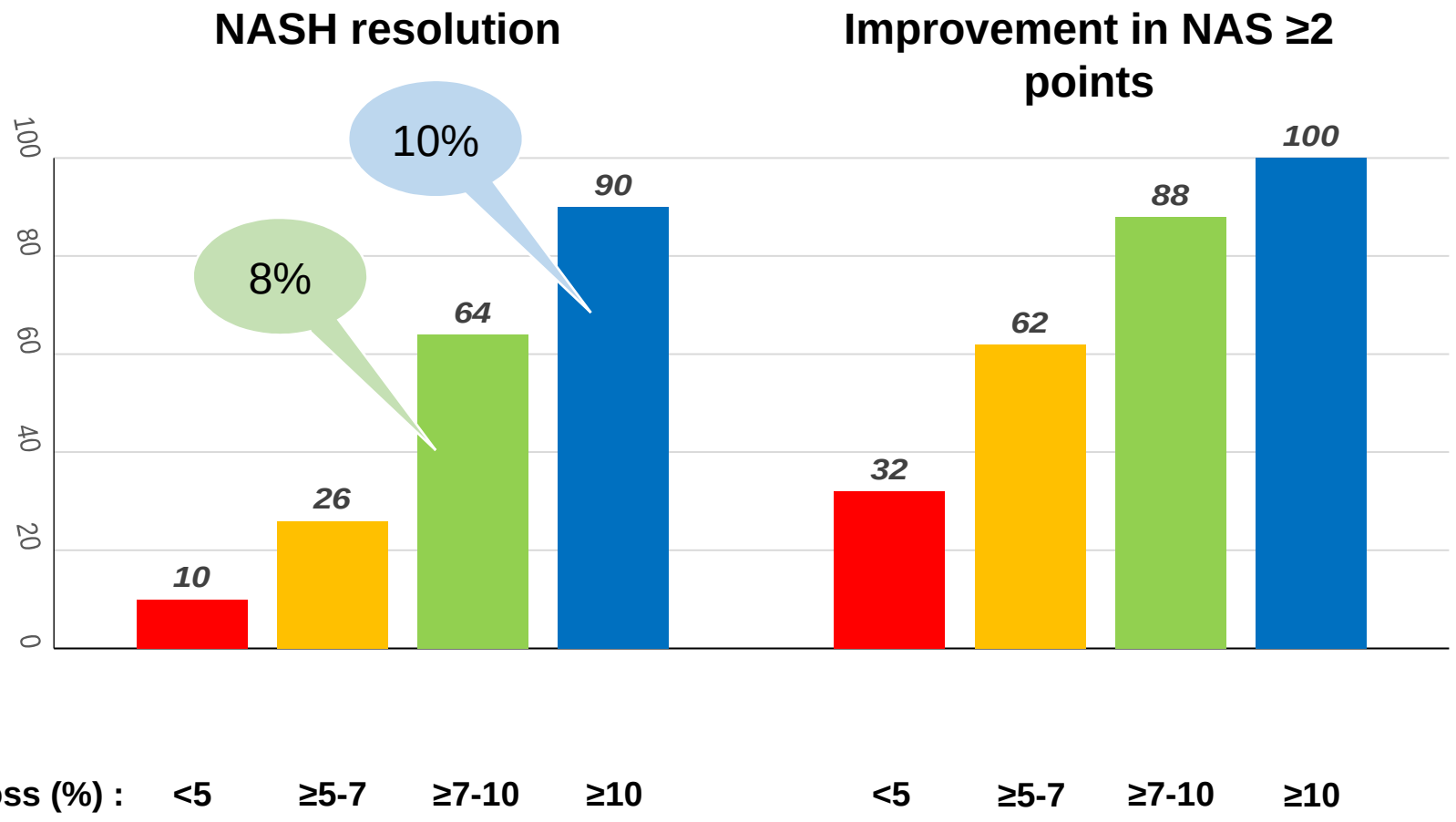
Augustin, Hepatology 2017

Question #8

Which specific treatment for the liver would you consider?

1. Lifestyle modification
2. Pharmacological treatment
3. Liver transplantation
4. Other

Lifestyle modification



Vilar-Gomes, Gastroenterology 2015

NAFLD : treatment options

Lifestyle modification

« non specific » pharmacological treatment

- ***Antioxidant (vit E)***
- ***Hepato-protective (UDCA)***
- ***Anti-inflammatory (pentoxyfylline)***
- ***Probiotics***
- ***Others (ARA2, PUFA…)***
- ***Antidiabetics : Glitazones, GLP1 agonist***

« specific » pharmacological treatment

- **FXR Agonist**
- **PPAR α/δ Agonist**
- **Cenicriviroc**
- **ASK-1 inhibitors**
- **Others…**

Endoscopic treatement

- **Endoscopic bypass**
- **Intragastric balloon**
- **Endoscopic sleeve**
- **Others…**

Results of studies in NASH cirrhotic patients

- **Guidelines EASL 2016 :** “Drug therapy should be indicated for progressive NASH (bridging fibrosis and cirrhosis)”

Cirrhotic patients in lifestyle and pharmacological studies :

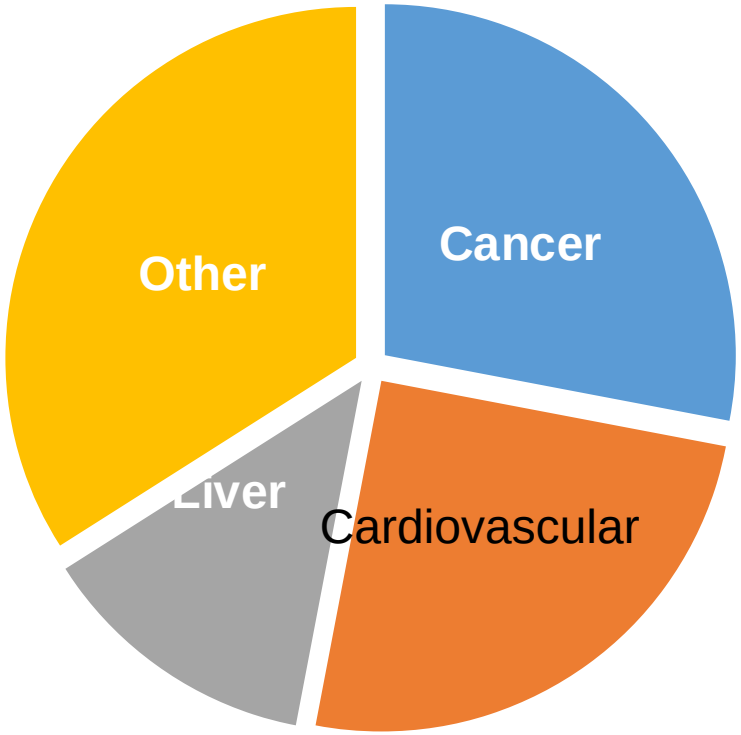
- Either excluded
- Or very few patients included

⇒ ***No strong data about the balance between <u>efficacy</u> and <u>safety</u> in this particular subgroup of patients***

- **Guidelines AASLD 2017 :** “Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in (…) NASH cirrhosis or cryptogenic cirrhosis. ”

Other medications

Causes of death in NAFLD



Metformin :

- ↓ Overall mortality
- ↓ Need for liver transplantation
- ↓ Hepatocellular carcinoma
- ↓ glutaminase activity and hepatic encephalopathy

Statins :

- ↓ Hepatocellular carcinoma
- ↓ Portal hypertension
- ↓Infection

NAFLD : treatment options

Lifestyle modification

« non specific » pharmacological treatment

- *Antioxidant (vit E)*
- *Hepato-protective (UDCA)*
- *Anti-inflammatory (pentoxyfylline)*
- *Probiotics*
- *Others (ARA2, PUFA…)*
- *Antidiabetics : Glitazones, GLP1 agonist*

« specific » pharmacological treatment

- FXR Agonist
- PPAR α/δ Agonist
- Cenicriviroc
- ASK-1 inhibitors
- Others…

Endoscopic treatement

- Endoscopic bypass
- Intragastric balloon
- Endoscopic sleeve
- Others…

Bariatric surgery

Question #9

One year later, the patient has lost 4 kg (4%, BMI: 36 kg/m2)

There is no sign of liver decompensation

The liver function is stable, as the Fibrocan result (XL: 15,0 kPa)

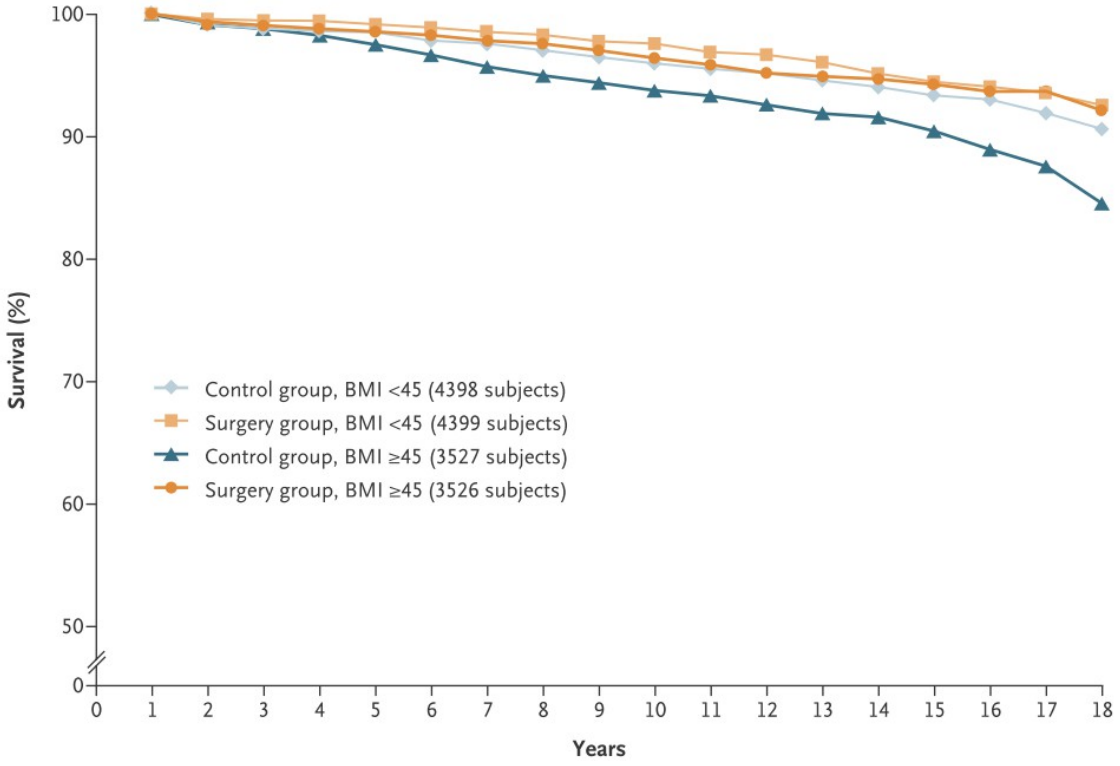
Would you consider bariatric surgery ?

1. No
2. Yes

Would you consider bariatric surgery ?

- Pro
  - Improves overall survival when indicated
  - Potential for cirrhosis regression

Long-term mortality after gastric bypass surgery



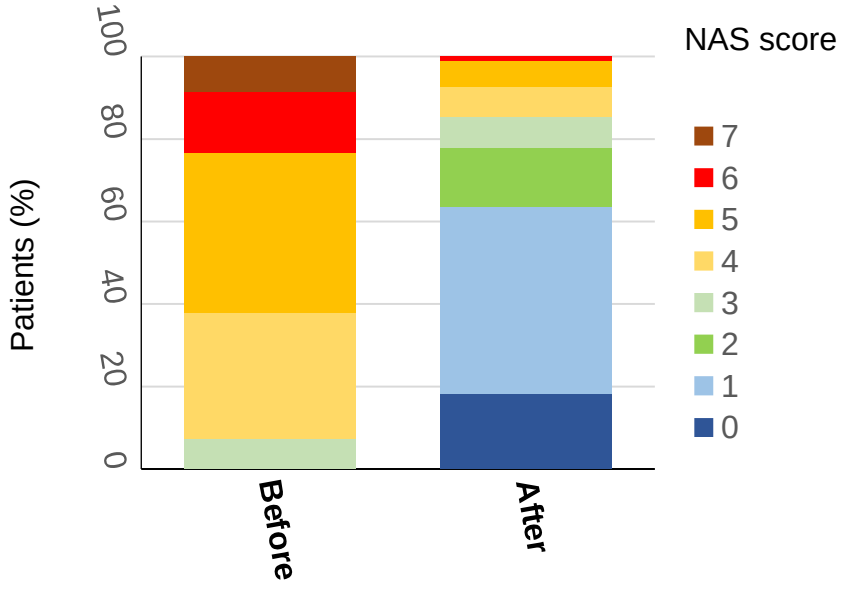
No. of Deaths																		
Control group	41	66	85	117	153	176	199	219	234	244	259	271	281	294	302	310	318	327
Surgery group	42	54	62	74	86	102	113	132	141	159	169	182	192	202	206	210	213	213

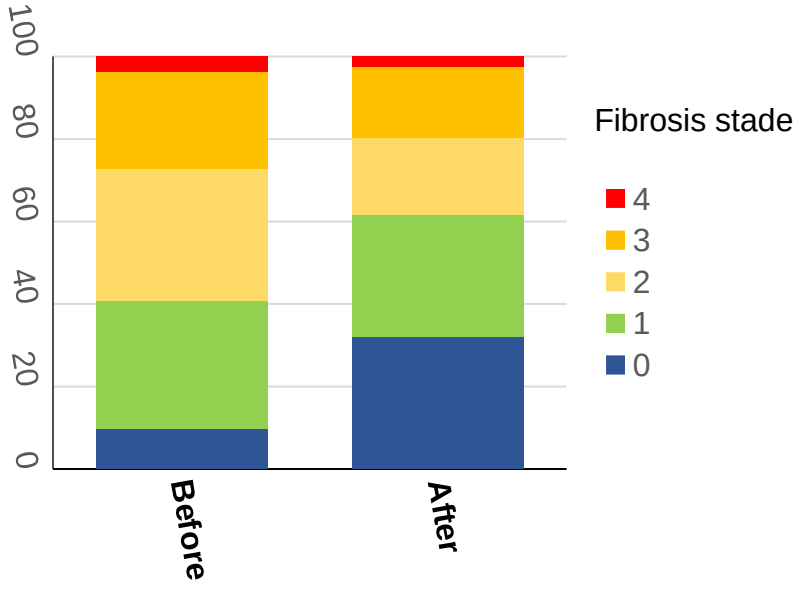
Adams, New Engl J Med 2007

Bariatric surgery

- 82 NASH patients who underwent bariatric surgery
- Paired liver biopsy (during surgery and one year after)

  At one year: 85% NASH resolution, 47% fibrosis improvement





Lassailly, Gastroenterology 2015

HAUTE AUTORITÉ DE SANTÉ

SYNTHÈSE DES RECOMMANDATIONS DE BONNE PRATIQUE

Obésité : prise en charge chirurgicale chez l'adulte

Indication for bariatric surgery in adults :

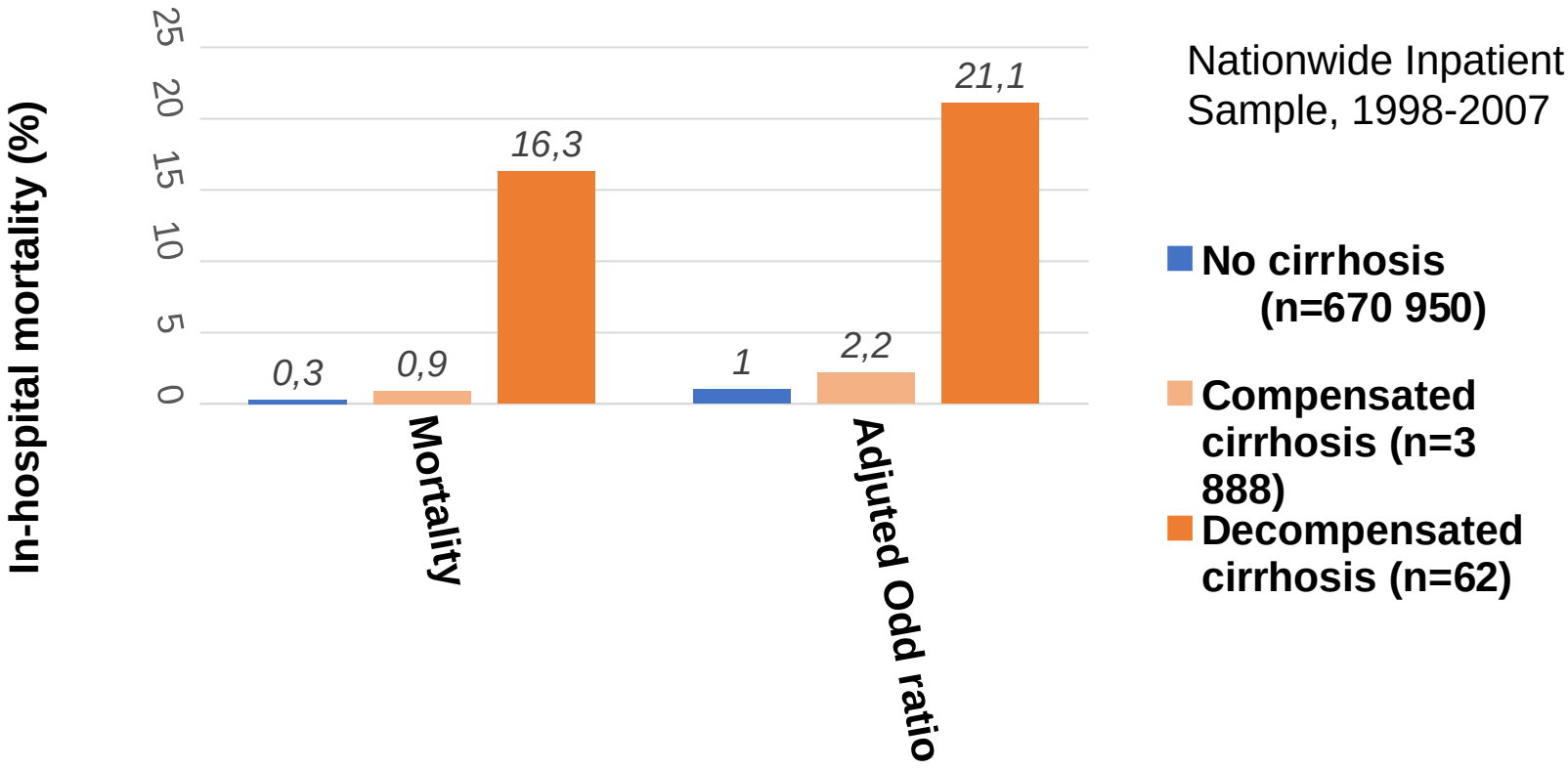
- BMI ≥40 kg/m2
- BMI ≥35 kg/m2 with at least one of the following comorbidities (that can be improved by the intervention)
  - Arterial hypertension
  - OSAS
  - T2DM
  - NASH
  - Osteo-articular disorders

#9. Would you consider bariatric surgery ?

- **Pro**
  - Improves overall survival when indicated
  - Potential for cirrhosis regression

- **Cons**
  - Arterial hypertension and T2DM are well controlled
  - No active liver disease (alcohol stopped, no NASH on liver biopsy)
  - No level 1 evidence for bariatric surgery in cirrhosis
  - Safety ?

Bariatric surgery in cirrhosis

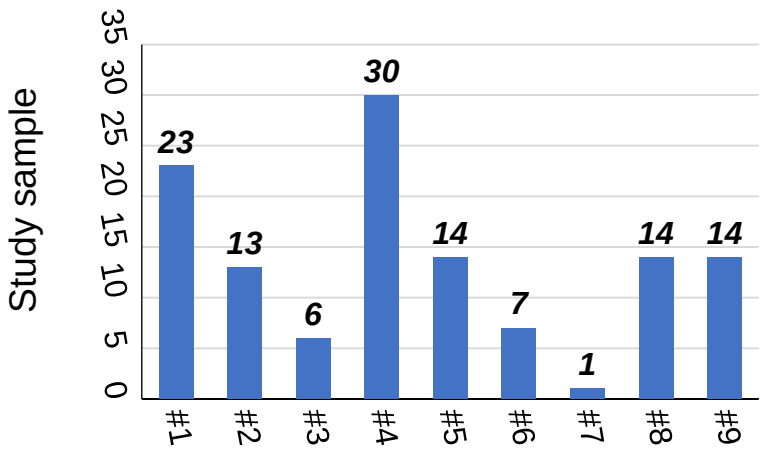


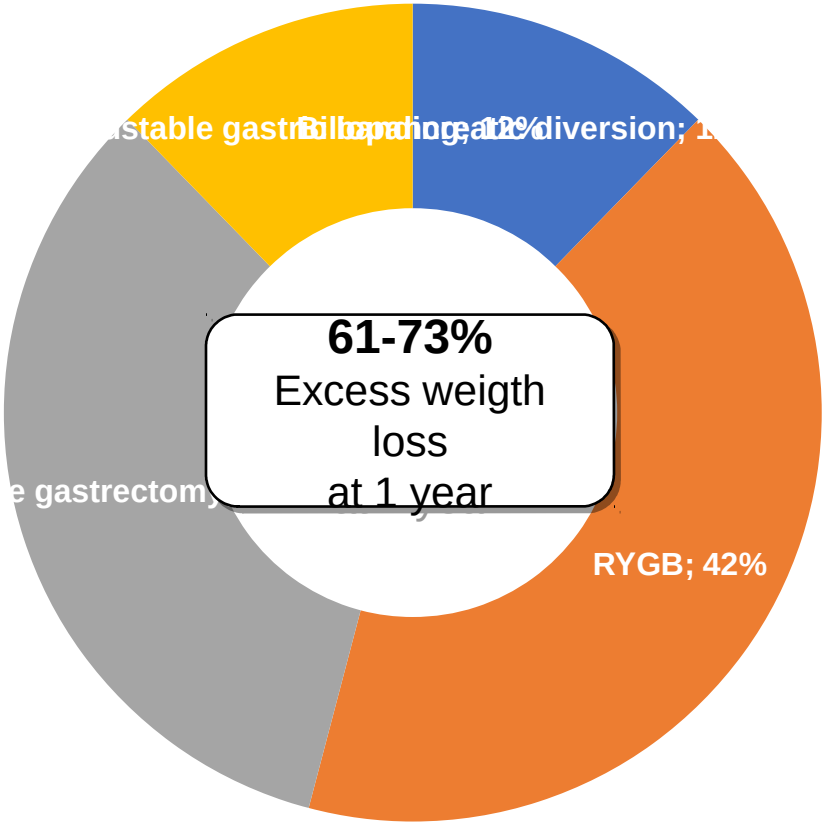
Mosk, Clin Gastroenterol Hepatol 2011

Bariatric surgery in cirrhosis

<u>Systematic review</u> : 9 articles / 122 patients

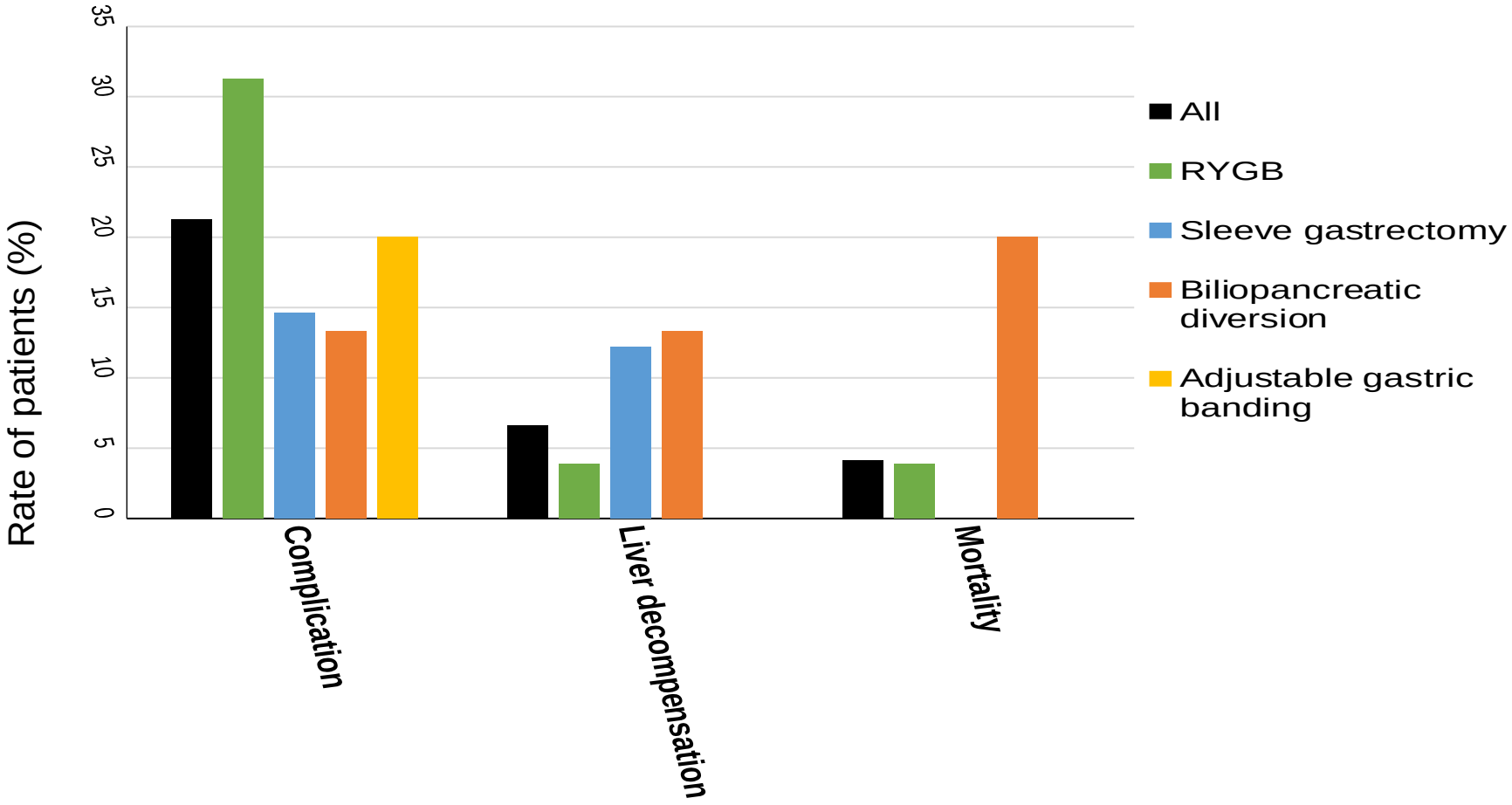
- All well compensated cirrhosis
- Portal hypertension : 7/122
- Female: 61%
- Mean age: 49,6 years
- Mean BMI: 50,4 kg/m2





Jan, Obes Surg 2015

Bariatric surgery in cirrhosis



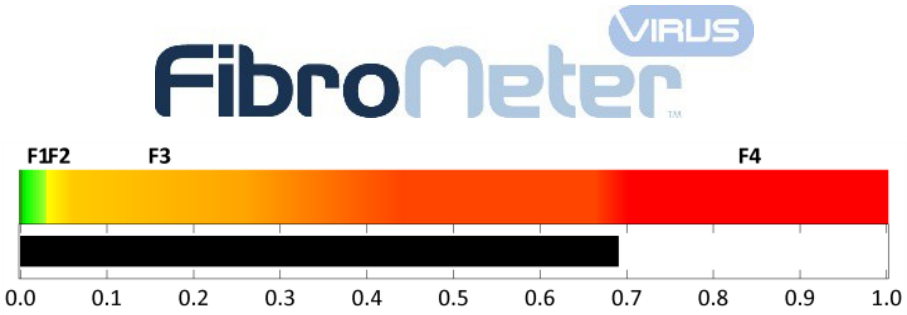
Jan, Obes Surg 2015

Clinical case

Man 63 years old, referred by his diabetologist for high NAFLD fibrosis score (1,37)

M probe
- 10/18 valid measures
- 16,2 kPa (IQR: 8,0)
- CAP: 289 dB/m (IQR 35)

Indication of XL probe
- 10/10 valid measures
- 14,5 kPa (IQR: 3,1)
- CAP: 275 dB/m (IQR 38)



Liver biopsy
(NASH CRN system)

- Steatosis : <10% of hepatocytes
- Lobular inflammation : 1
- Ballooning : 0
- Portal inflammation : 0
- Fibrosis : 4