Epidemiology, Diagnosis, and Risk Stratification of NAFLD

NCSCG Post-AASLD Review
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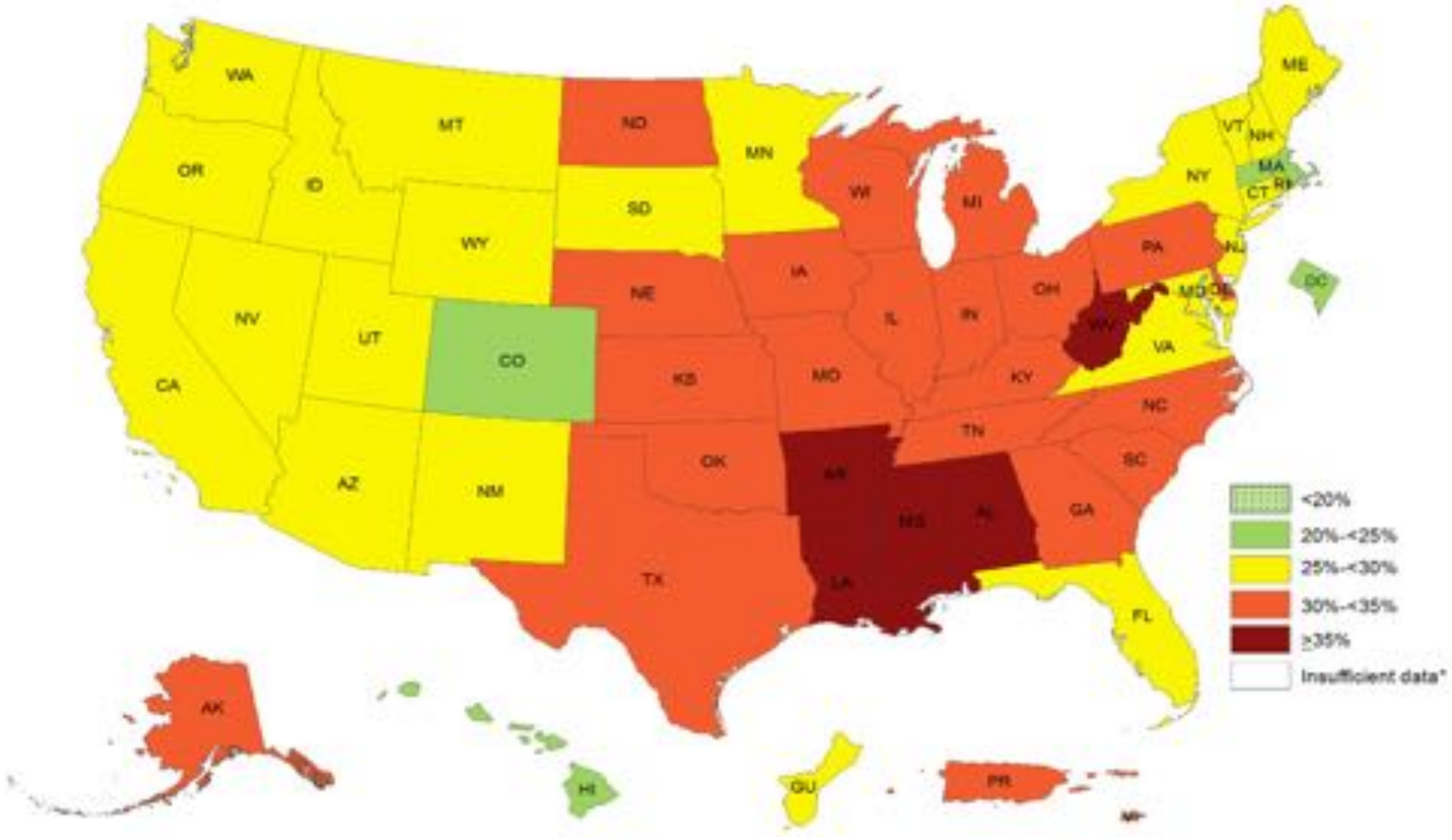
Danielle Brandman, MD, MAS
Associate Professor of Clinical Medicine
UCSF, Division of Gastroenterology/Hepatology
Associate Program Director
UCSF, Transplant Hepatology Fellowship

Prevalence of Obesity, US 2016

¶ Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



***Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.**

Epidemiology of NAFLD

- Prevalence of NAFLD: 16-29% US population
  - 2/3 of obese adults
  - 84-96% bariatric surgery population
  - Up to 76% of diabetics
- Prevalence of NASH: 2-7% population
  - 10-30% of NAFLD
  - 20% of obese adults

Farrell, *Hepatology*, 2006.

Younoussi, *Hepatology*, 2015.

Case

- 55yo Asian man is referred to hepatology for evaluation of an echogenic liver seen on abdominal ultrasound, done to evaluate RUQ pain

Case

- 55yo Asian man is referred to hepatology for evaluation of an echogenic liver seen on abdominal ultrasound, done to evaluate RUQ pain
- The pain has since resolved, but he wonders how worried he should be about fatty liver

Case (cont'd)

- His weight has fluctuated within the past few years, during which time his BMI has ranged from 29-30
- PMH: prediabetes (HbA1c 5.9), dyslipidemia (HDL 36, TGs 180), HTN
- Meds: atorvastatin, lisinopril
- Family history: Parents with diabetes

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- Meds: atorvastatin, lisinopril
- Family history: Parents with diabetes
- Labs: AST 38, ALT 71, albumin 4.1, INR 1.0, platelets 200

What further work-up is needed?

NAFLD: A clinically silent disease

- Symptoms:
  - None: 20 - 77%
  - Right upper quadrant pain: 25 - 48%
  - Fatigue: 50 - 75% (Obstructive sleep apnea in 40%)
- Signs:
  - Overweight/Obese: 85 - 95%
  - Acanthosis nigricans: 10 -15%
  - Hepatomegaly: 25 - 50%
- Laboratory:
  - ALT, AST - modest elevation
  - "Normal enzymes"
    - Normal ALT <19 for women, <30 for men

NAFLD Diagnostic Criteria

- Diagnostic criteria
  - Hepatic steatosis on imaging or liver biopsy
  - Ethanol intake <20-30g daily
  - Absence of other causes of liver disease
  - No medications known to cause hepatic steatosis

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NAFLD is a diagnosis of exclusion

Evaluation of Suspected NAFLD

- Liver tests
- Abdominal ultrasound
- Other serologic evaluation:
  - HBsAg, sAb, cAb
  - HCV Ab
  - [AMA, IgM (for PBC)]
  - ASMA, ANA, IgG
  - A1AT phenotype
  - Iron, Tsat, ferritin
  - Ceruloplasmin age < 45
  - HAV Ab (for vaccination status)

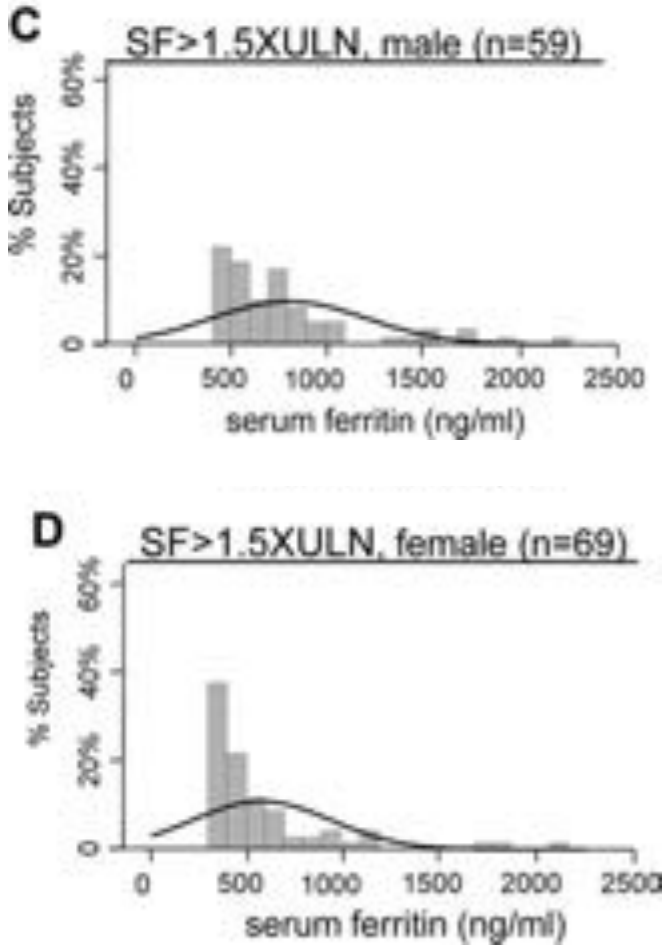
Autoantibodies and NAFLD

- Present in about 1/3 of patients with NAFLD
- ANA: 15-20%
- Smooth muscle Ab: 3-12%
- Mitochondrial Ab: ≤1%
- Rarely patients with NAFLD have concomitant autoimmune hepatitis
  - Autoantibody titers tend to be low (≤80) in NAFLD

Brunt, *Hepatology*, 2009.
Adams, *AJG*, 2004.
Ravi, *Dig Dis Sci*, 2015.
Vuppalanchi, *Hepatol Int*, 2012.

Ferritin and NAFLD

- 20% of patients with NAFLD had ferritin >1.5 times upper limit of normal (>300 women, >450 men)
- Ferritin level does not appear to have a significant impact on NAFLD histology
- Phlebotomy does not improve NAFLD



Kowdley, *Hepatology*, 2012.
Adams, *Hepatology*, 2015.

Does our patient need a liver biopsy?

NAFLD: Non-Alcoholic Fatty Liver Disease

Spectrum of disease

NAFLD

NAFL
Steatosis

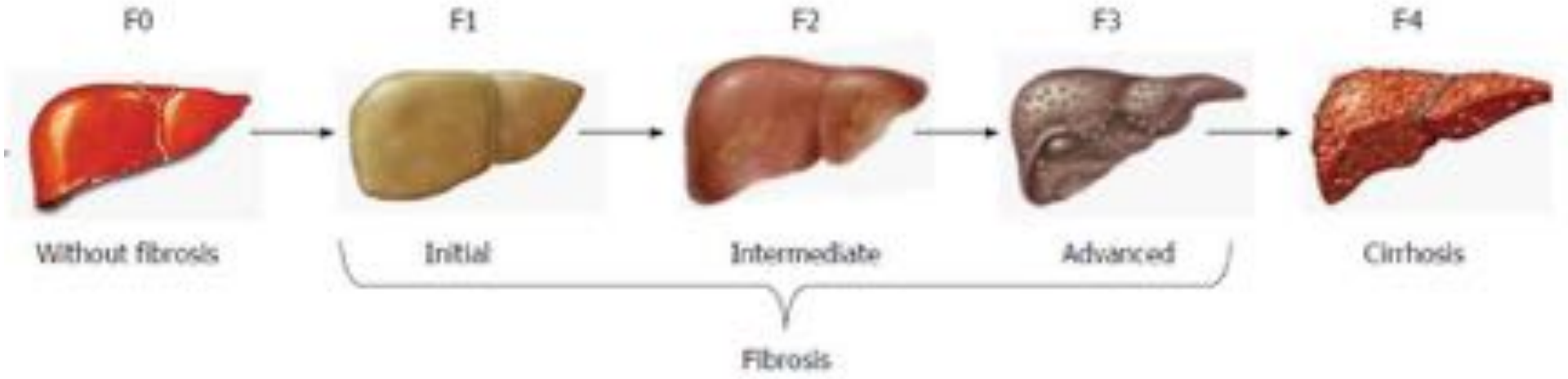
NASH
Steatosis + inflammation

NASH
+
fibrosis

Cirrhosis

HCC

NAFLD: Non-Alcoholic Fatty Liver Disease
Spectrum of disease



NASH →

7 years per 1 stage
~28 years 0→ cirrhosis

NAFL →

14 years per 1 stage
~56 years 0→ cirrhosis

Steatosis detection - Imaging

- Ultrasound
  - 60–94% sensitivity and 84–95% specificity
- Fibroscan Controlled Attenuation Parameter (CAP)
  - AUROC 0.90-0.95 depending on steatosis grade
  - Not well validated
- CT scan
  - Specific but not sensitive for mild/moderate steatosis
- MRI and MR spectroscopy
  - Can detect small quantity of fat
  - Time consuming, expensive

Ultrasound Med. Biol. 36, 1825–1835 (2010)
Liver Int. 32, 902–910 (2012)
Radiology 250, 95–102 (2009)

Diagnosis and staging of NAFL vs NASH

- Liver biopsy is the only method to reliably distinguish between NAFL and NASH

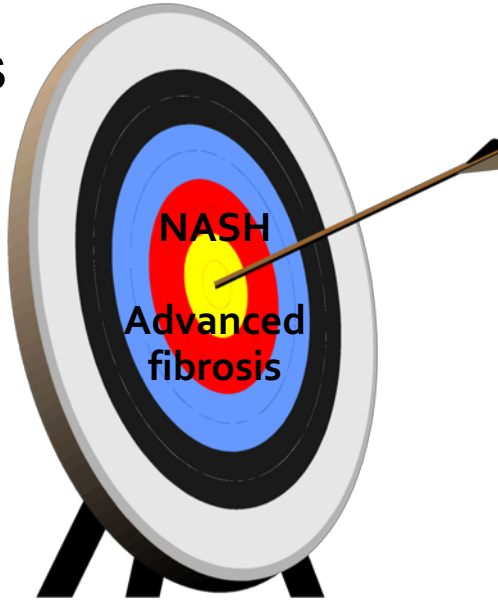
Diagnosis and staging of NAFL vs NASH

- Liver biopsy is the only method to reliably distinguish between NAFL and NASH
- CK18 shows promise as a biomarker that may be elevated in NASH and not NAFL
  - Marker of hepatocyte apoptosis
- Noninvasive assessment of fibrosis
  - Fibroscan
  - Clinical prediction rules (e.g., NAFLD fibrosis score)

Indications for Liver Biopsy

Indications for Liver Biopsy

- Suspicious for NASH
  - Significant liver enzyme elevation
  - Hepatomegaly
  - Diabetes
- Suspicious for advanced fibrosis or cirrhosis
  - Thrombocytopenia
  - Imaging (e.g., splenomegaly)
  - Noninvasive assessment: NAFLD fibrosis score, Fibroscan
  - Diabetes
  - Older age



Chalassani, *Hepatology* 2017.
Chalassani, *Hepatology* 2012.

Liver Biopsy in NAFLD

Tarnished gold standard

Pros

- Most reliable means for excluding alternative etiology/co-existing liver disease
- "Gold standard" for establishing:
  - Grade of disease (NAFL vs. NASH)
  - Stage of fibrosis

Cons

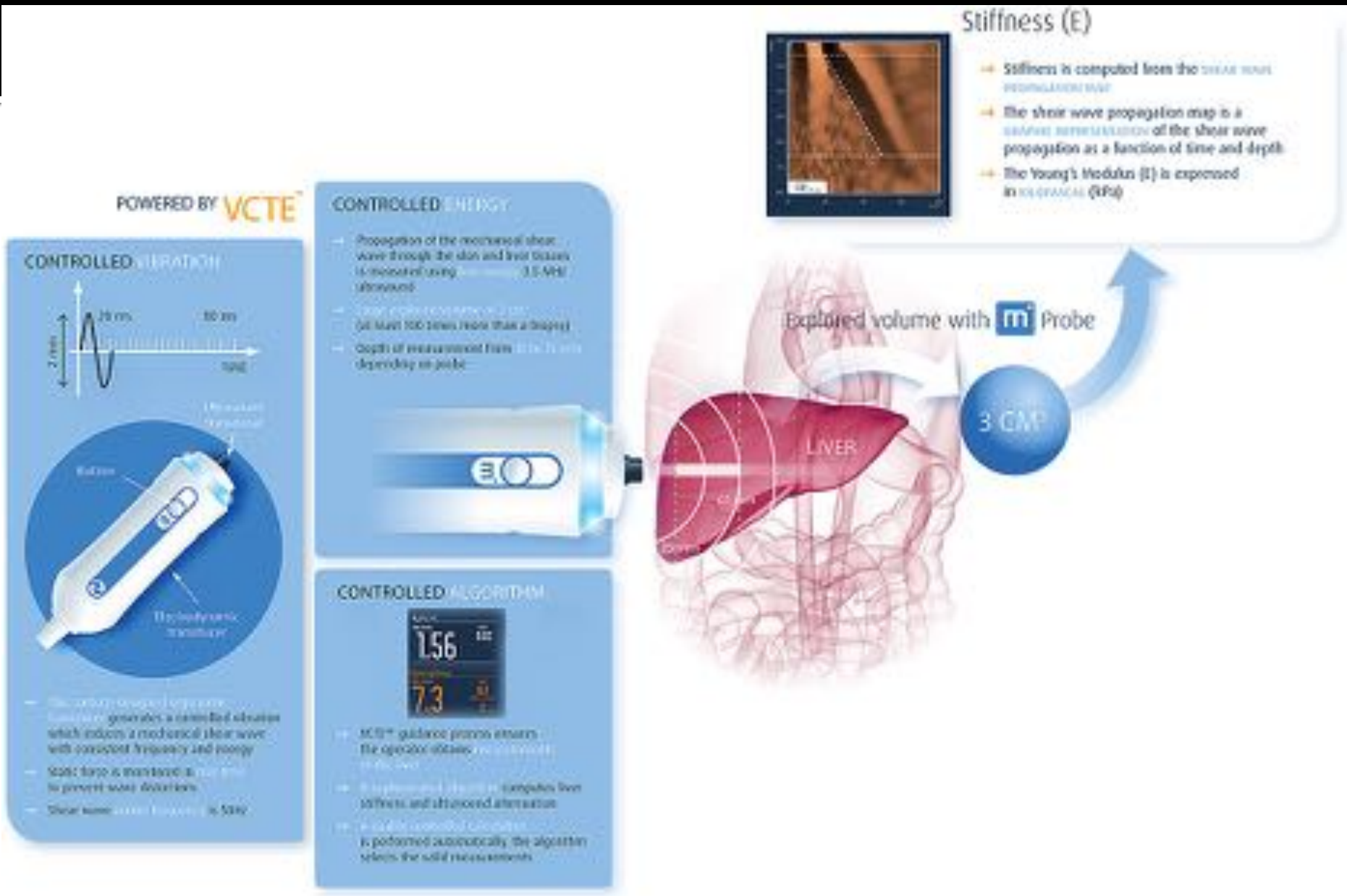
- Sampling error
- Morbidity (pain, bleeding, rarely death)
- Expense
- Impossible to apply to large NAFLD population

Noninvasive staging of NAFLD

	AUROC			
	Any fibrosis	≥F2	F3-4	Cirrhosis
Transient elastography	0.74-0.78	0.79-0.84	0.83-0.88	0.86-0.93
MR elastography	0.83	0.91	0.89	0.97
NAFLD fibrosis score	0.82	0.72-0.82	0.73-0.86	0.77-0.92
APRI	0.61	0.54-0.72	0.61-0.75	0.65-0.77
FIB-4	0.8	0.72-0.83	0.78-0.86	0.78-0.88

Boursier, J Hepatol 2016.
Imajo, Gastroenterology 2016.
Siddiqui, . . .Brandman et al. *Clin Gastro Hep,* 2018.
Hsu, *Clin Gastro Hep*, 2018.

Transient Elastography: Fibroscan

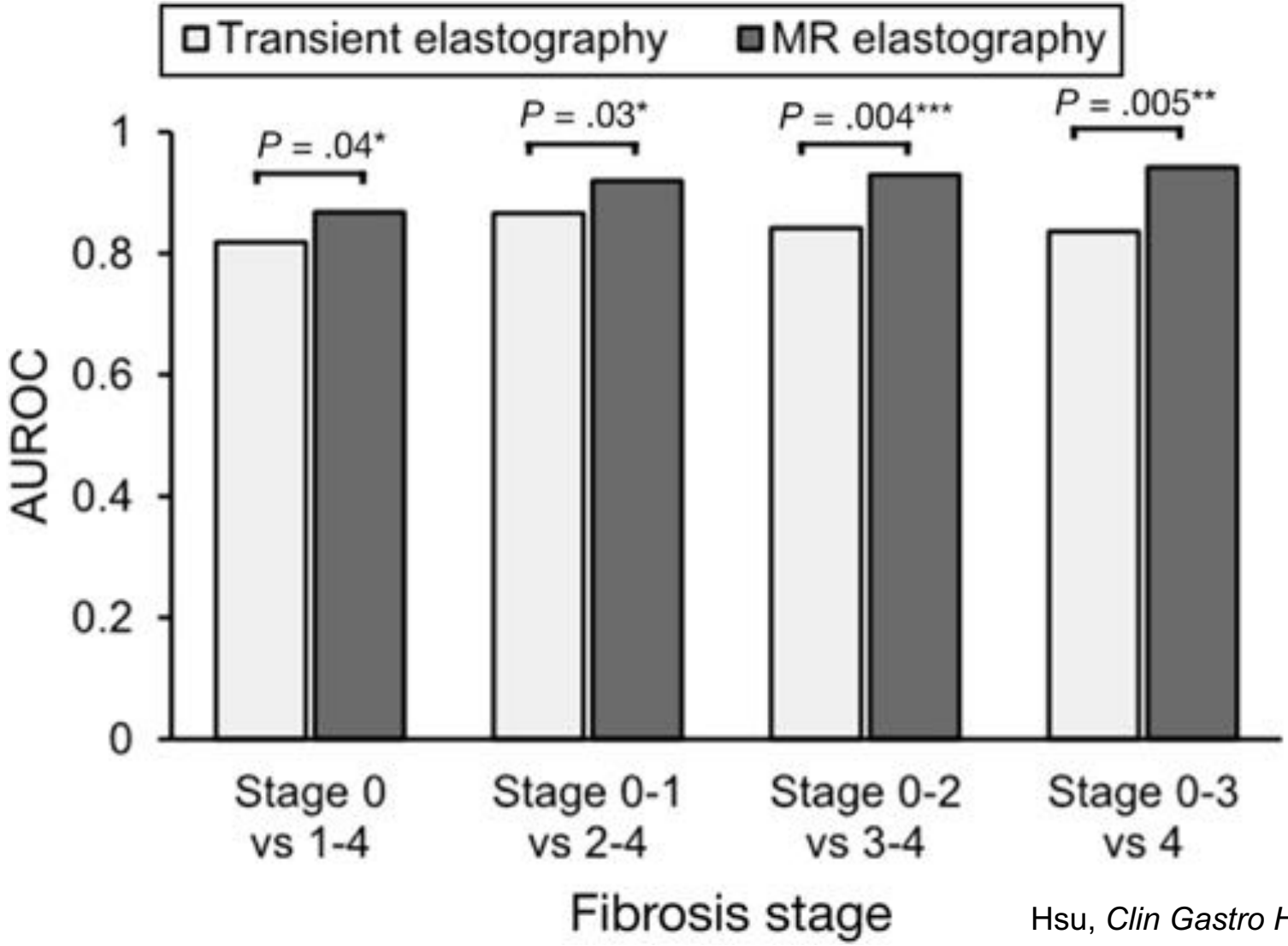


Fibroscan

- Factors that may produce inaccurate results:
  - Obesity
  - Steatohepatitis
  - Alcohol use
  - Nonfasting state
  - Cholestasis
  - Hispanic ethnicity
- Requires adequate experience to produce reliable results

Vuppalanchi, *Hepatology*, 2017.

Fibroscan vs MR elastography



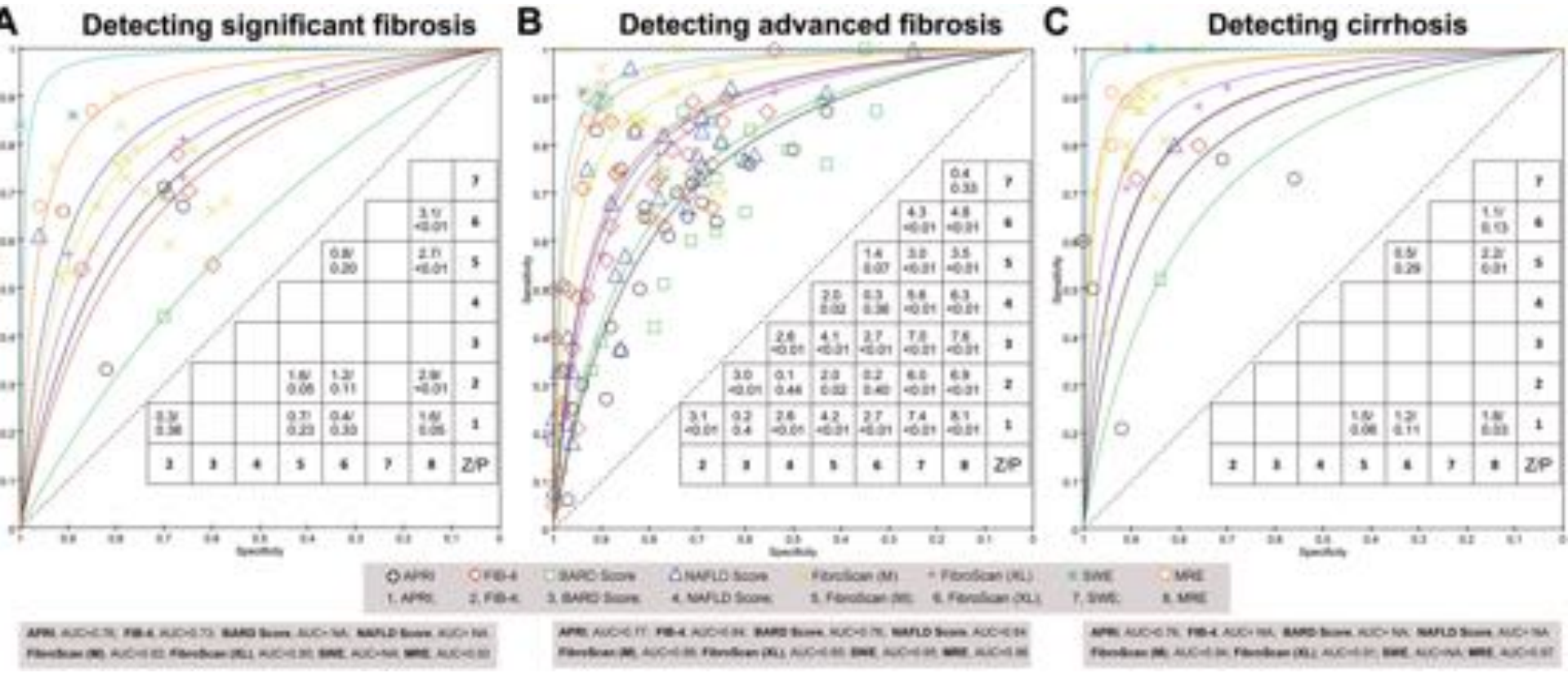
Hsu, *Clin Gastro Hep,* 2018.

Fibroscan vs MR elastography

	Sensitivity		Specificity		PPV		NPV	
	TE	MRE	TE	MRE	TE	MRE	TE	MRE
Any fibrosis	66%	71%	67%	73%	81%	85%	48%	54%
F2-4	76%	85%	80%	85%	72%	80%	89%	83%
F3-4	77%	82%	78%	83%	54%	62%	94%	91%
F4	80%	80%	81%	86%	34%	41%	97%	97%

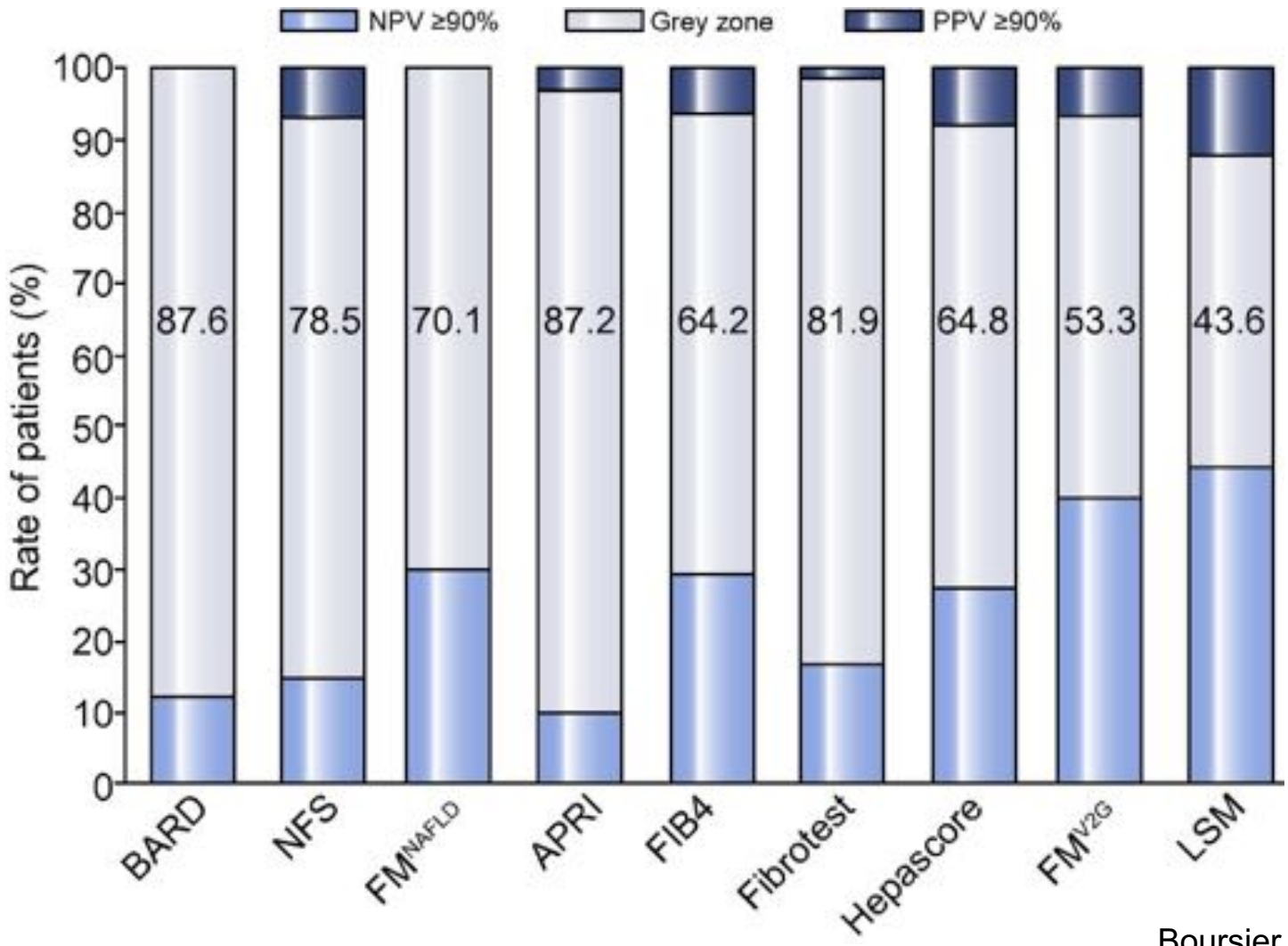
Hsu, *Clin Gastro Hep,* 2018.

Comparison of noninvasive methods



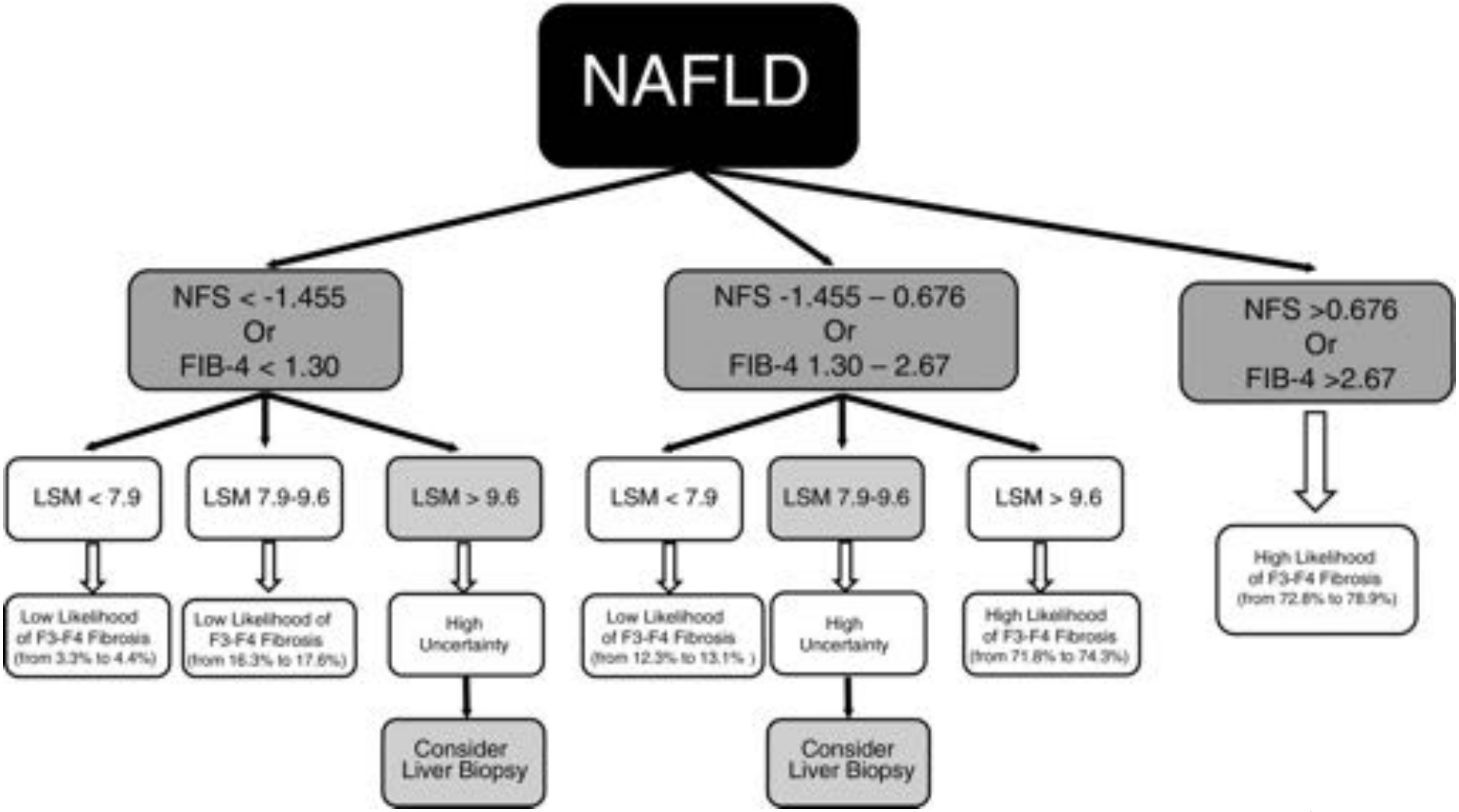
Xiao, *Hepatology,* 2017.

Variable performance of noninvasive assessment of fibrosis



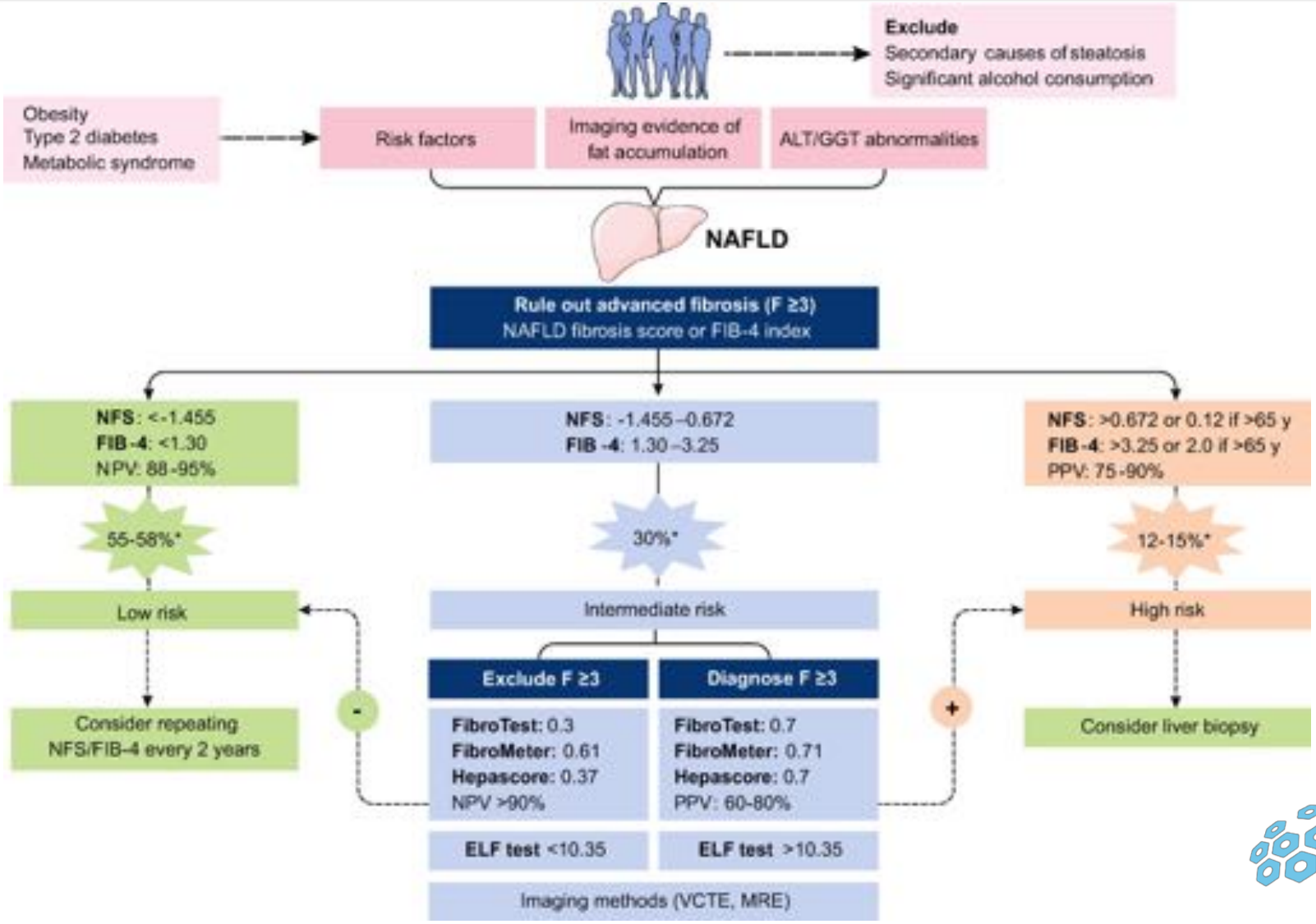
Boursier, *J Hep* 2016.

Serial use of NFS/FIB-4 and TE



Petta, *AP&T,* 2017.

Algorithm to triage suspected NAFLD



EASL
The Home of Hepatology

Case (cont'd)

- The patient was reluctant to undergo liver biopsy and opted instead for Fibroscan

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Case (cont'd)

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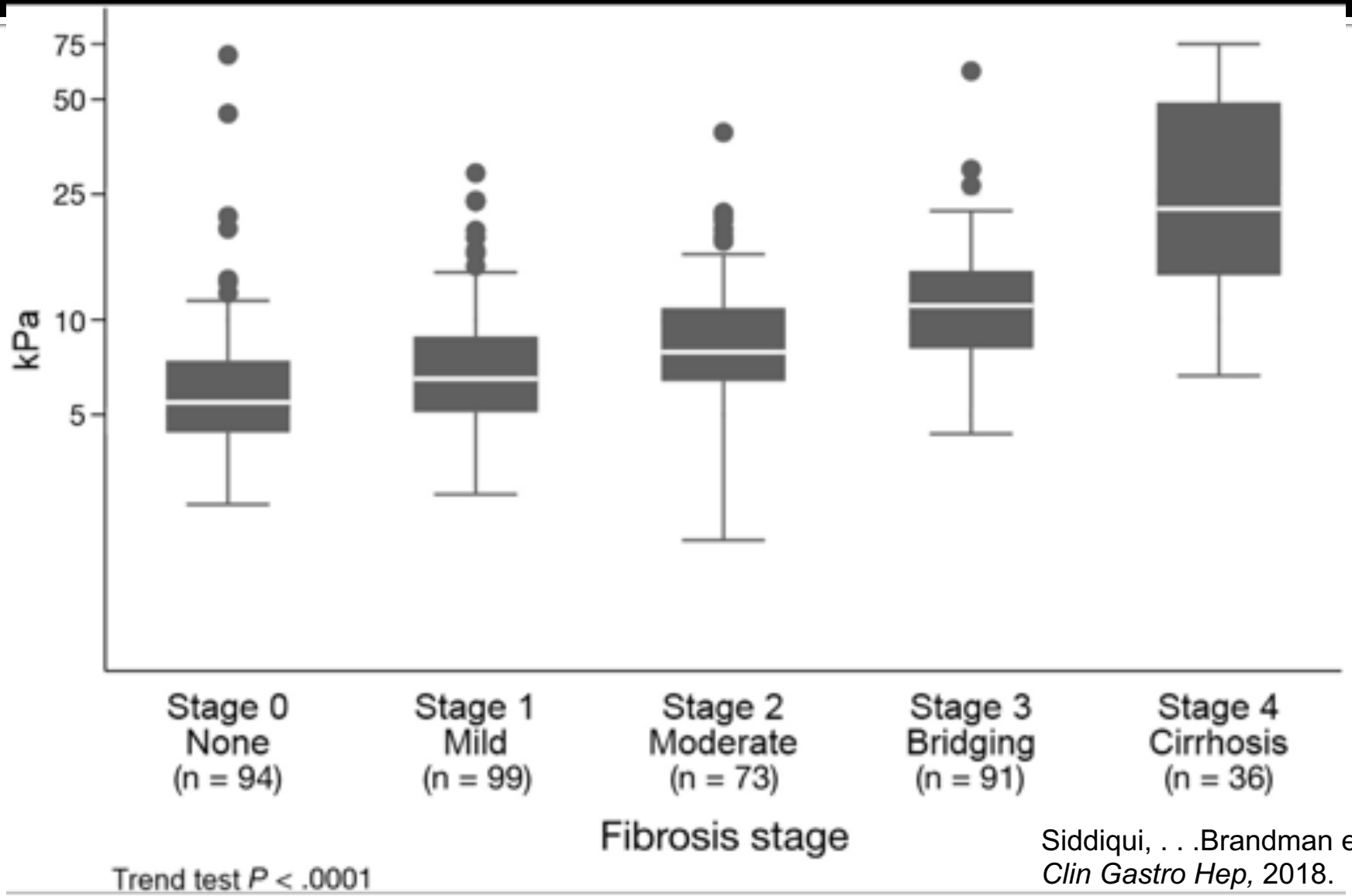
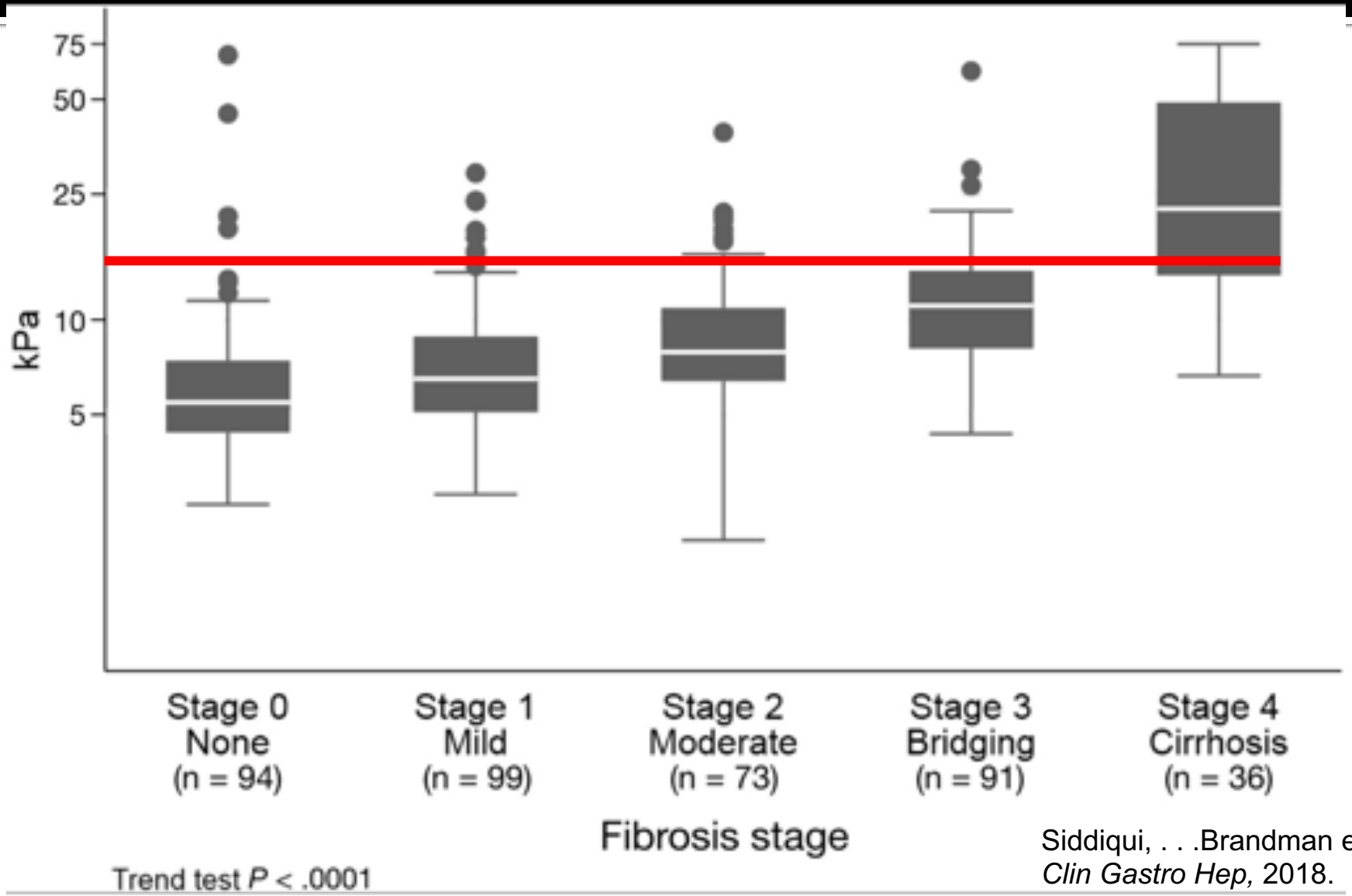
  - CAP score: 330 (IQR 13)
  - Interpretation: Cirrhosis (F4), though LSM could be overestimated due to the presence of severe steatosis (CAP>300)
  - NFS -0.4 (indeterminate), FIB-4 1.24 (90% NPV for advanced fibrosis)

Interpretation of LSM measurements



Siddiqui, . . .Brandman et al. *Clin Gastro Hep,* 2018.

Interpretation of LSM measurements



Siddiqui, . . .Brandman et al. *Clin Gastro Hep,* 2018.

Case (cont'd)

- Because of the concern for cirrhosis, you again recommend liver biopsy for more definitive diagnosis and staging

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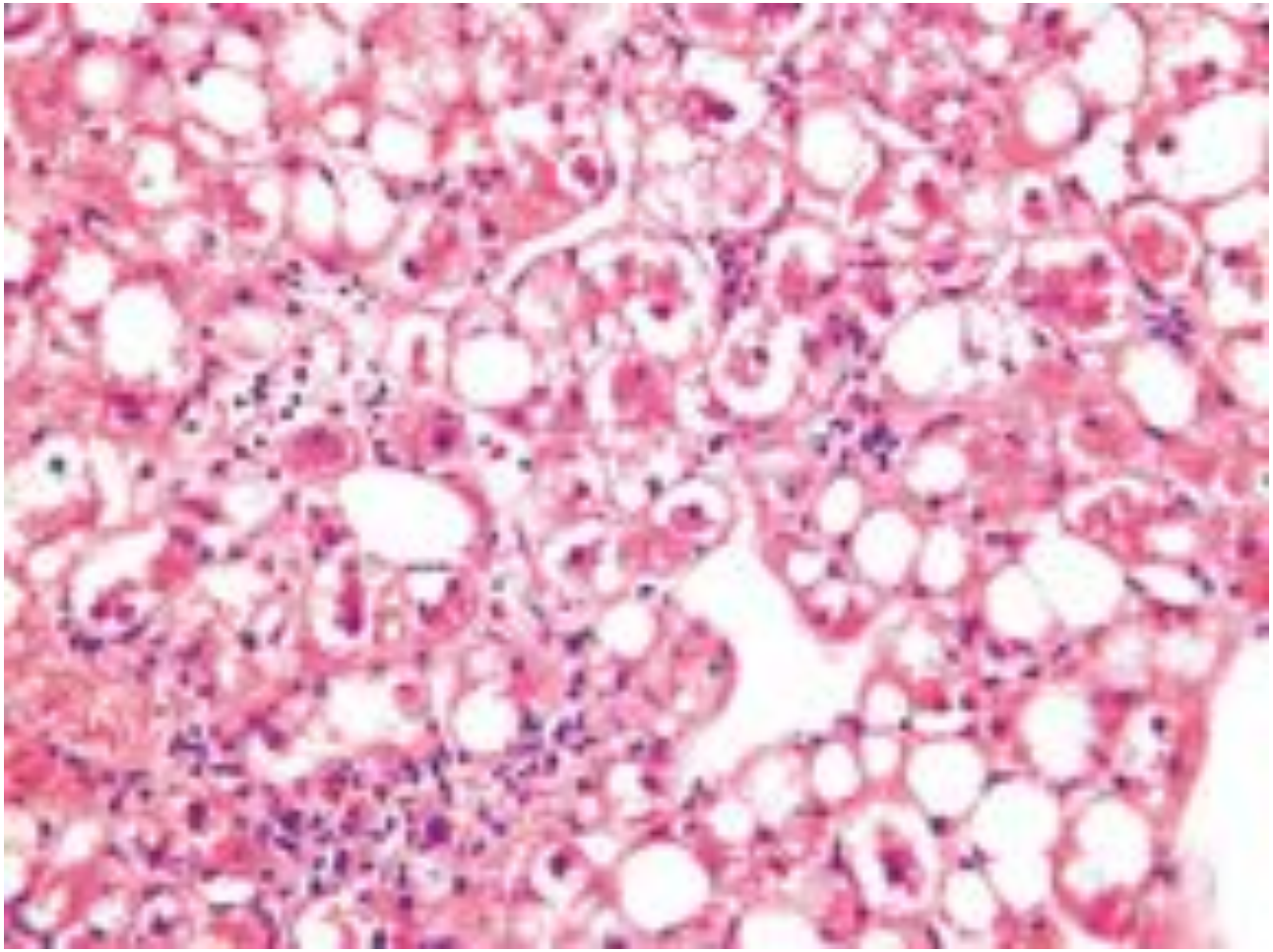
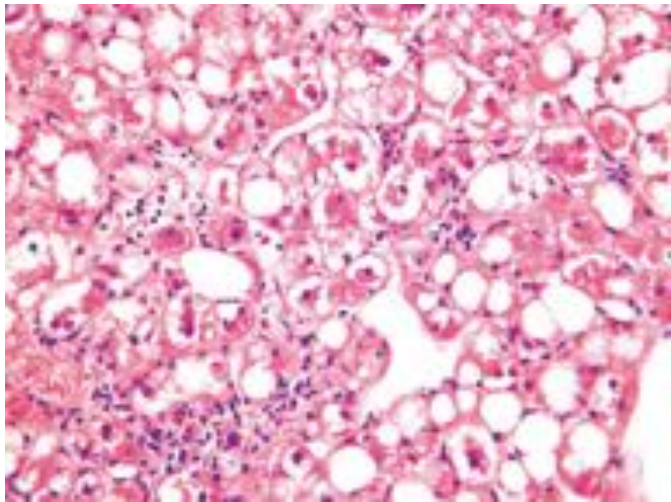
- Because of the concern for cirrhosis, you again recommend liver biopsy for more definitive diagnosis and staging
- The patient is now amenable to liver biopsy

Case (cont'd)



Case (cont'd)

- Impression: steatohepatitis
  - >20 portal tracts present, no fragmentation
  - Severe steatosis (>66%)
  - Ballooned hepatocytes
  - Moderate lobular inflammation
  - Fibrosis: stage 3, with bridging fibrosis and areas of centrizonal fibrosis



What do you tell the patient about his disease?

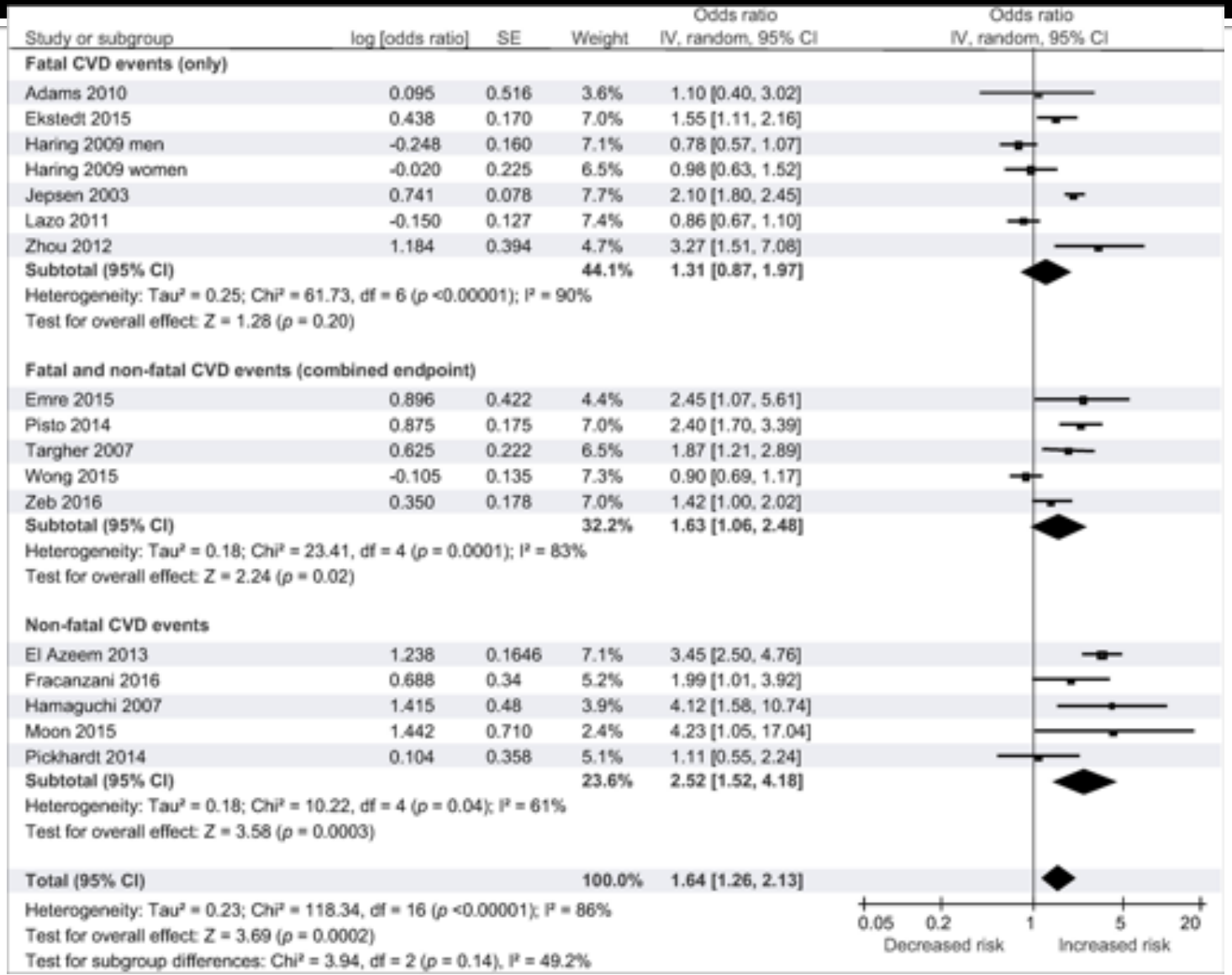
Leading causes of death in NAFLD

1. Coronary artery disease
2. Malignancy
3. Liver disease

Leading causes of death in NAFLD

1. **Coronary artery disease**
2. Malignancy
3. Liver disease

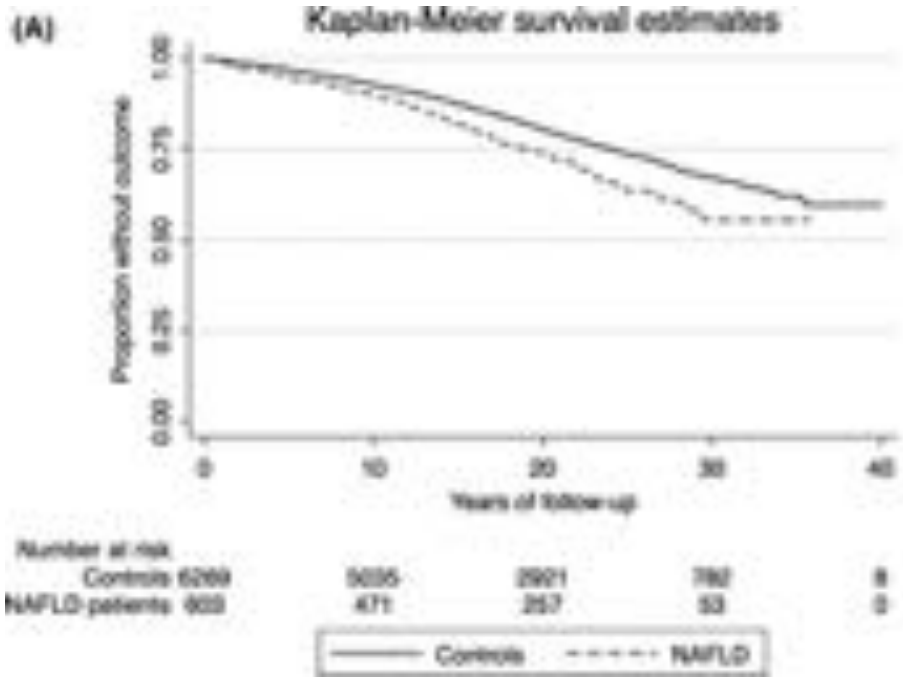
NAFLD is associated with increased risk of non-fatal CV events

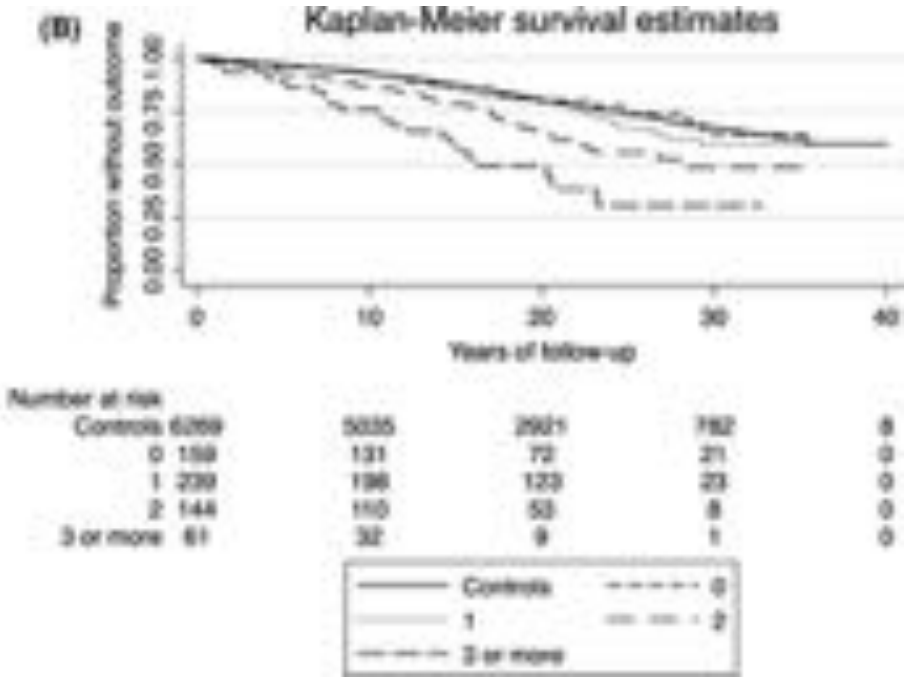


Study or subgroup	log [odds ratio]	SE	Weight	Odds ratio IV, random, 95% CI
Fatal CVD events (only)				
Adams 2010	0.095	0.516	3.6%	1.10 [0.40, 3.02]
Ekstedt 2015	0.438	0.170	7.0%	1.55 [1.11, 2.16]
Haring 2009 men	-0.248	0.160	7.1%	0.78 [0.57, 1.07]
Haring 2009 women	-0.020	0.225	6.5%	0.98 [0.63, 1.52]
Jepsen 2003	0.741	0.078	7.7%	2.10 [1.80, 2.45]
Lazo 2011	-0.150	0.127	7.4%	0.86 [0.67, 1.10]
Zhou 2012	1.184	0.394	4.7%	3.27 [1.51, 7.08]
Subtotal (95% CI)			**44.1%**	**1.31 [0.87, 1.97]**
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 61.73$, df = 6 ($p < 0.00001$); $I^2 = 90\%$				
Test for overall effect: Z = 1.28 ($p = 0.20$)				
Fatal and non-fatal CVD events (combined endpoint)				
Emre 2015	0.896	0.422	4.4%	2.45 [1.07, 5.61]
Pisto 2014	0.875	0.175	7.0%	2.40 [1.70, 3.39]
Targher 2007	0.625	0.222	6.5%	1.87 [1.21, 2.89]
Wong 2015	-0.105	0.135	7.3%	0.90 [0.69, 1.17]
Zeb 2016	0.350	0.178	7.0%	1.42 [1.00, 2.02]
Subtotal (95% CI)			**32.2%**	**1.63 [1.06, 2.48]**
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 23.41$, df = 4 ($p = 0.0001$); $I^2 = 83\%$				
Test for overall effect: Z = 2.24 ($p = 0.02$)				
Non-fatal CVD events				
El Azeem 2013	1.238	0.1646	7.1%	3.45 [2.50, 4.76]
Fracanzani 2016	0.688	0.34	5.2%	1.99 [1.01, 3.92]
Hamaguchi 2007	1.415	0.48	3.9%	4.12 [1.58, 10.74]
Moon 2015	1.442	0.710	2.4%	4.23 [1.05, 17.04]
Pickhardt 2014	0.104	0.358	5.1%	1.11 [0.55, 2.24]
Subtotal (95% CI)			**23.6%**	**2.52 [1.52, 4.18]**
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 10.22$, df = 4 ($p = 0.04$); $I^2 = 61\%$				
Test for overall effect: Z = 3.58 ($p = 0.0003$)				
Total (95% CI)			**100.0%**	**1.64 [1.26, 2.13]**
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 118.34$, df = 16 ($p < 0.00001$); $I^2 = 86\%$				
Test for overall effect: Z = 3.69 ($p = 0.0002$)				
Test for subgroup differences: $Chi^2 = 3.94$, df = 2 ($p = 0.14$), $I^2 = 49.2\%$				

Targher, *J Hep,* 2016.

Increased risk of incident CV in NAFLD



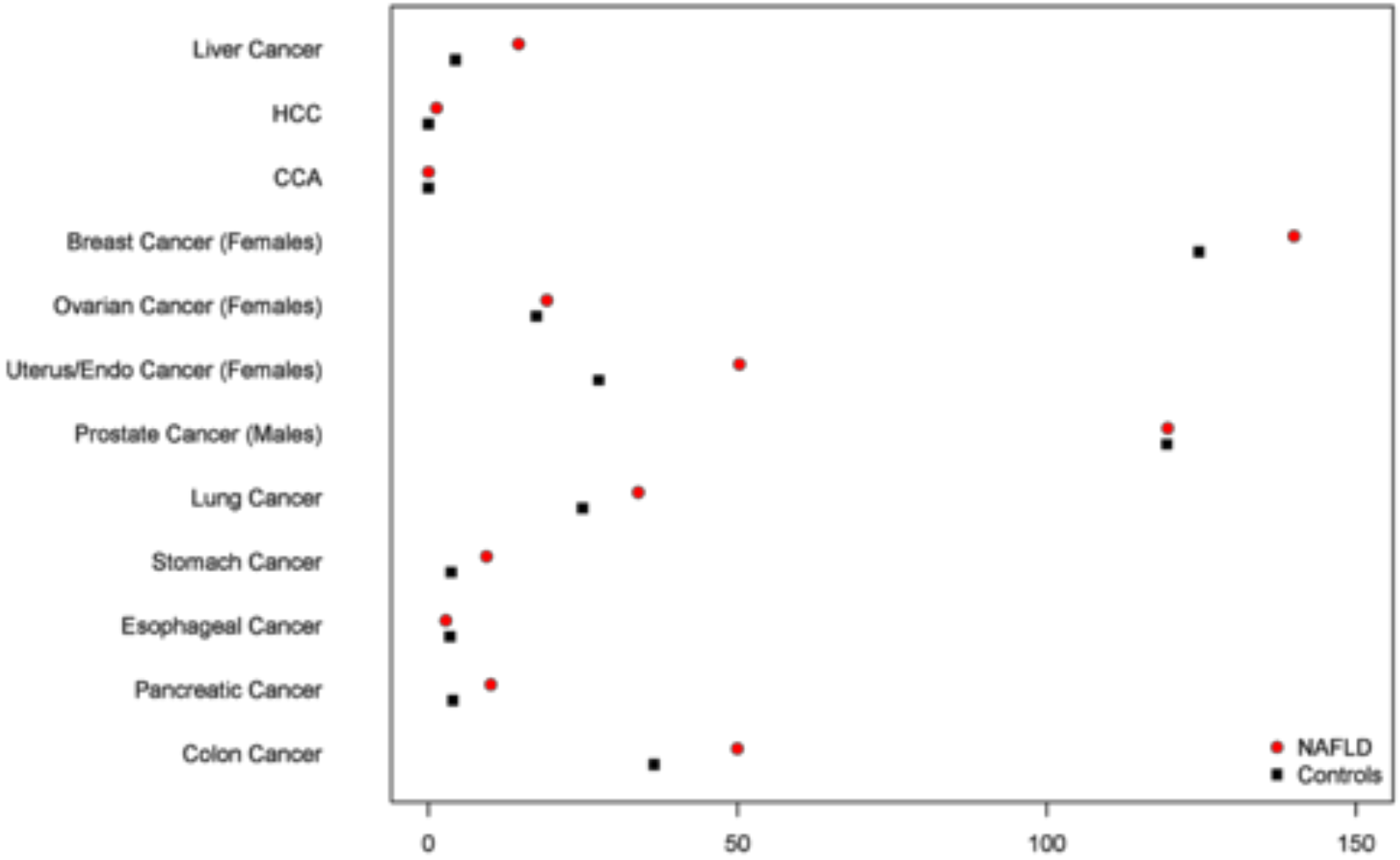


Hagstrom, *J Hep,* 2018.

Leading causes of death in NAFLD

1. Coronary artery disease
2. **Malignancy**
3. Liver disease

Incidence of malignancy in NAFLD is higher than in control patients



Allen, *AASLD*, 2018.

HCC Risk in NASH

- Diabetes may be playing an important role in pathogenesis of HCC
- Annual incidence of HCC in NASH: 0.3-4.3%
- Up to 50% of HCC may develop in absence of cirrhosis
- HCC surveillance
  - Cirrhosis: yes
  - Non-cirrhotic NASH: ???

Rinella ME, JAMA 2015
Perumpail et al. Dig Dis Sci 2015
Starley et al, Hepatology 2010.
Ascha et al. Hepatology 2010.
Younossi et al. Hepatology 2016.

Risk of cirrhosis/HCC in NAFLD and normal liver enzymes

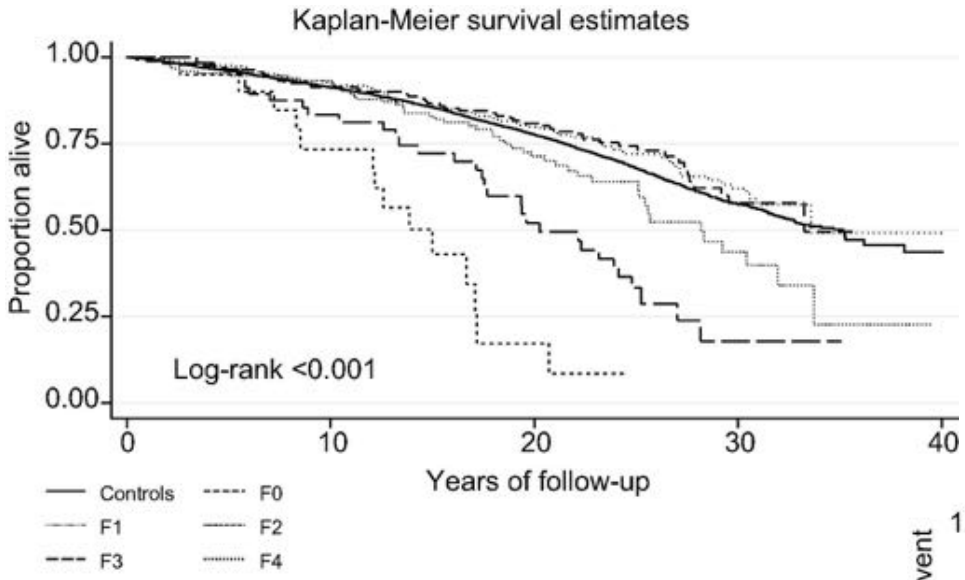
	Positive Controls N=42,901	Steatosis/Normal Liver Enzymes N=11,415	Negative Controls N=24,645
Age	53.3 (SD 12.1)	56.3 (SD 10.3)	58.1 (SD 10.7)
Incidence Rate per 1000 Person-Years (95% CI)			
Cirrhosis	4.93 (4.70-5.17)	2.50 (2.19-2.85)	2.40 (2.19-2.64)
HCC	0.49 (0.42-0.57)	0.16 (0.09-0.27)	0.13 (0.08-0.20)
Hazard Ratio (95 % CI)			
Cirrhosis	2.3 (2.0-2.5)	1.1 (0.9-1.3)	Ref
HCC	4.6 (3.0-7.0)	1.3 (0.7-2.5)	Ref

Natarajan, *AASLD*, 2018.

Leading causes of death in NAFLD

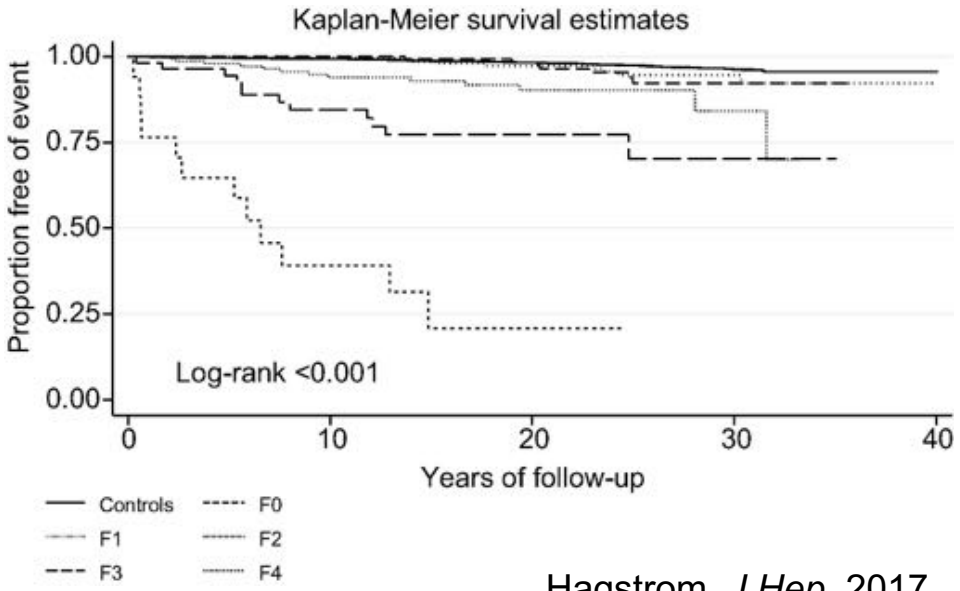
1. Coronary artery disease
2. Malignancy
3. **Liver disease**

Fibrosis stage is the strongest predictor of outcomes in NASH



Overall mortality

Liver-related event



Hagstrom, *J Hep,* 2017.

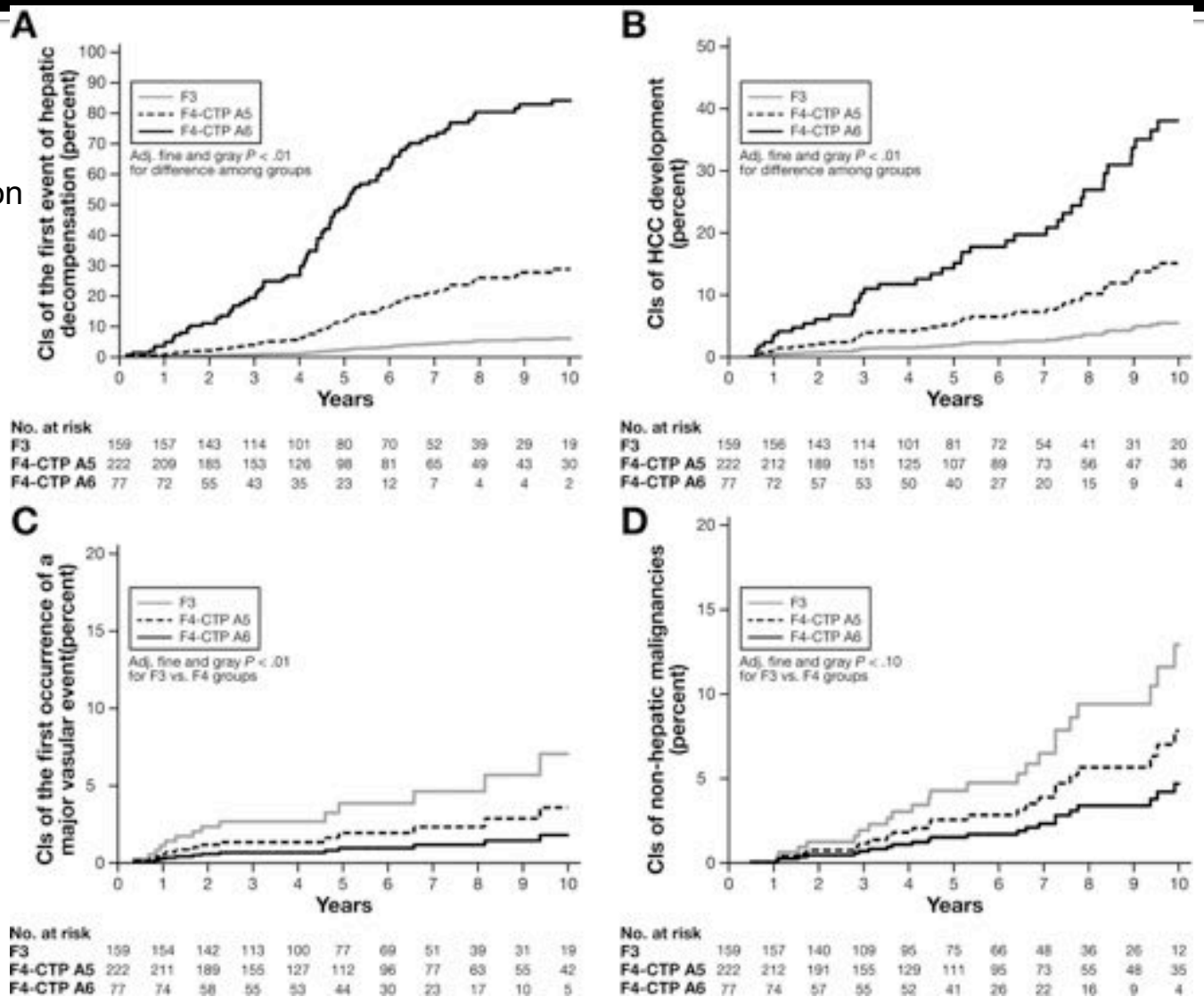
Outcomes in NAFLD with F3-4 fibrosis

Decompensation

HCC

CV events

Non-HCC malignancy

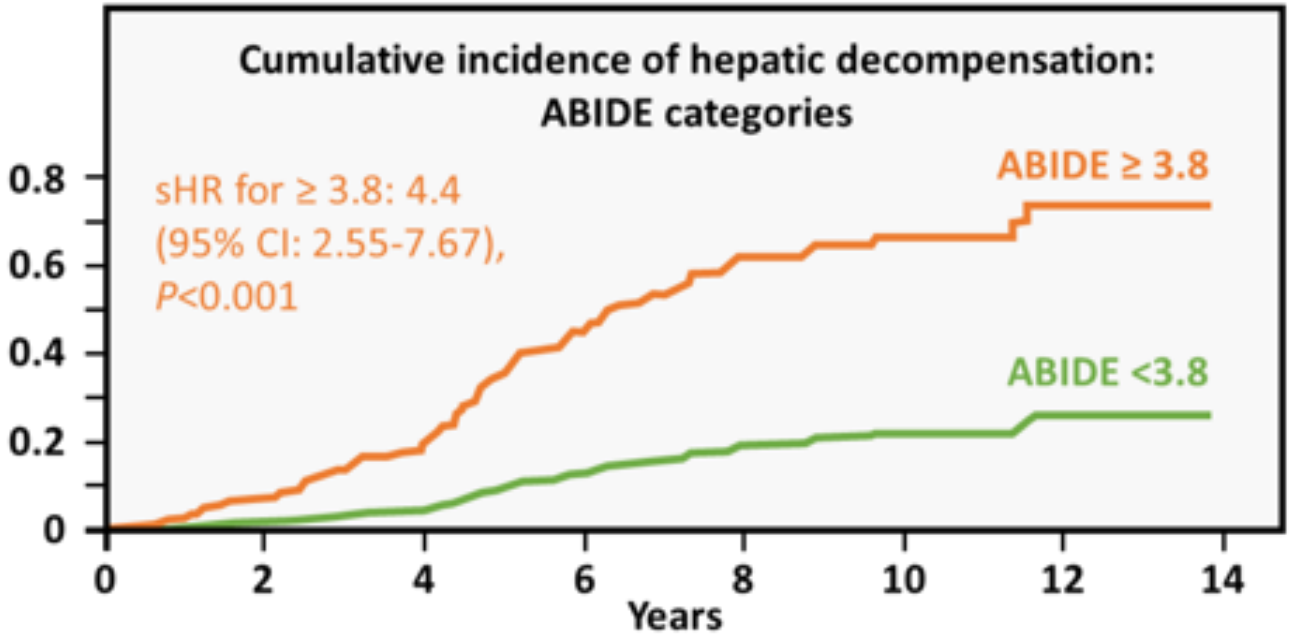


Vilar-Gomez, Gastro, 2018.

ABIDE: a novel predictor model of liver decompensation in NAFLD cirrhosis

Harrell's C index (95% CI) validation cohort (n=149)

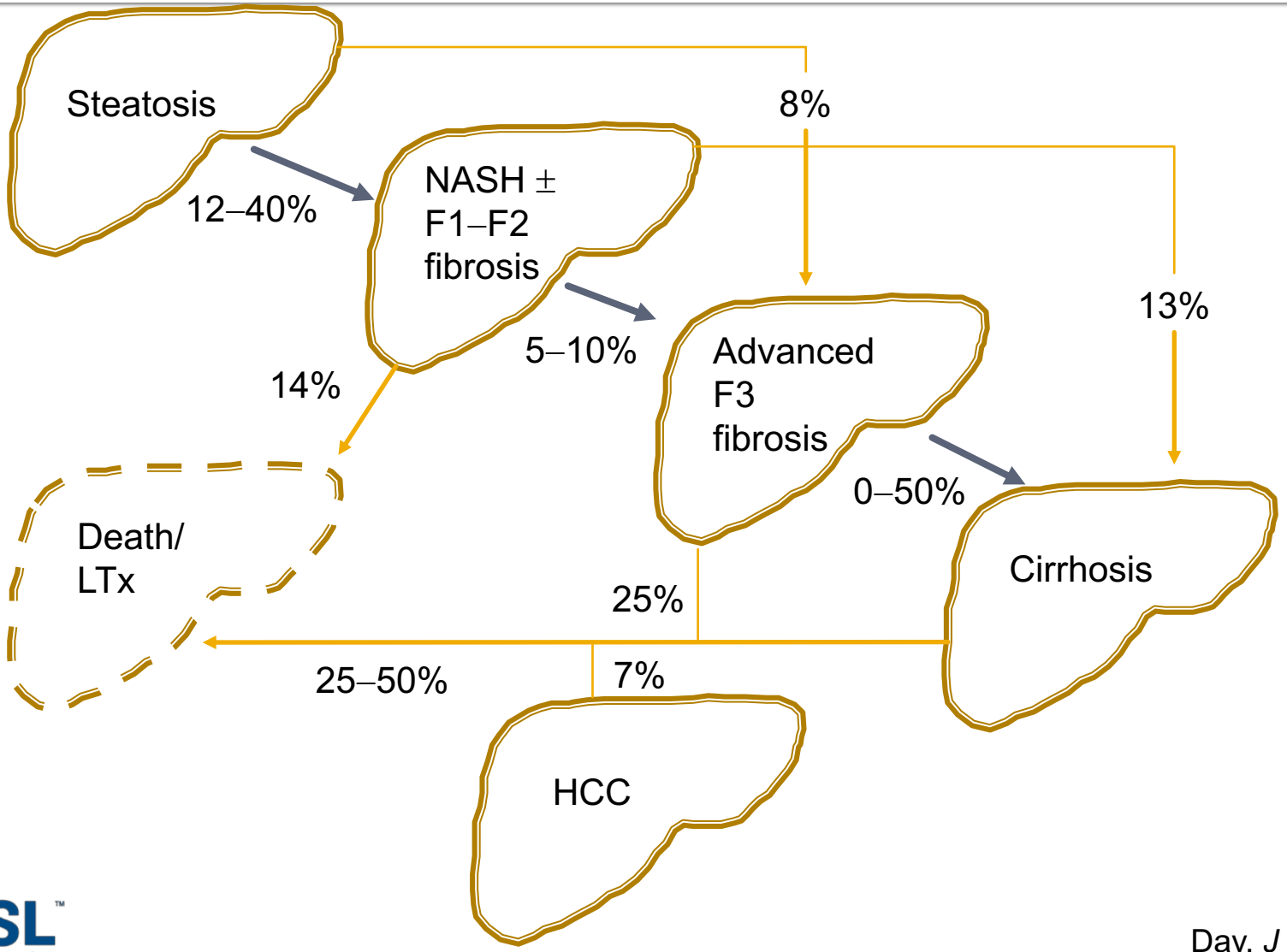
Scores	Overall Follow-Up	Five Years
ABIDE	0.76 (0.66-0.89)	0.84 (0.76-0.92)
NAFLD-FS	0.65 (0.52-0.77)	0.71 (0.67-0.82)
FIB-4	0.67 (0.55-0.79)	0.72 (0.70-0.85)



AST/ALT ratio
Bilirubin
INR
Diabetes
Esophageal varices

Bertot, *AASLD*, 2018.

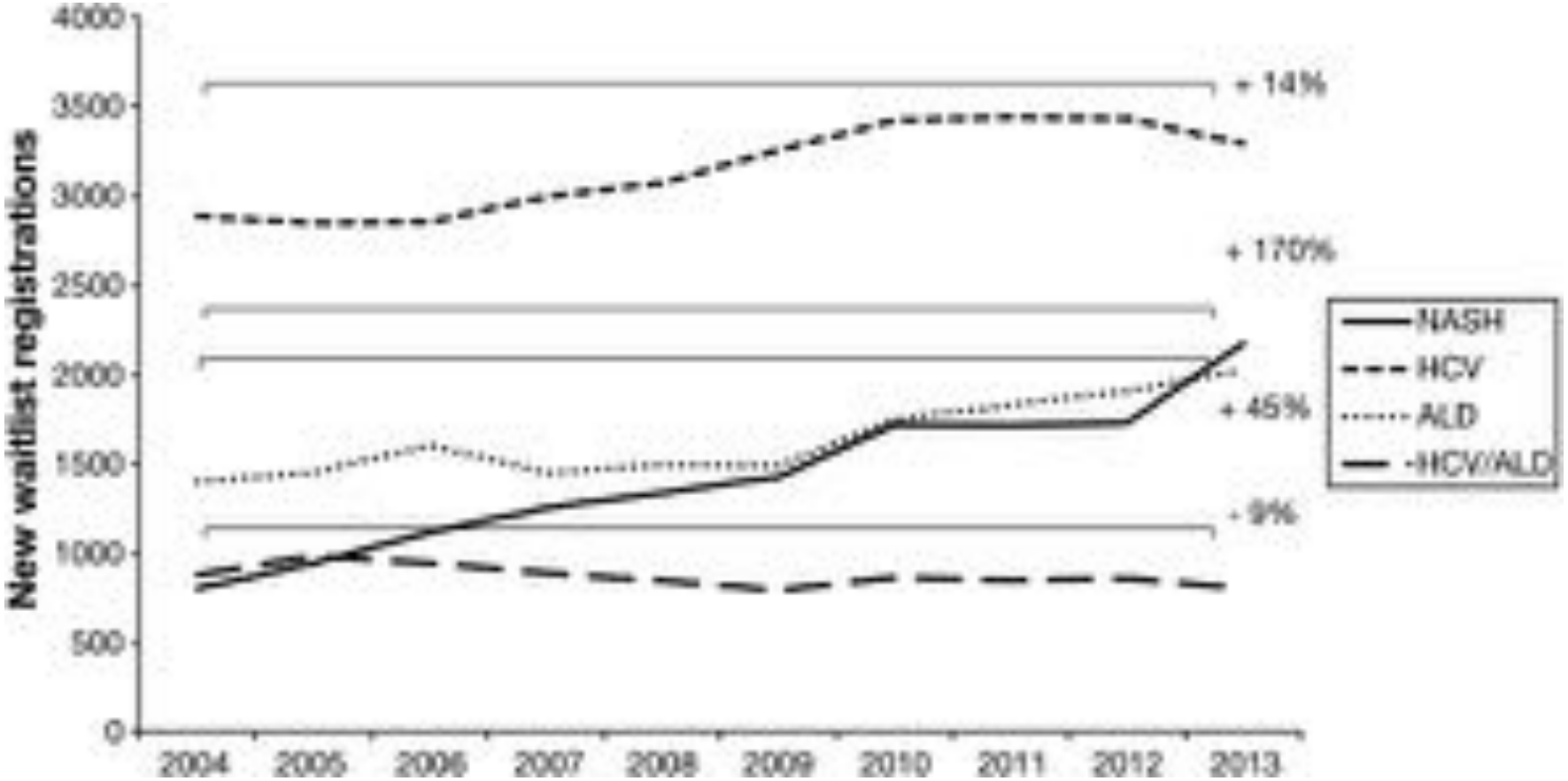
Prognosis of NAFLD by fibrosis stage



EASL The Home of Hepatology

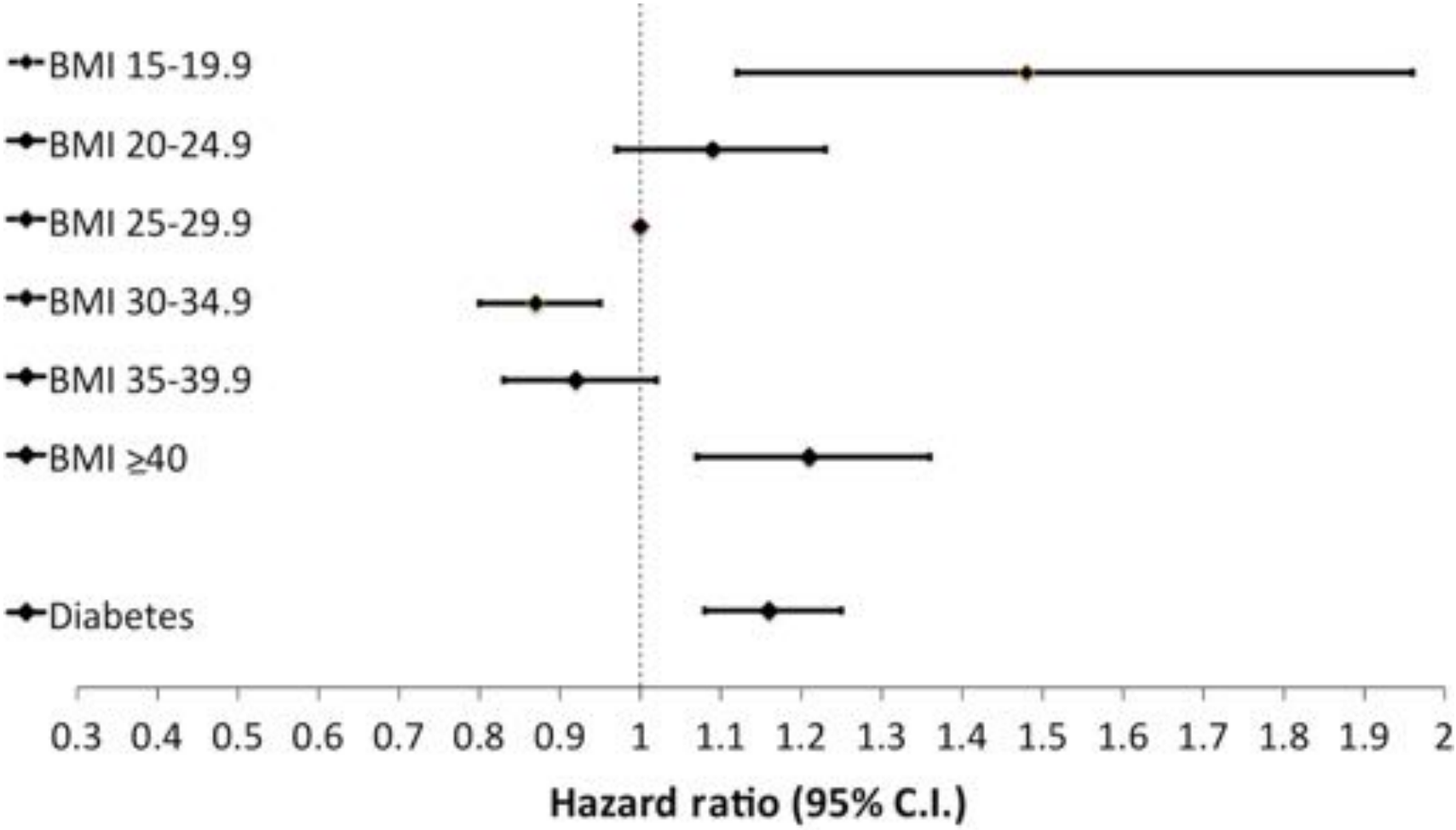
Day, *J Hep,* 2008.

NASH is increasing as an indication for liver transplantation



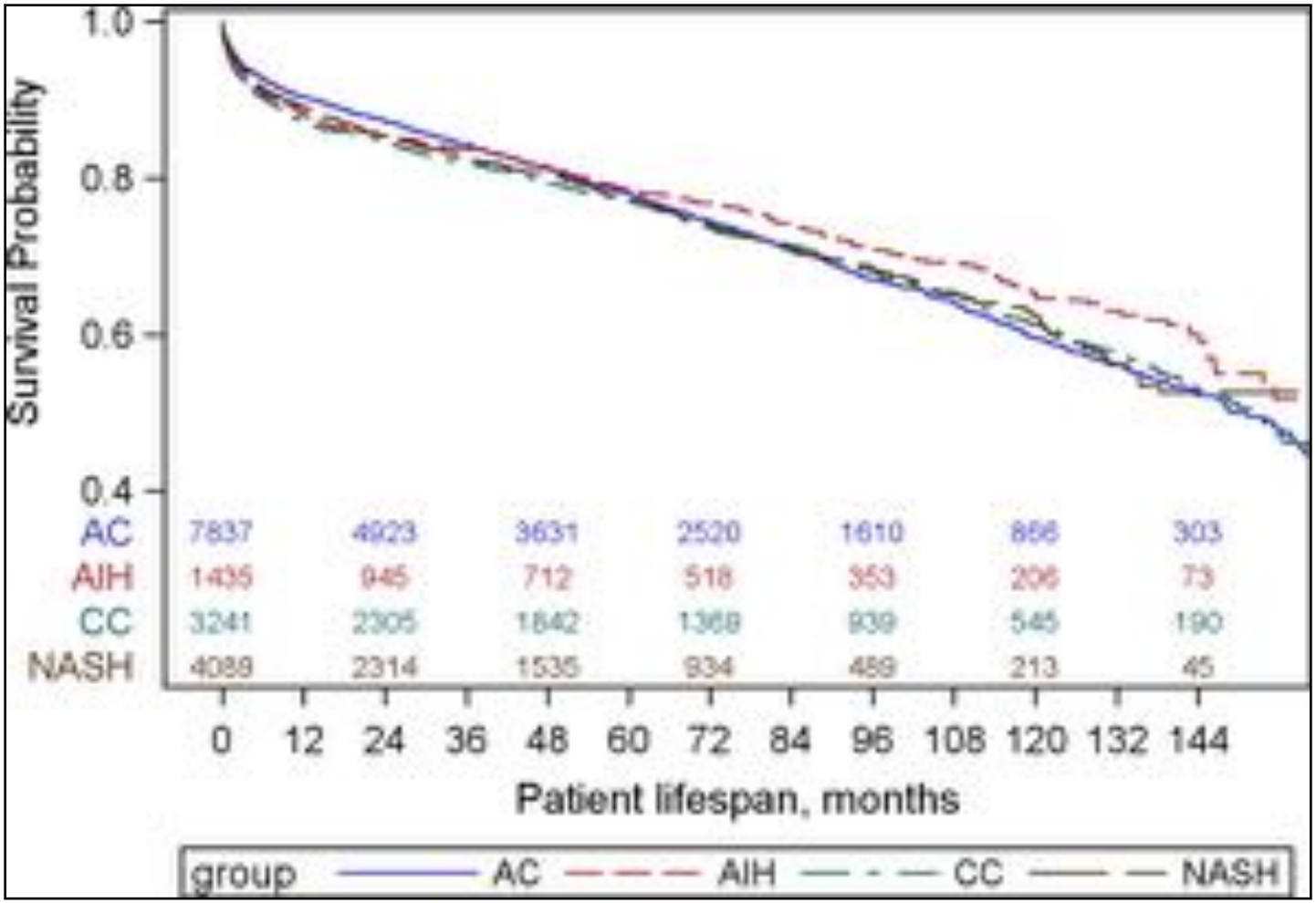
Wong, *Gastroenterology*, 2015.

Patients with NASH + BMI ≥40 or DM have high risk of LT waitlist dropout



Kardashian, . . .Brandman, *Liver Int*, 2018.

Post-LT survival for NASH is excellent



Thuluvath, *Transplantation*, 2018.

Case (cont'd)

- The patient is interested to know what can be done to treat disease and prevent or reverse fibrosis

Weight Loss

- Goal: loss of 7-10% baseline weight to improve NASH and fibrosis

- Diet
  - Portion control and simple carbohydrate avoidance
  - Avoid fructose-sweetened beverages

Harrison. *Hepatology*, 2009.
Promrat, *Hepatology* , 2010
Vilar-Gomez, *Gastro*, 2015
Chalasani , *Hepatology* 2012 .

Weight Loss

- Exercise
  - Exercise alone reduces liver fat
    - Aerobic >150-250 minutes per week
    - Resistance training 45 minutes/day x 3 days/week

Harrison. *Hepatology*, 2009.
Promrat, *Hepatology* , 2010
Vilar-Gomez, *Gastro*, 2015
Chalasani , *Hepatology* 2012 .

#10		I am dead!!!
#9		I am probably going to die!
#8		I can grunt in response to your questions and can only keep this pace for a short time period.
#7		I can still talk but I don't really want to and I am sweating like a pig!
#6		I can still talk but I am slightly breathless and definitely sweating.
#5		I'm just above comfortable, I am sweating more and can talk easily.
#4		I'm sweating a little, but I feel good and I can carry on a conversation comfortably.
#3		I am still comfortable, but I'm breathing a bit harder.
#2		I'm comfortable and I can maintain this pace all day long.
#1		I'm watching TV and eating bon bons.

Weight Loss

- Bariatric Surgery
  - Foregut procedures (Sleeve gastrectomy, Roux-en-Y gastric bypass, Lap band)
  - Improvement in NAFL/NASH +/- fibrosis
  - Relatively contraindicated in patients with cirrhosis
    - If needed, laparoscopic sleeve gastrectomy by an experienced surgeon is the operation of choice

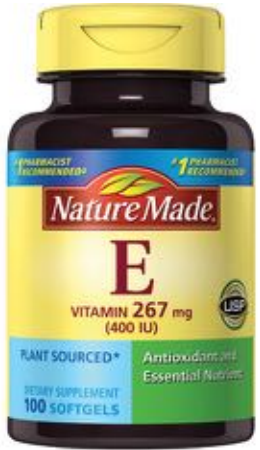
Harrison. *Hepatology*, 2009.
Promrat, *Hepatology* , 2010
Chalasani , *Hepatology* 2012 .

Metabolic syndrome management

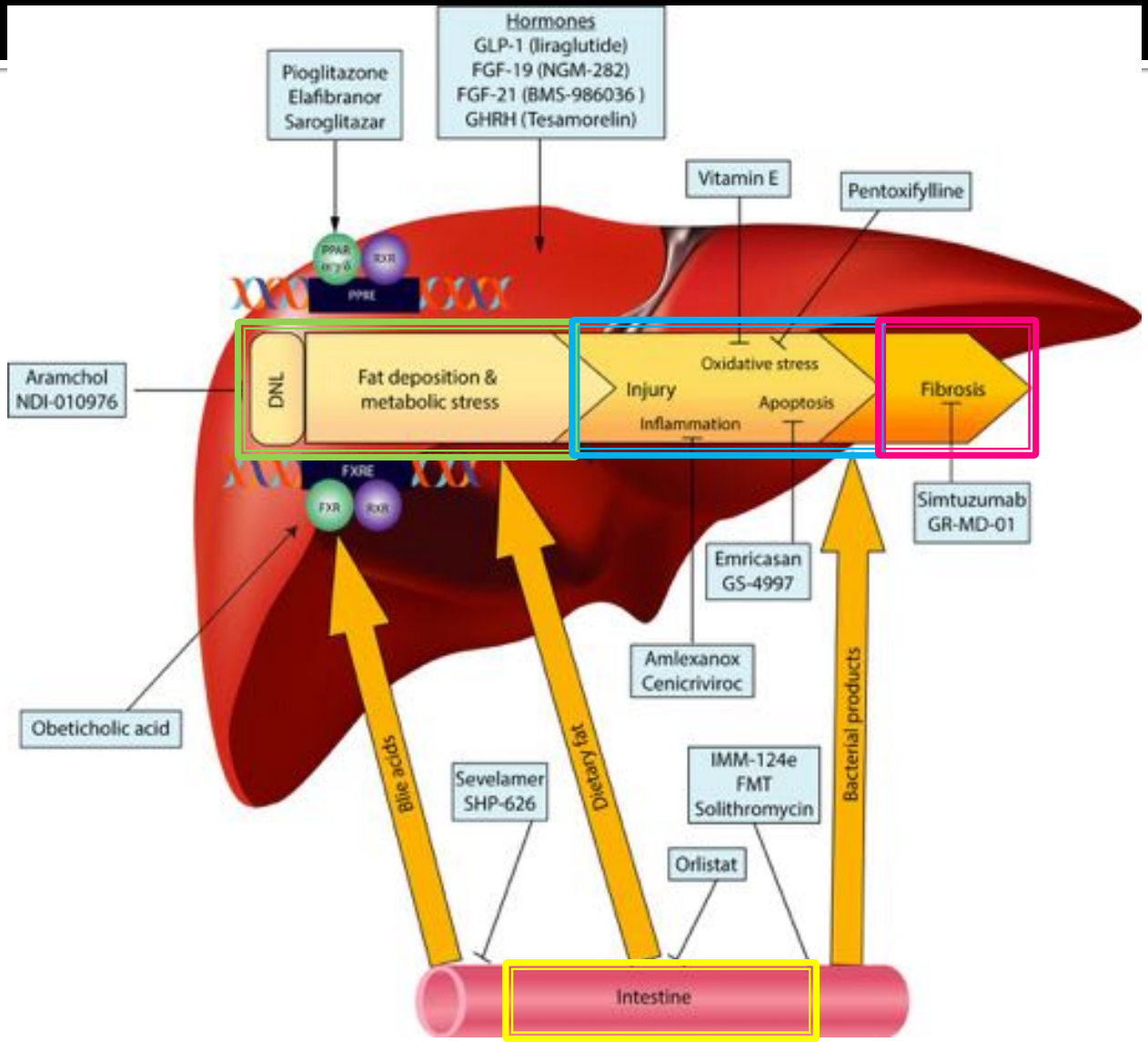
- Statins
  - **Safe for use in NAFLD**
  - Potential benefits of NAFLD/liver enzyme improvement and reduced risk of liver death or HCC
    - Not proven in randomized controlled trials
- Metformin
  - **Safe for use in NAFLD**
  - Some studies show improvement in liver biopsy and liver enzymes
    - Not proven in randomized controlled trials
  - Possible anti-neoplastic effects

Medications to treat NAFLD

- Only patients with biopsy-proven NASH need liver-specific treatment
- Medications currently available recommended for treatment of NASH
  - Vitamin E
  - Pioglitazone (Actos)



NAFLD pathways/targets for treatment



Rotman, *Gut*, 2017.

Summary

- NAFLD is a major public health problem worldwide
- NASH>>>NAFL has risk of progression to cirrhosis
  - Biopsy is needed to characterize NAFLD
  - Noninvasive assessment may help to identify higher risk patients
- Leading cause of death in NAFLD: Heart disease
- NAFLD is an important contributor to liver cancer and need for liver transplant

Summary

- Management hinges on weight loss, exercise, avoiding carbohydrates, metabolic syndrome control
  - Vitamin E (?pioglitazone) possibly for biopsy-proven NASH
  - Many drugs in the pipeline for NASH and fibrosis

Thank you!

Danielle.Brandman@ucsf.edu