Nonalcoholic Fatty Liver Disease

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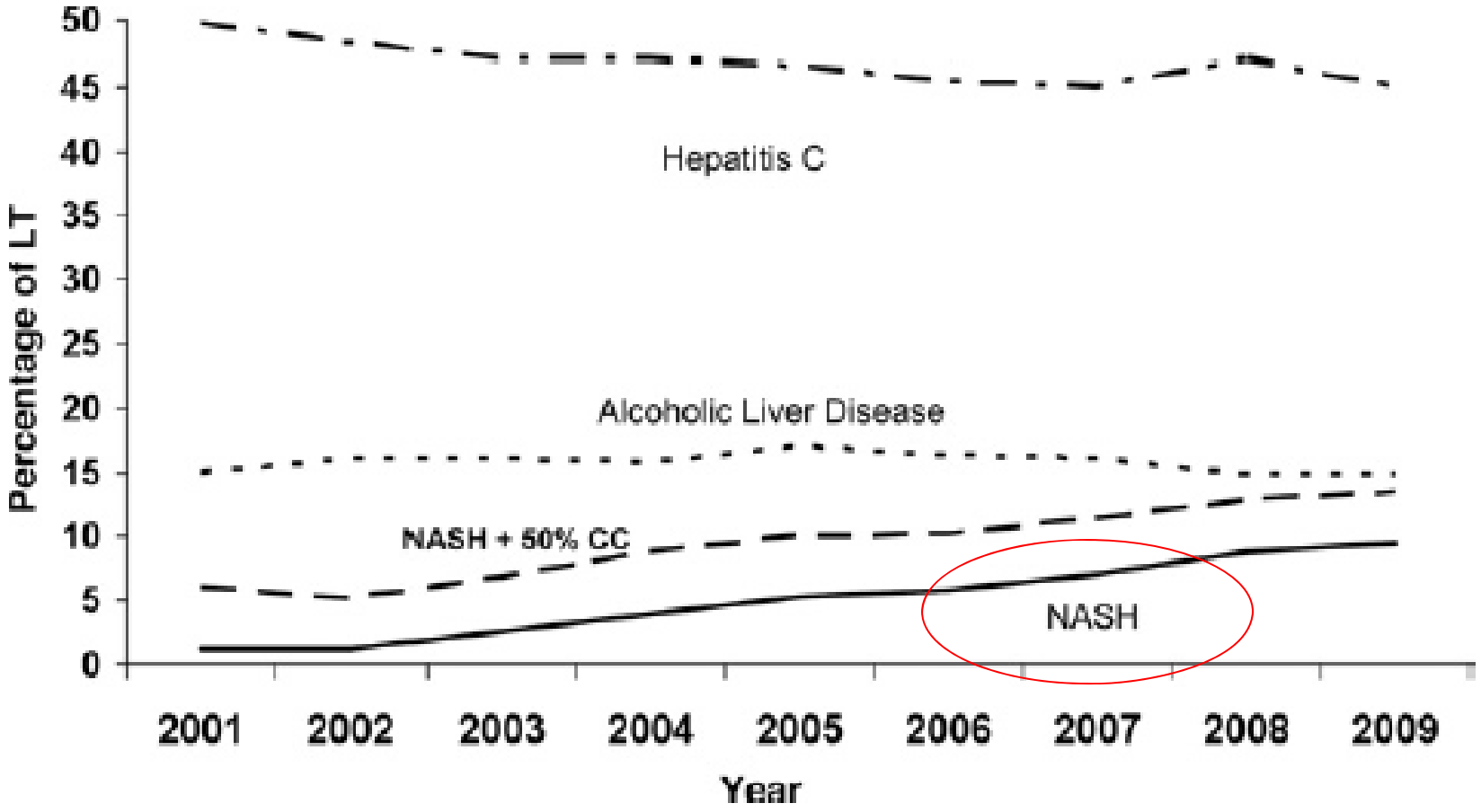
Outline

- Background
  - Epidemiology
- Clinical challenges
  - prediction of prognosis
  - noninvasive diagnosis/staging
- Treatment

Current challenges/unmet needs:

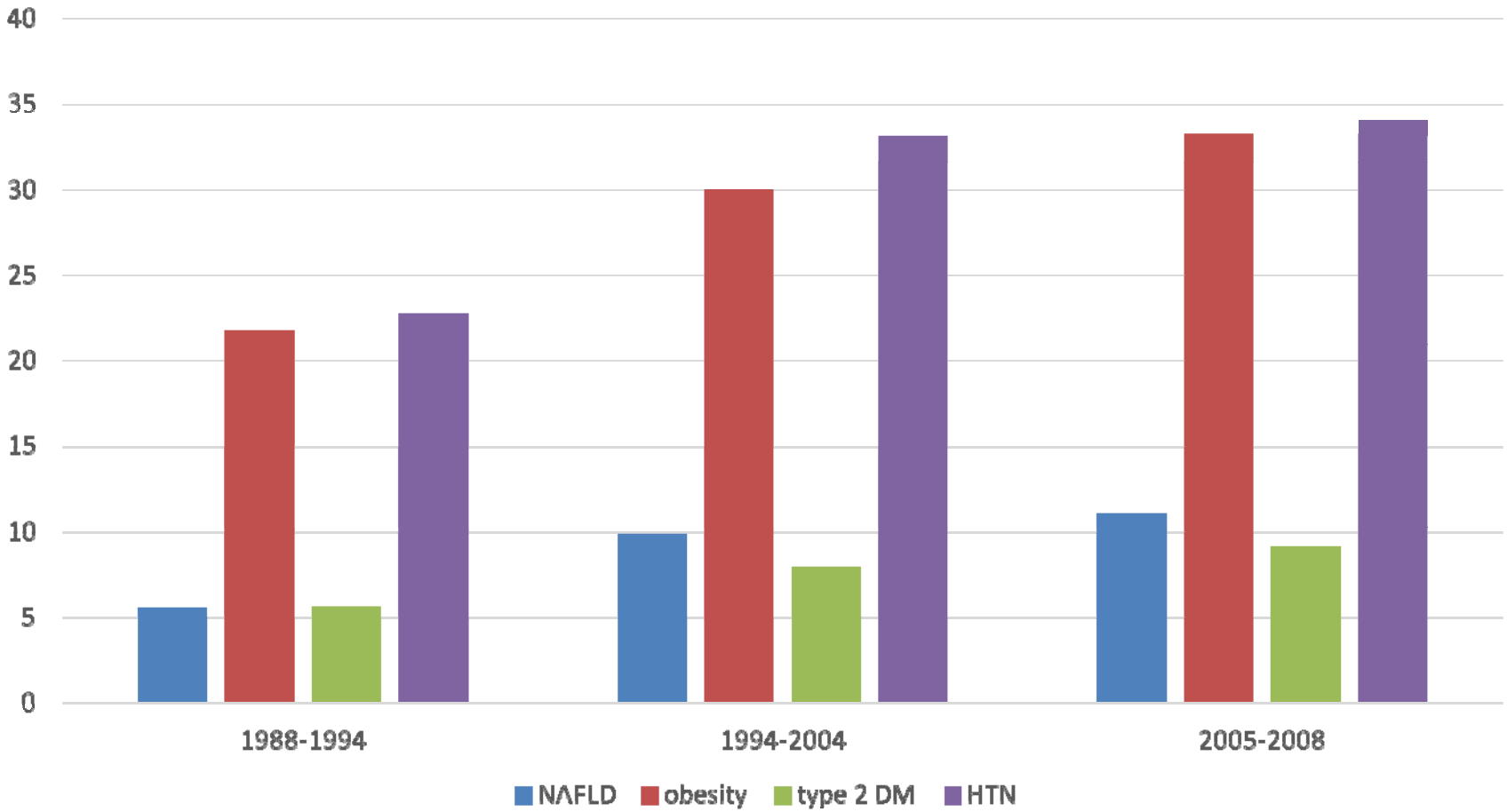
- rising prevalence of NASH
- variable prognosis/difficulty counseling patients what to expect over time
- lack of effective pharmacologic therapies
- systemic disease process with significant comorbidities (diabetes, obesity, cardiovascular disease)

Indications for liver transplantation in the United States (2001-2009)



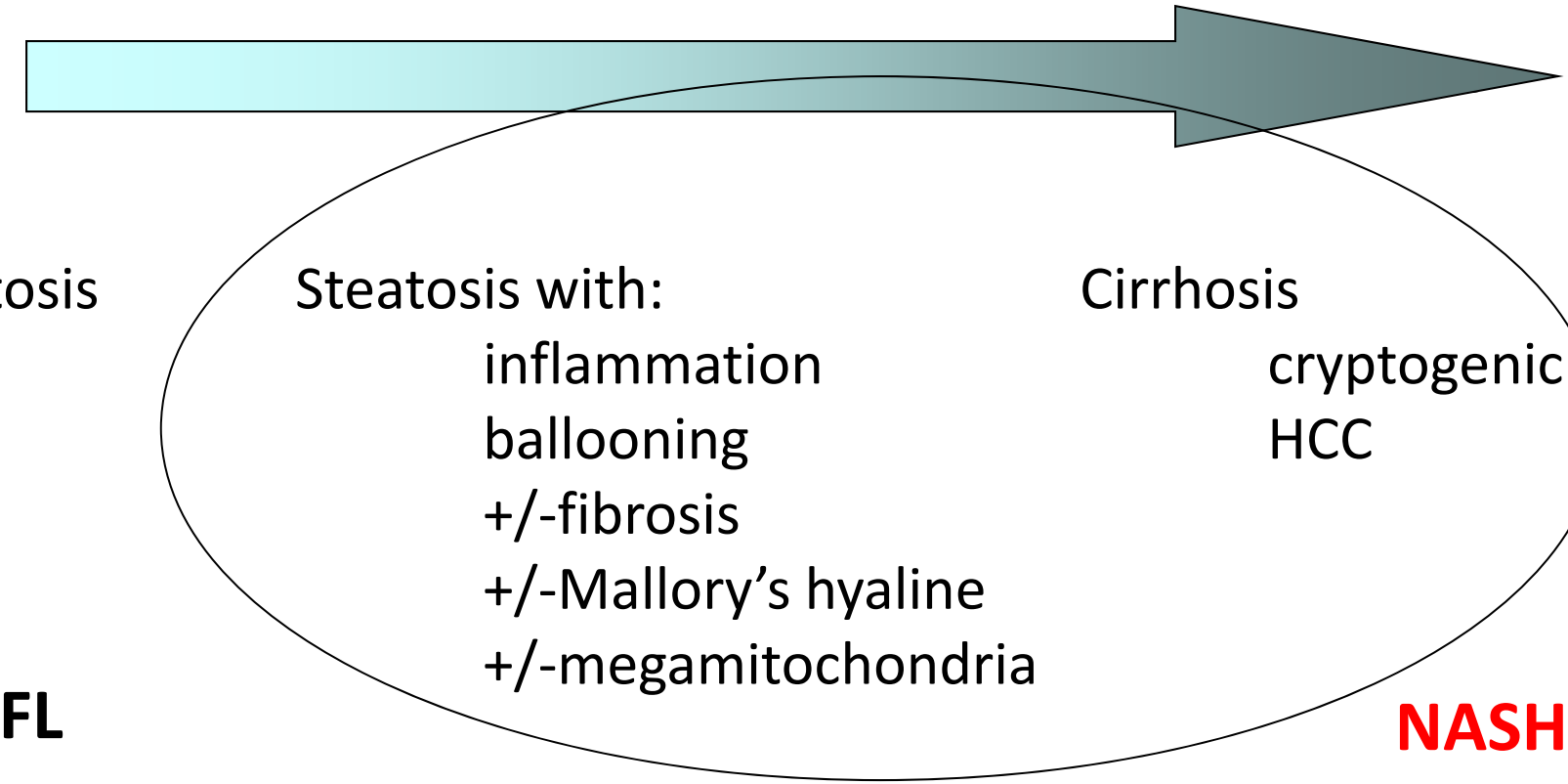
Charlton Gastro 2011

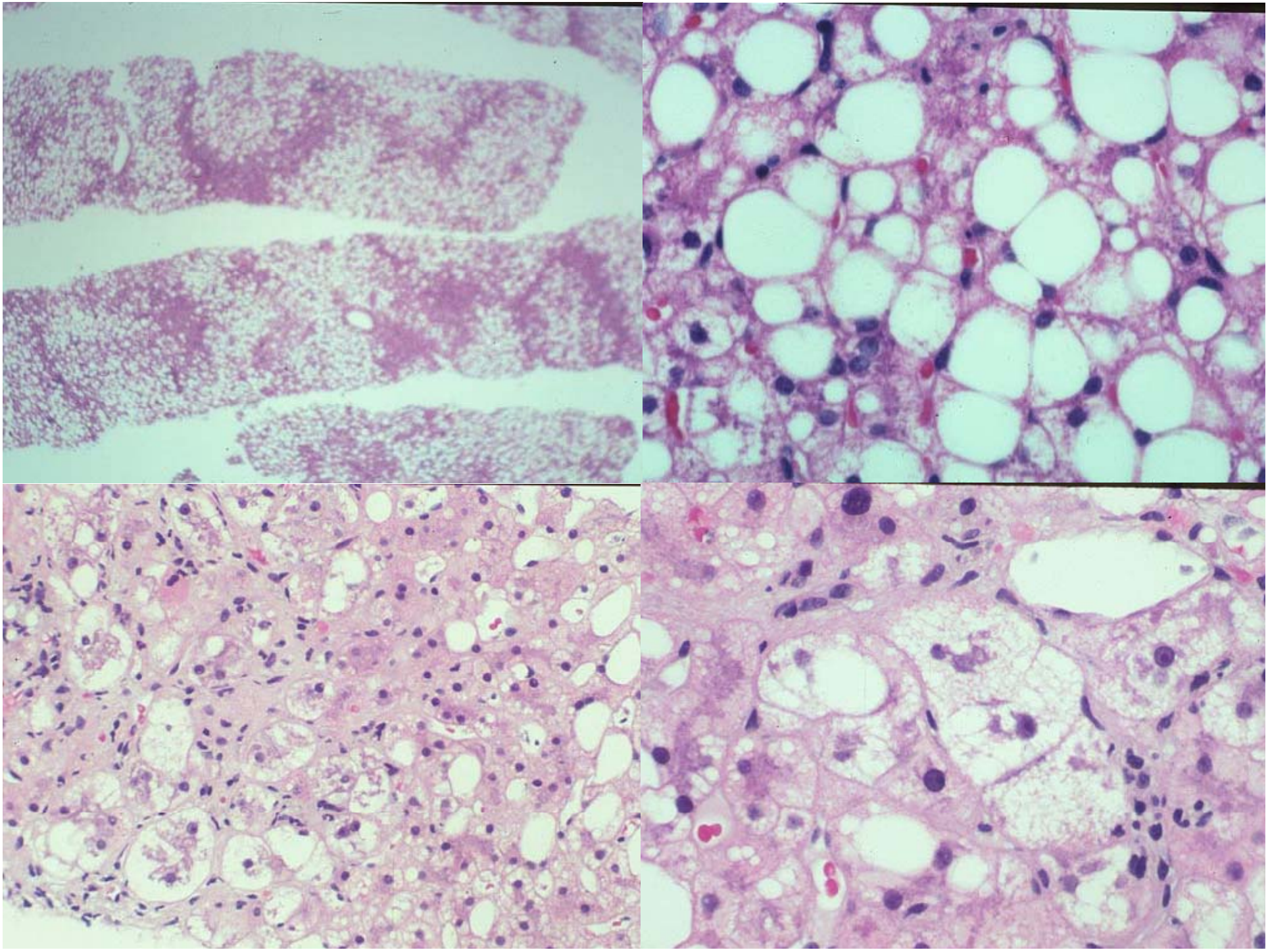
Rising Prevalence of NAFLD in the US (NHANES data)

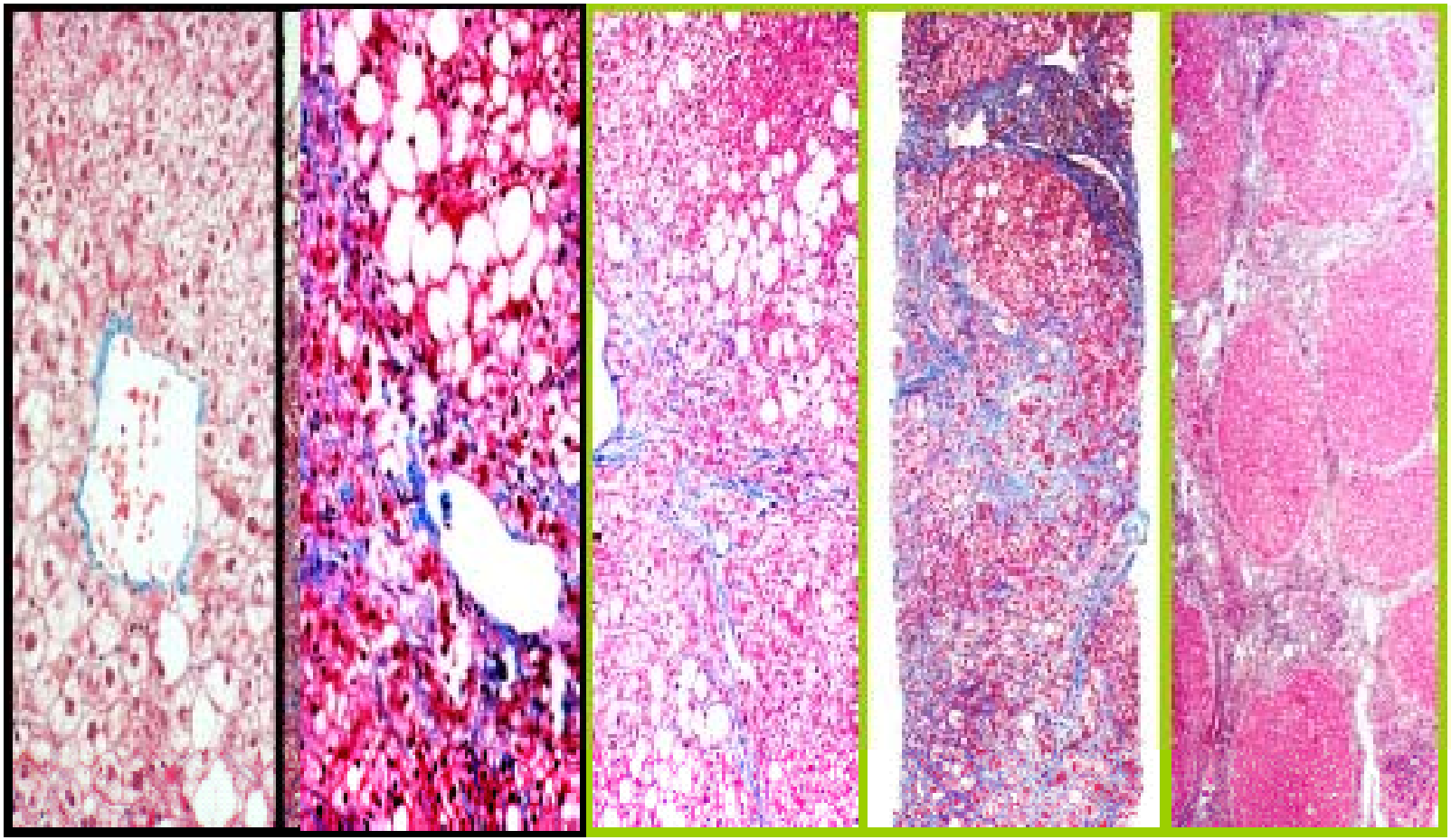


Younossi Clin Gastro Hepatol 2011

Spectrum of NAFLD







Stage 0 Stage 1 Stage 2 Stage 3 Stage 4

Perisinusoidal or portal

bridging

Perisinusoidal + portal

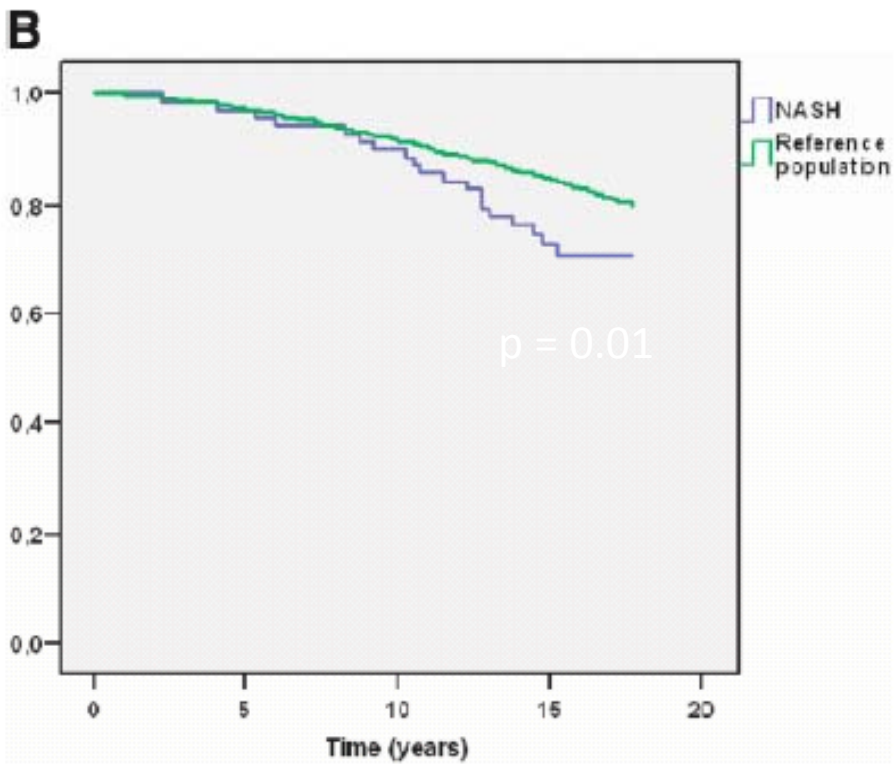
cirrhosis

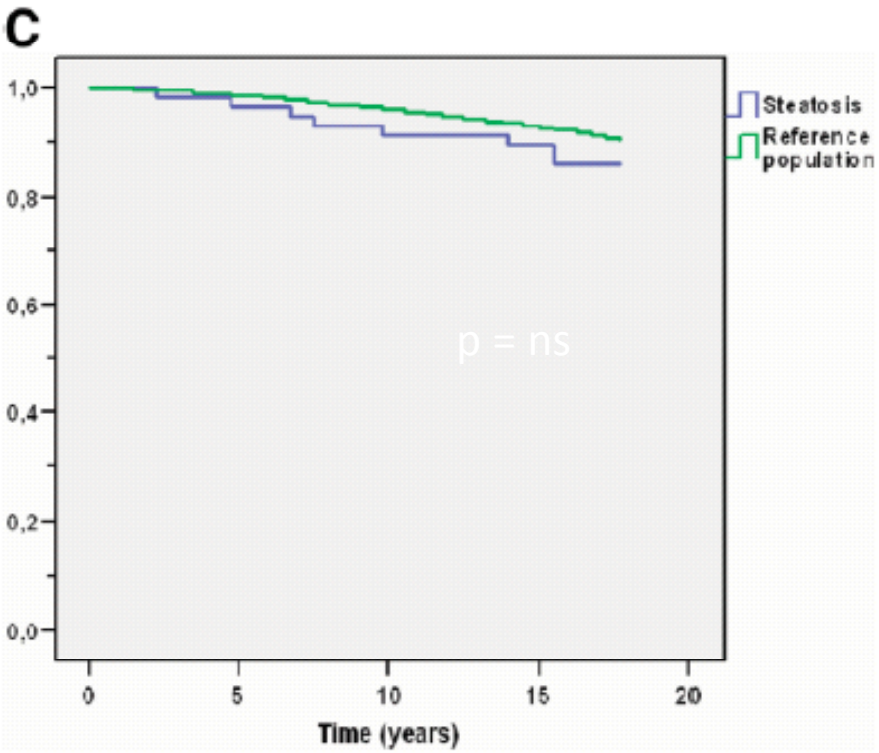
Prevalence of NAFLD/NASH

	NAFLD	NASH
General adult population, US	17-50%	3-5%
Metabolic syndrome	59%	
Dyslipidemia	50%	
Diabetes	50-70%	25-30%
Obese	70%	25-30%
Morbidly obese	90%	35%

Musso Annals of Medicine 2011, Chalasani Hepatology 2012

Survival is decreased in NASH, but not in simple steatosis





Ekstedt Hepatology 2006

Mortality is increased in NASH compared to simple steatosis

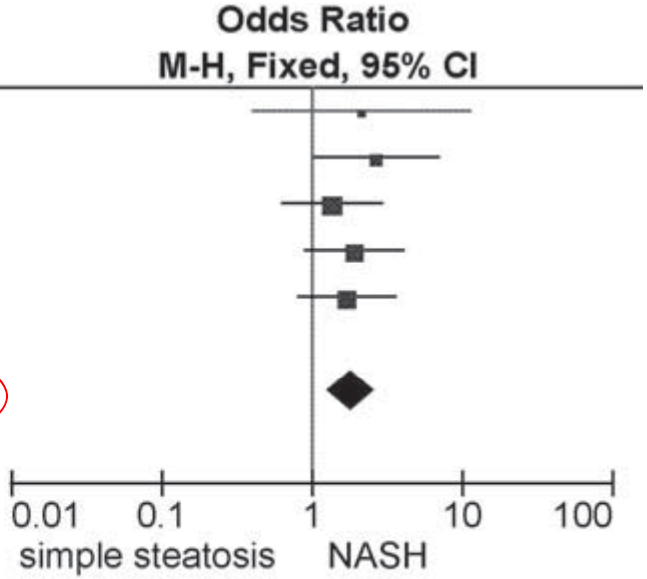
overall mortality

Study or Subgroup	Weight	Odds Ratio M-H, Fixed, 95% CI
Adams 2005	5.4%	2.13 [0.41, 11.15]
Ekstedt 2006	14.1%	2.66 [1.03, 6.87]
Matteoni 1999	28.9%	1.36 [0.64, 2.90]
Rafiq 2009	25.2%	1.91 [0.90, 4.04]
Soderberg 2009	26.3%	1.70 [0.81, 3.59]
Total (95% CI)	**100.0%**	**1.81 [1.24, 2.66]**

Total events

Heterogeneity: $Chi^2 = 1.26$, $df = 4$ ($P = 0.87$); $I^2 = 0\%$

Test for overall effect: $Z = 3.05$ ($P = 0.002$)



Musso Ann Med 2011

Liver-related mortality is increased in NASH compared to simple steatosis

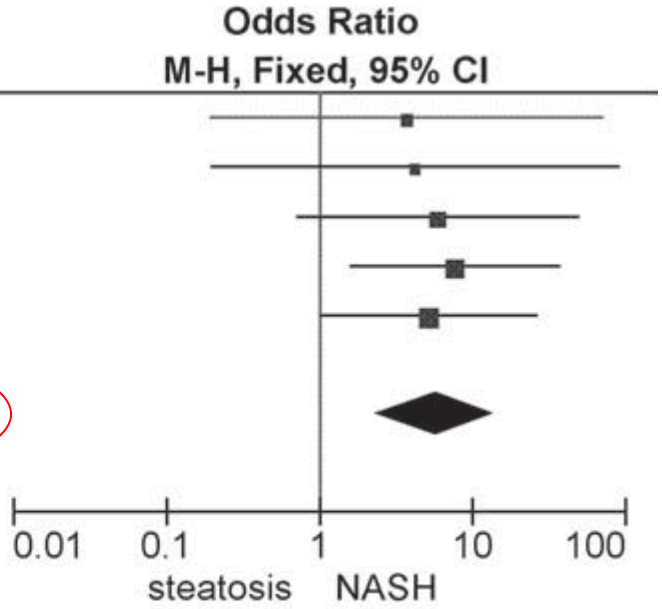
liver-related mortality

Study or Subgroup	Weight	Odds Ratio M-H, Fixed, 95% CI
Adams 2005	13.3%	3.71 [0.20, 70.19]
Ekstedt 2006	10.2%	4.21 [0.20, 89.42]
Matteoni 1999	20.4%	5.91 [0.71, 48.83]
Rafiq 2009	27.5%	7.66 [1.61, 36.52]
Soderberg 2009	28.6%	5.17 [1.03, 26.06]
Total (95% CI)	**100.0%**	**5.71 [2.31, 14.13]**

Total events

Heterogeneity: Chi² = 0.27, df = 4 (P = 0.99); I² = 0%

Test for overall effect: Z = 3.77 (P = 0.0002)

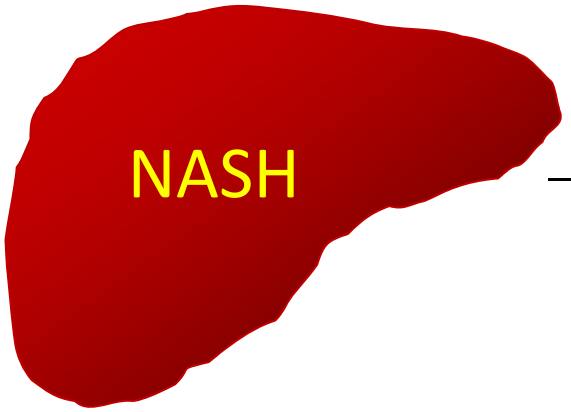


Musso Ann Medicine 2011

Take home point #1

- Not all patients with fatty liver are the same- important to distinguish patients with “simple steatosis” from those with NASH

Natural History of NASH



16% improvement

43% stable

41% fibrosis progression

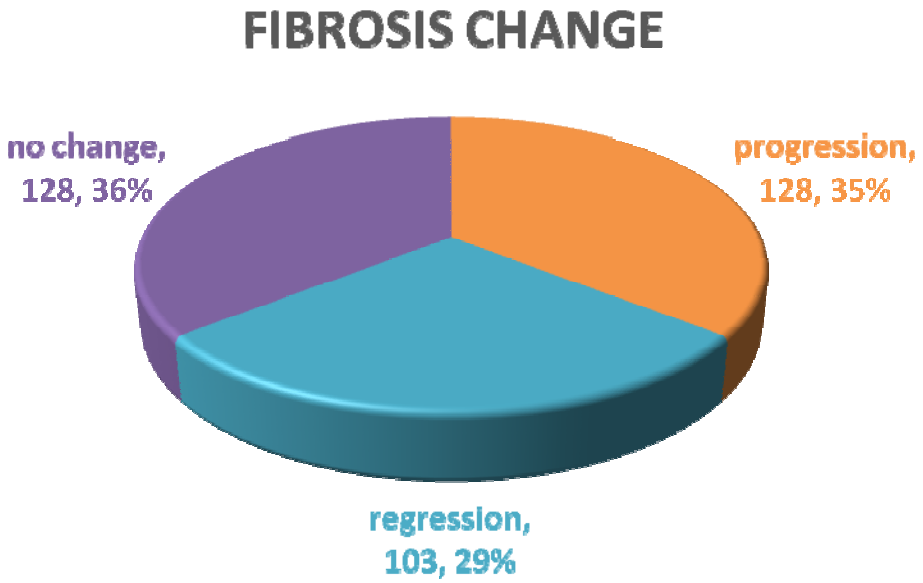
N = 68
mean follow-up 13.7 years

5.4% cirrhosis-related complications

Ekstedt Hepatology 2006

AASLD Liver Meeting 2013 Abstract #577 (Kleiner, et al): Natural History of Non-alcoholic Fatty Liver Disease in Adults: A Paired Biopsy Study from the NASH CRN

- n=359 patients
  mean age 47
  mean time between biopsies: 4.4 years
  (range: 1 – 17.3)



Factors associated with fibrosis progression:

Ballooning
Mallory-Denk bodies
Caucasian race

AASLD Liver Meeting 2013 Abstract #602: (Brunt, et al) Progression to bridging fibrosis in NAFLD over 4 years in the NASH CRN

- Aim: Identify predictors of progression to advanced stage NASH
- Methods:
  adults enrolled in NASH CRN with paired biopsies
  first biopsy fibrosis stage < 3
  endpoint- progression to bridging fibrosis or cirrhosis
- Compare baseline factors between progressors vs non-progressors

Abstract #602: (Brunt, et al)
Progression to bridging fibrosis in NAFLD over 4 years in the NASH CRN

- Results:
  270 patients
  mean 4.4 years between biopsies
  16% with progression to bridging fibrosis/cirrhosis

- Statistically significant baseline predictors of progressors as compared to non-progressors:

  older age
  higher ALT, AST, glucose
  DM
  metabolic syndrome

Abstract #602: (Brunt, et al)
Progression to bridging fibrosis in NAFLD over 4 years in the NASH CRN

Predictors of progression (multivariate model):

	OR	95% CI	p
Portal inflammation	2.14	1.01-4.53	0.047
Acidophil bodies	2.3	1.03-5.16	0.04
Mallory Denk bodies	4.91	1.68-14.37	0.004
Metabolic syndrome	6.46	0.98-42.53	0.05
ALT	5.24	1.78-15.40	0.003

Summary

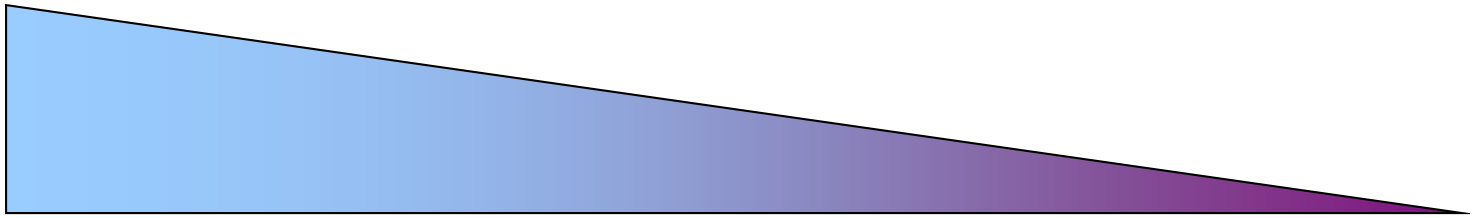
- Patients with NASH have a variable prognosis
- Older age, metabolic syndrome, DM, and elevated ALT correlate with progression to advanced fibrosis
- Baseline histologic features aid in prediction of fibrosis progressors
- Consider liver biopsy in patients with these high risk clinical features for fibrosis staging and prognosis estimation

Diagnosis

Clinical Presentation

Asymptomatic

Symptomatic

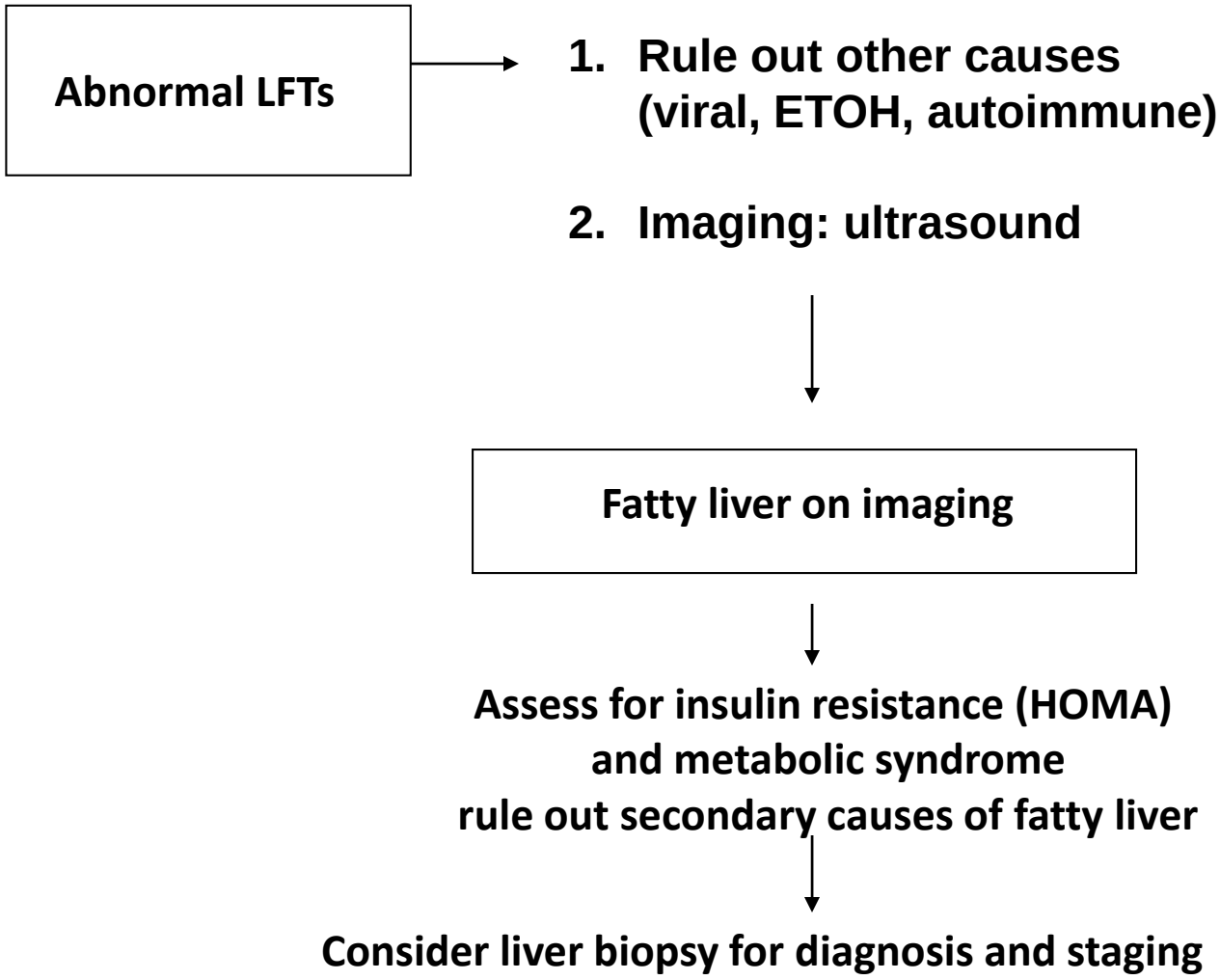


liver enzyme elevation
fatty liver on imaging

Decompensated cirrhosis
Hepatocellular carcinoma

hepatomegaly
fatigue

Clinical Approach:

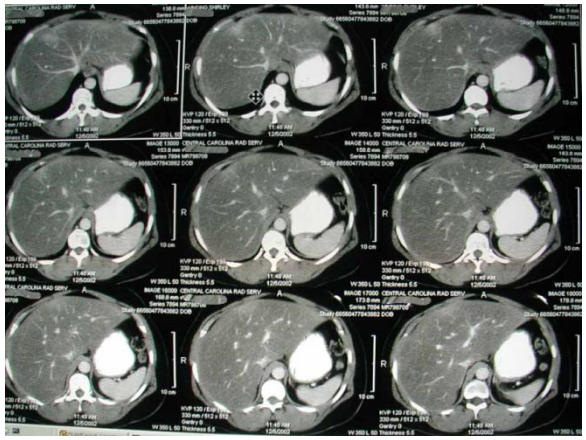


Challenges in the Diagnosis of NASH

- Imaging does not distinguish between simple steatosis and NASH
- Aminotransferases not reliable
- Liver biopsy subject to sampling variability
- Noninvasive tests for diagnosis and staging of NASH under investigation

Noninvasive diagnosis of steatosis

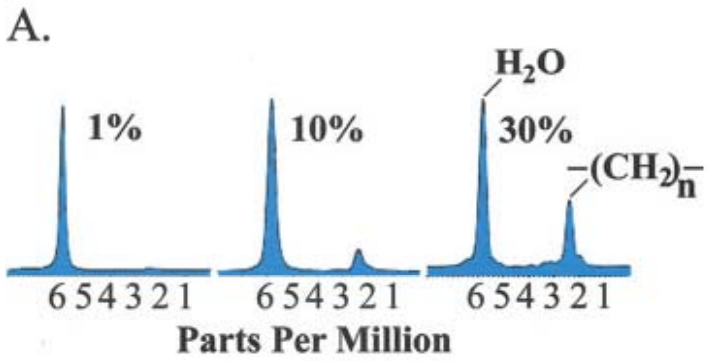
<u>Ultrasound</u>
Sensitivity 83-89%
Specificity 93-100%



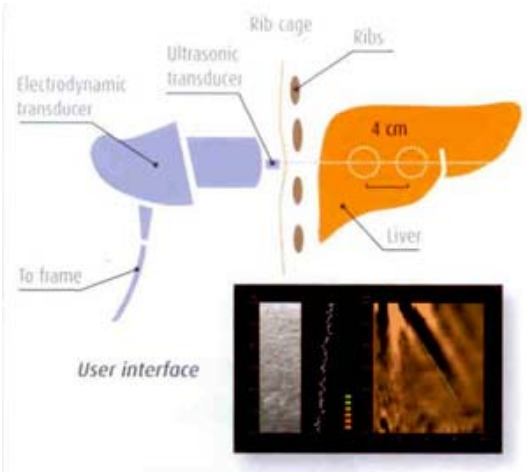
<u>CT</u>
Sensitivity 86%
Specificity 87%

Noninvasive diagnosis of steatosis

Magnetic Resonance Spectroscopy

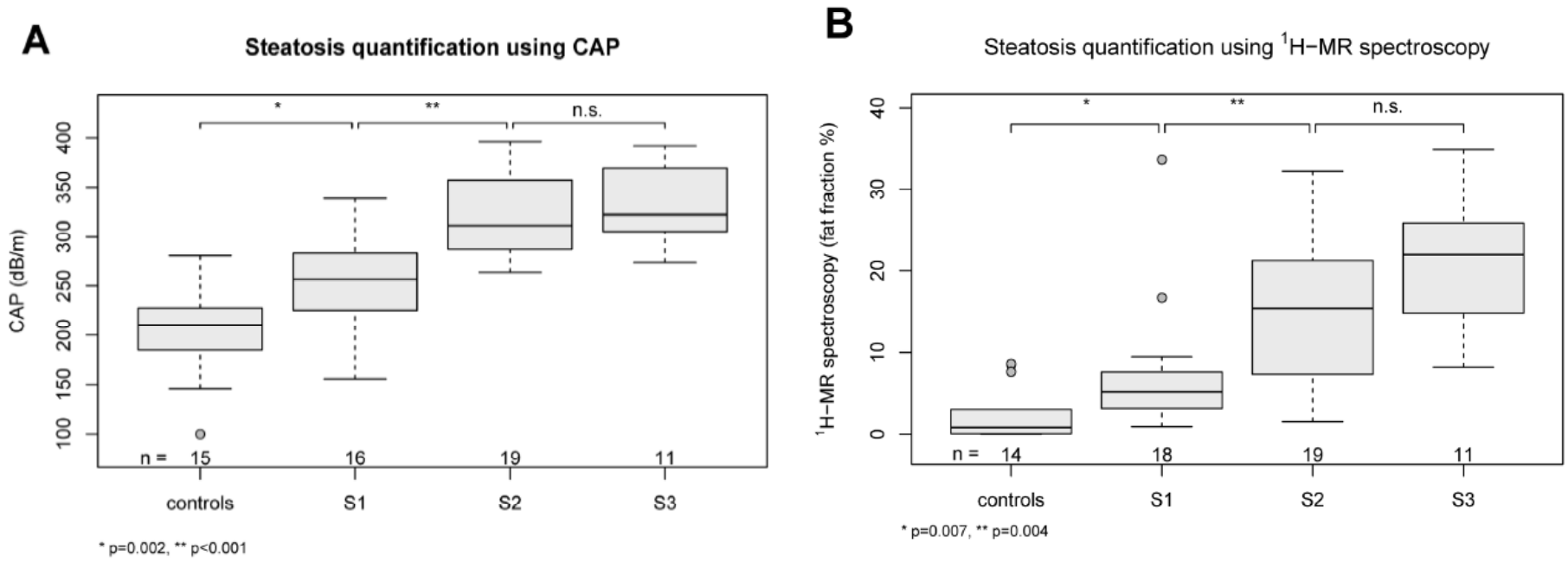


Transient Elastography- CAP



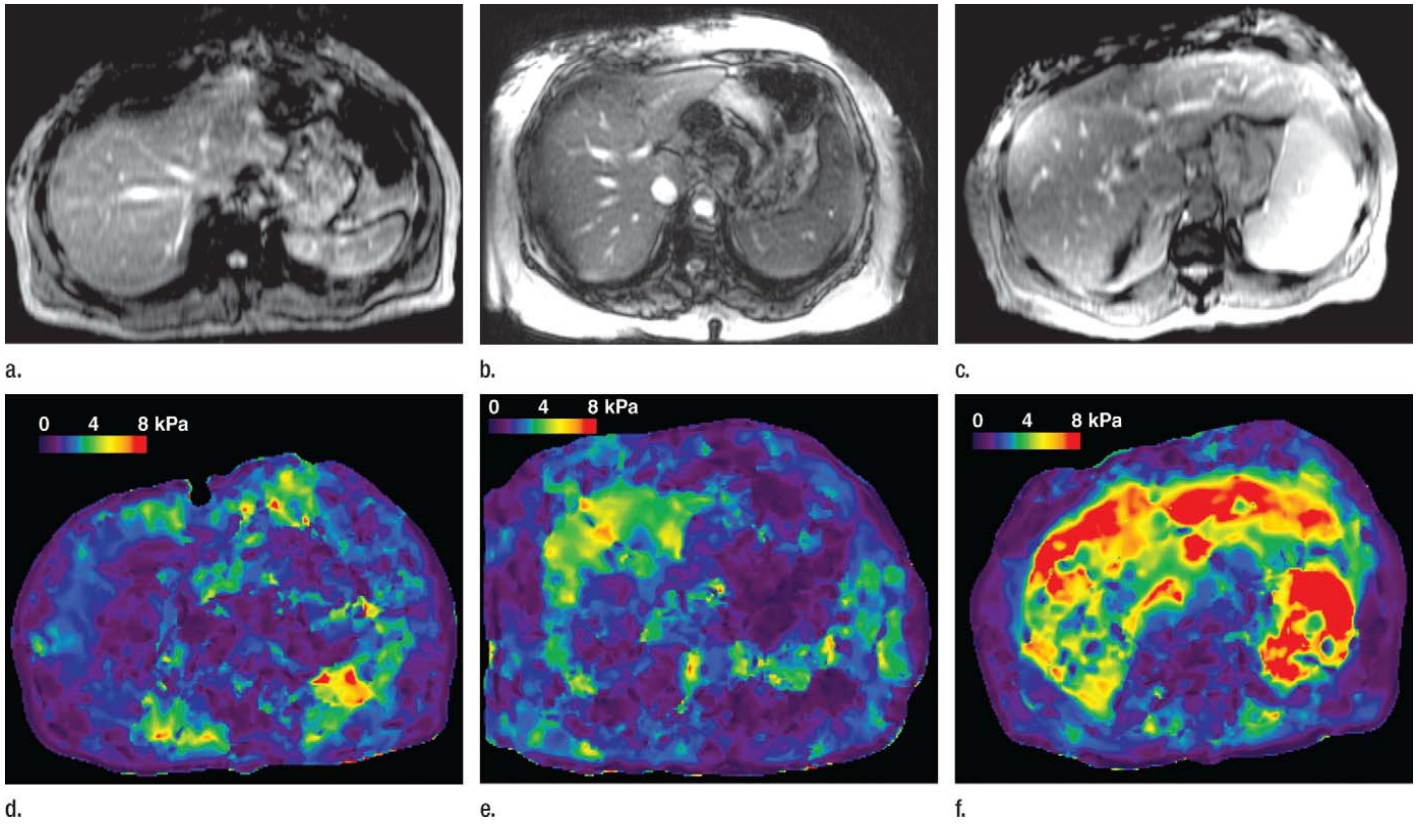
Sensitivity>90%

Controlled Attenuation Parameter



Karlas PLOS One 2014

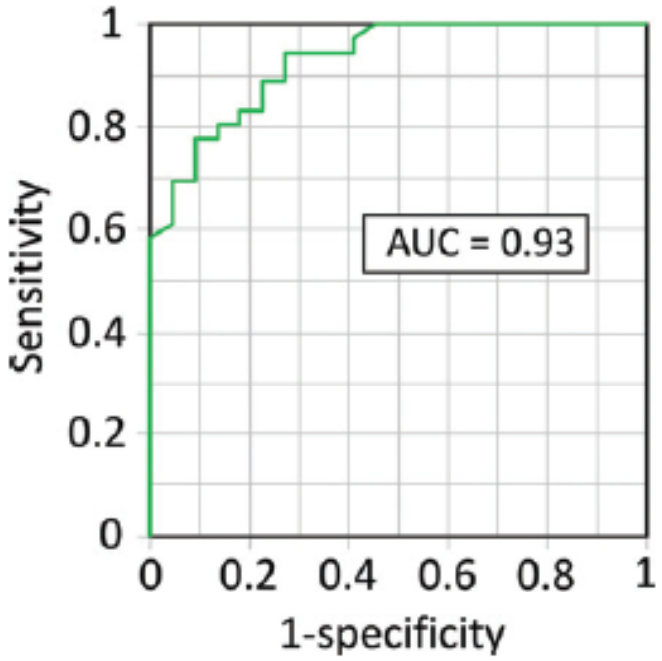
Magnetic Resonance Elastography



Simple steatosis inflammation without fibrosis fibrosis

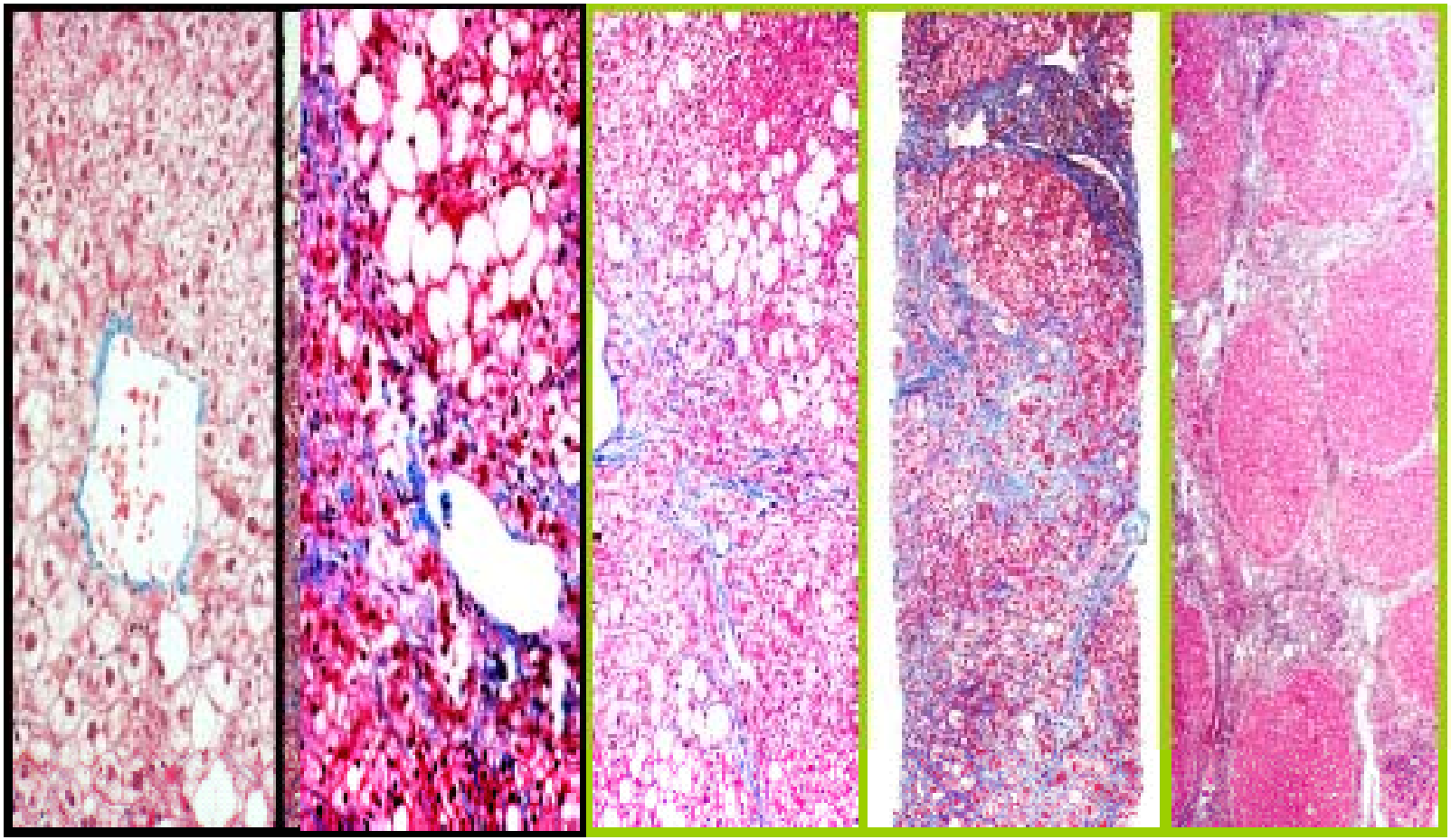
Chen Radiology 2011

MR Elastography for distinguishing NASH vs simple steatosis



Threshold (kPa)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
2.74	94	73	85	89
2.90	83	82	88	75

Chen Radiology 2011



Stage 0 Stage 1 Stage 2 Stage 3 Stage 4

Perisinusoidal or portal

bridging

Perisinusoidal + portal

cirrhosis

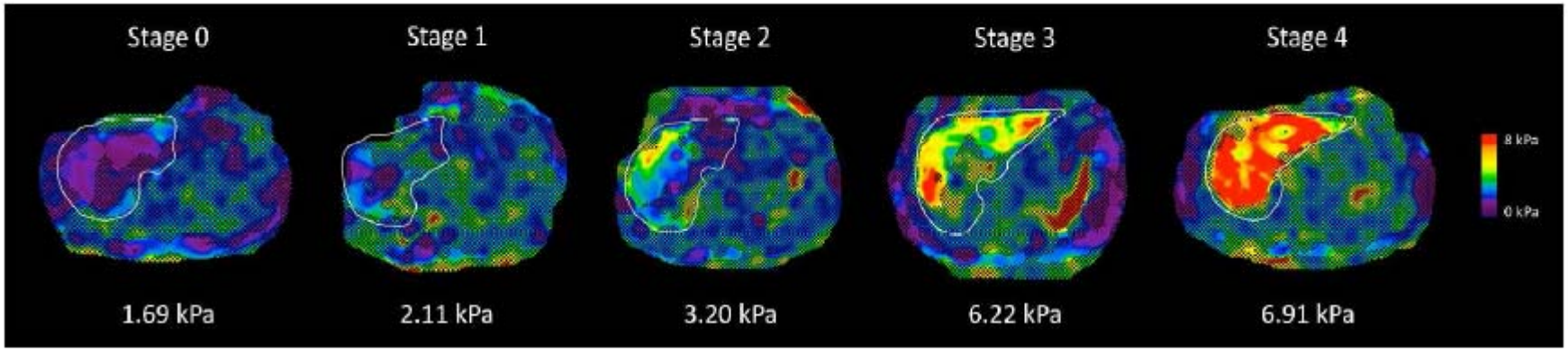


Figure 2. Distribution of fibrosis and MR elastography readings for the entire cohort

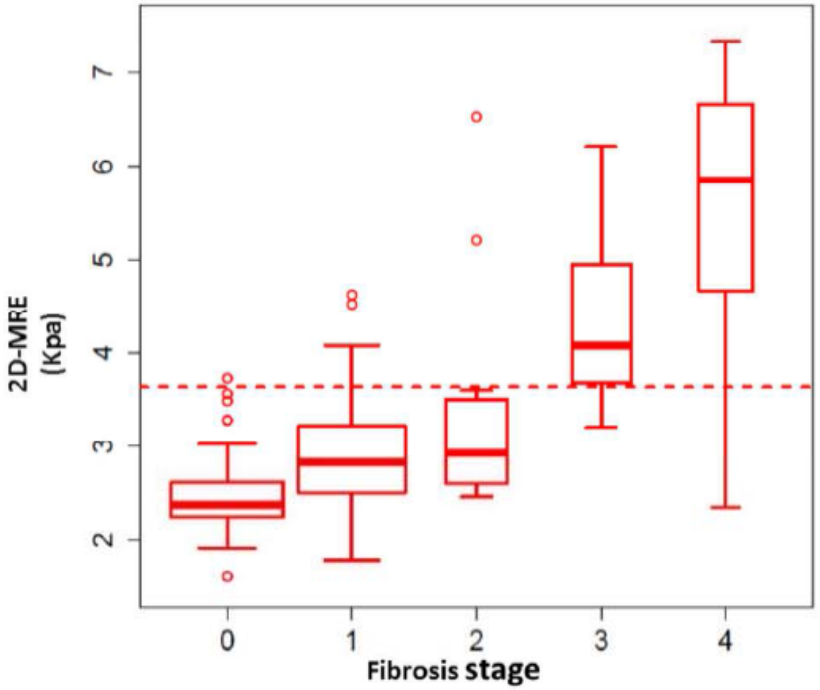


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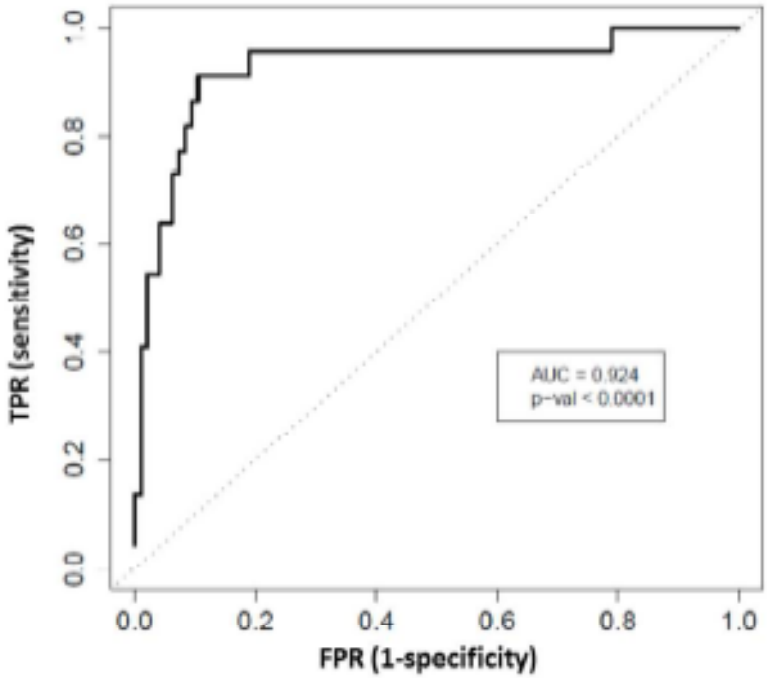
Figure 1. Diagnostic accuracy for MR elastography for advanced fibrosis in NAFLD



Sensitivity	0.86 (0.65-0.97)
Specificity	0.91 (0.83-0.96)
PPV	0.68 (048-0.84)
NPV	0.97 (0.91-0.99)

Loomba et al Hepatology 2014

Noninvasive scoring systems

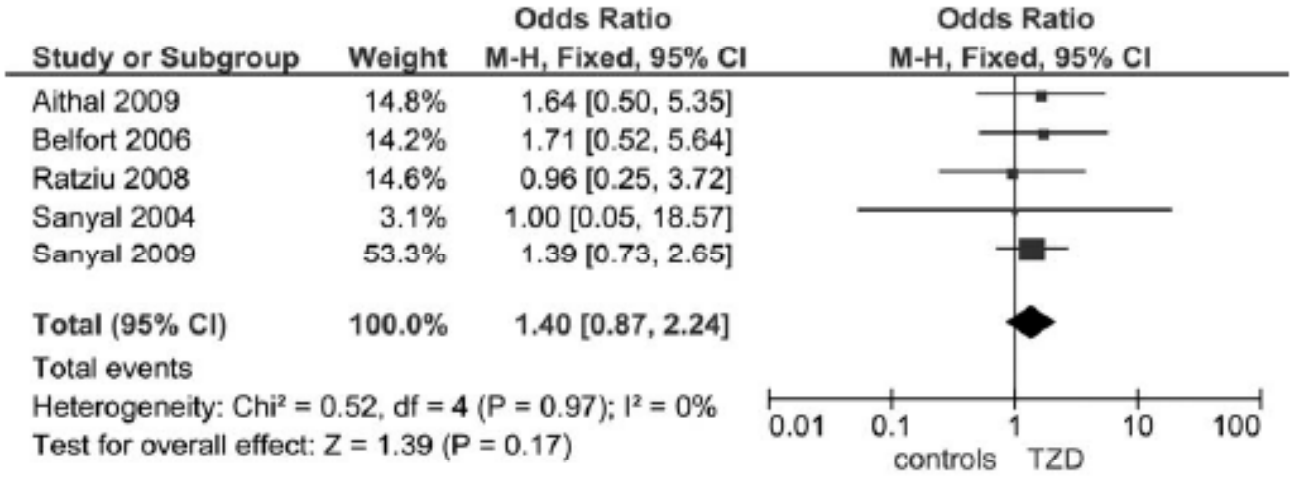
1. NAFLD Fibrosis score (http://nafldscore.com)
   - age, BMI
   - hyperglycemia
   - platelet count, albumin
   - AST/ALT ratio
2. APRI
   - AST/platelet ratio index
3. FIB-4 score
   - age, AST, platelets, ALT
4. BARD score
   - BMI, AST, ALT, DM

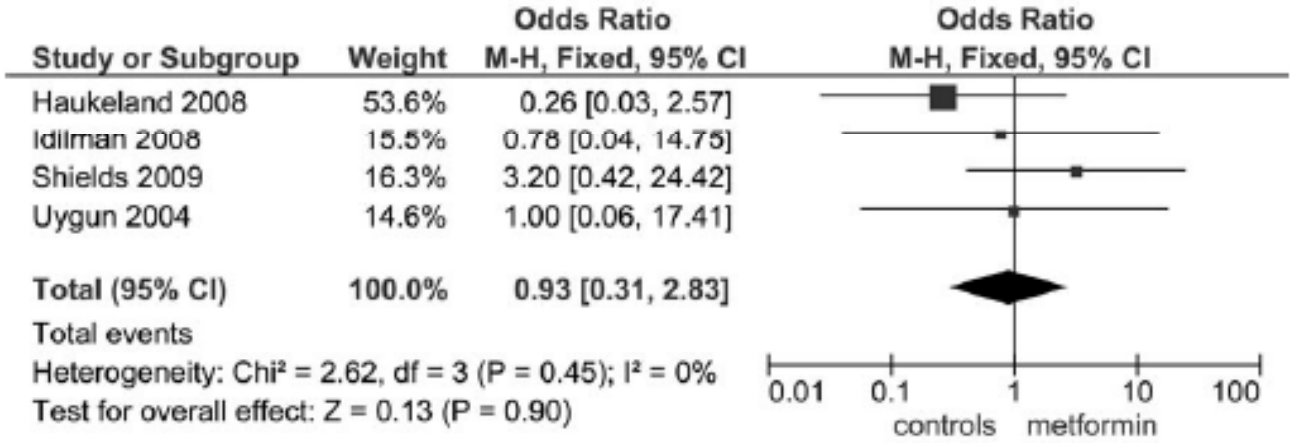
Treatment

Published randomized controlled treatment trials for NASH

- Insulin sensitizers
  - Pioglitazone — Belfort NEJM 2006; Sanyal NEJM 2010 (PIVENS)
  - Rosiglitazone — Ratziu Gastro 2008 (FLIRT); Ratziu Hepatol 2010 (FLIRT-2)
  - Rosiglitazone + Metformin — Torres Hepatol 2011
- Vitamin E — Sanyal NEJM 2010 (PIVENS)
- Pentoxifylline — Zein Hepatol 2011

Meta Analysis:
Insulin sensitizing agents for NASH





Musso Hepatology 2010

Challenges in identifying pharmacologic treatment for NASH

- Rebound effect after discontinuation of treatment
- Long term safety concerns:

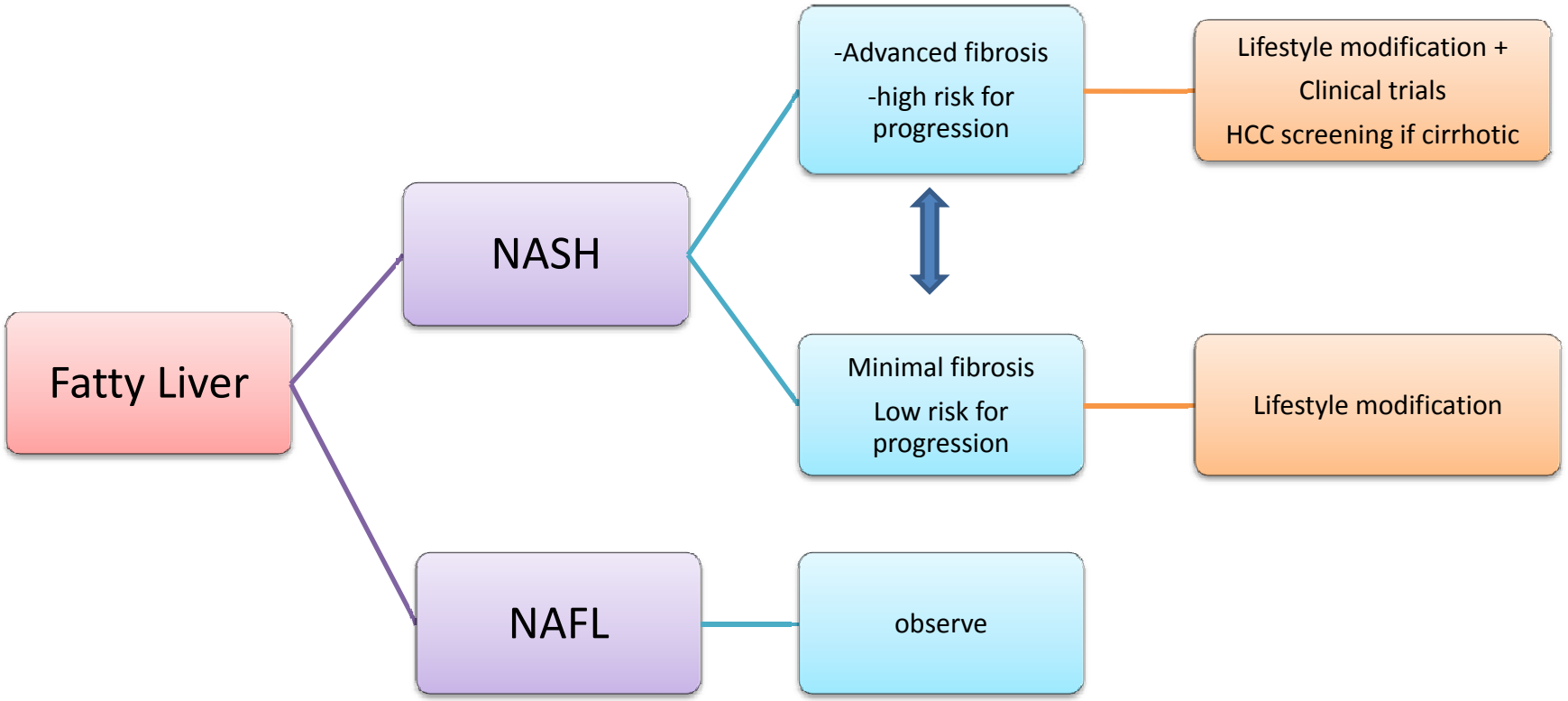
Rosiglitazone	Rosen NEJM 2010
Vitamin E	Miller Ann Int Med 2005
	Klein JAMA 2011

- Identification of appropriate therapeutic targets
  - insulin resistance
  - inflammation
  - altered lipid metabolism
  - obesity
  - fibrosis
- Validation of noninvasive markers of disease activity and staging

Current management approach

- Lifestyle modification
  - weight loss
    - (3-5% improves steatosis
    - >9% improves necroinflammation)
  - exercise
  - diet
- Diagnose and manage any comorbid features of metabolic syndrome

NAFLD: proposed clinical approach



Summary

- Patients with NASH have a variable risk for disease progression
- Older age, DM, metabolic syndrome and elevated ALT are associated with advanced fibrosis
- Effective pharmacologic treatments are still lacking
- Target higher risk individuals for staging liver biopsy, aggressive lifestyle modification, and therapeutic clinical trials
- Don’t overlook comorbid metabolic syndrome in patients with NASH- cardiovascular disease remains the leading cause of mortality in patients with NASH