Evaluation and Management of Alcohol-associated Liver Disease

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Disclosures

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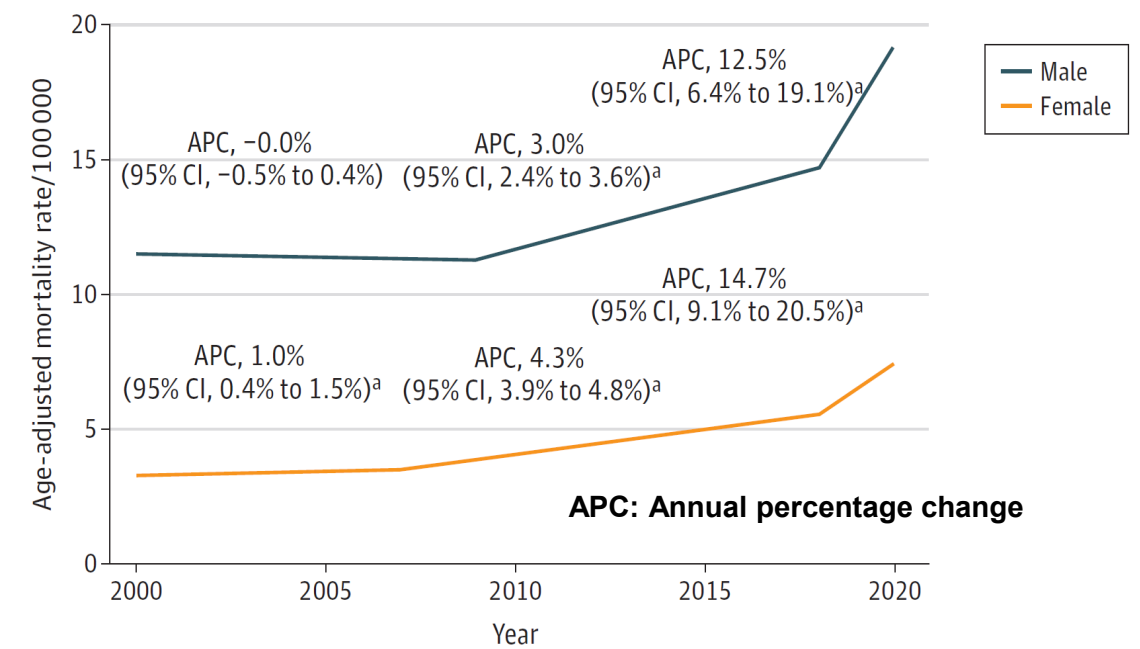
- Consulting: TransMedics, Pfizer, Spruce

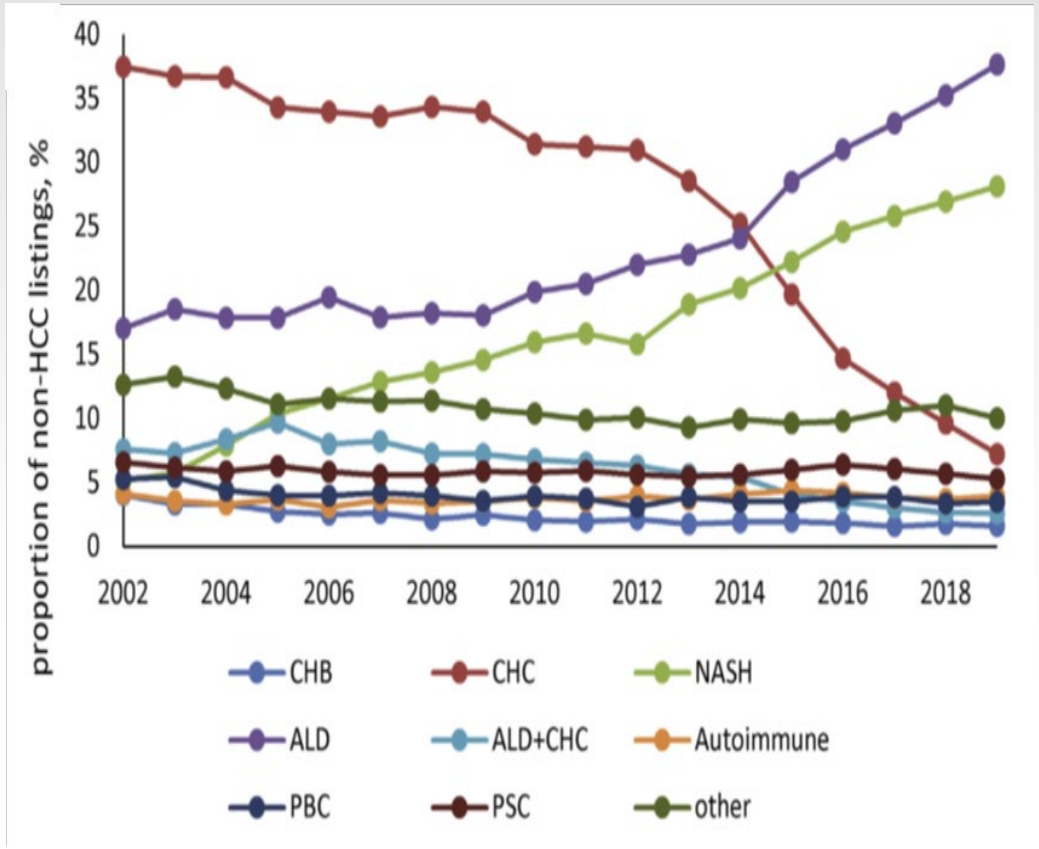
Outline

- Healthcare impact
- What is harmful/hazardous alcohol use?
- Spectrum & presentation
- Factors affecting risk
- Diagnosis
- Prognosis
- Management

Increasing alcohol-related mortality and liver transplant listing for ALD in US

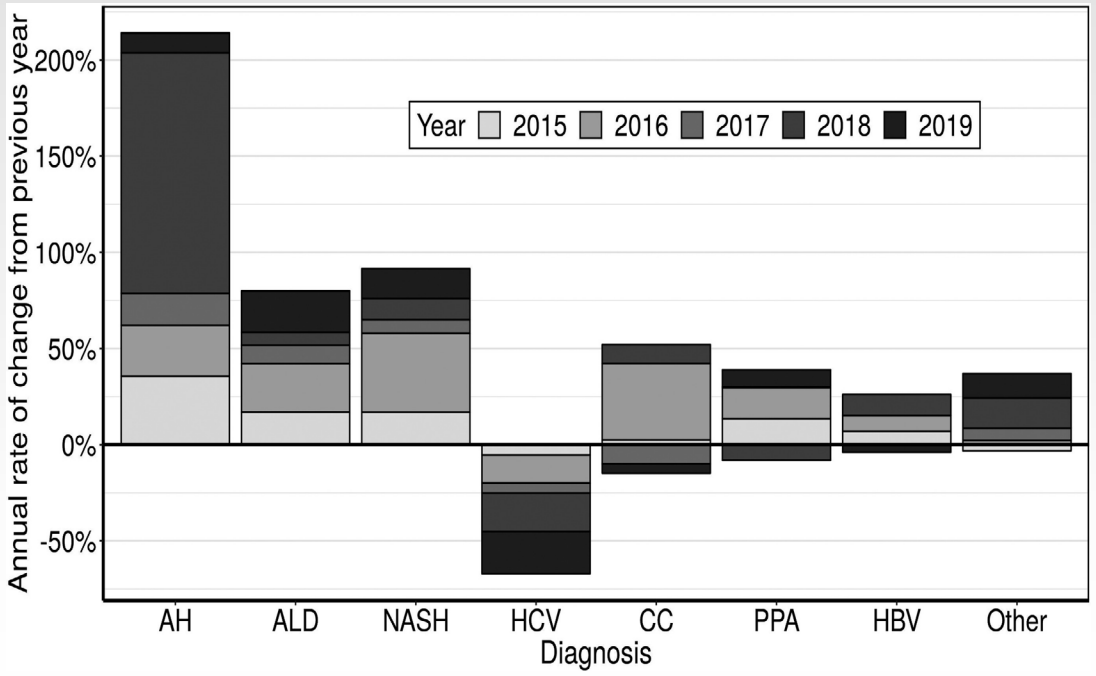


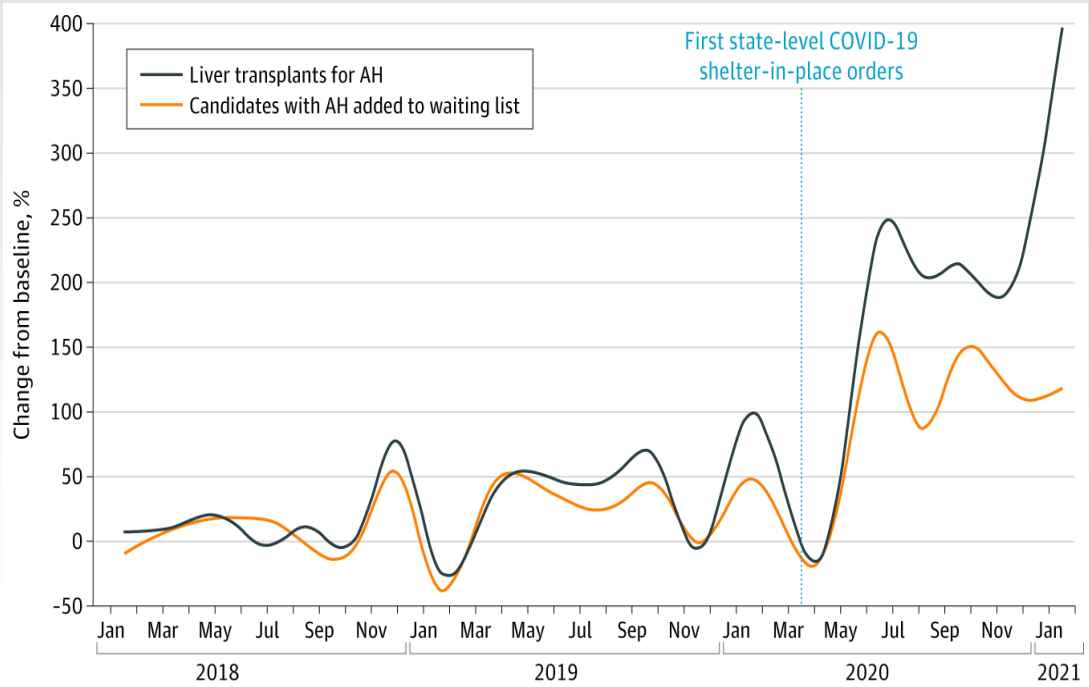
Karaye IM et al. JAMA Open 2023



Younossi Z et al. Clin Gastroenterol Hepatol. 2021

Increased rates of liver transplant listing for severe alcohol-associated hepatitis (AH) in the US





Cotter TG. Am J Transplantation 2021

Bittermann T et al. JAMA Open 2021

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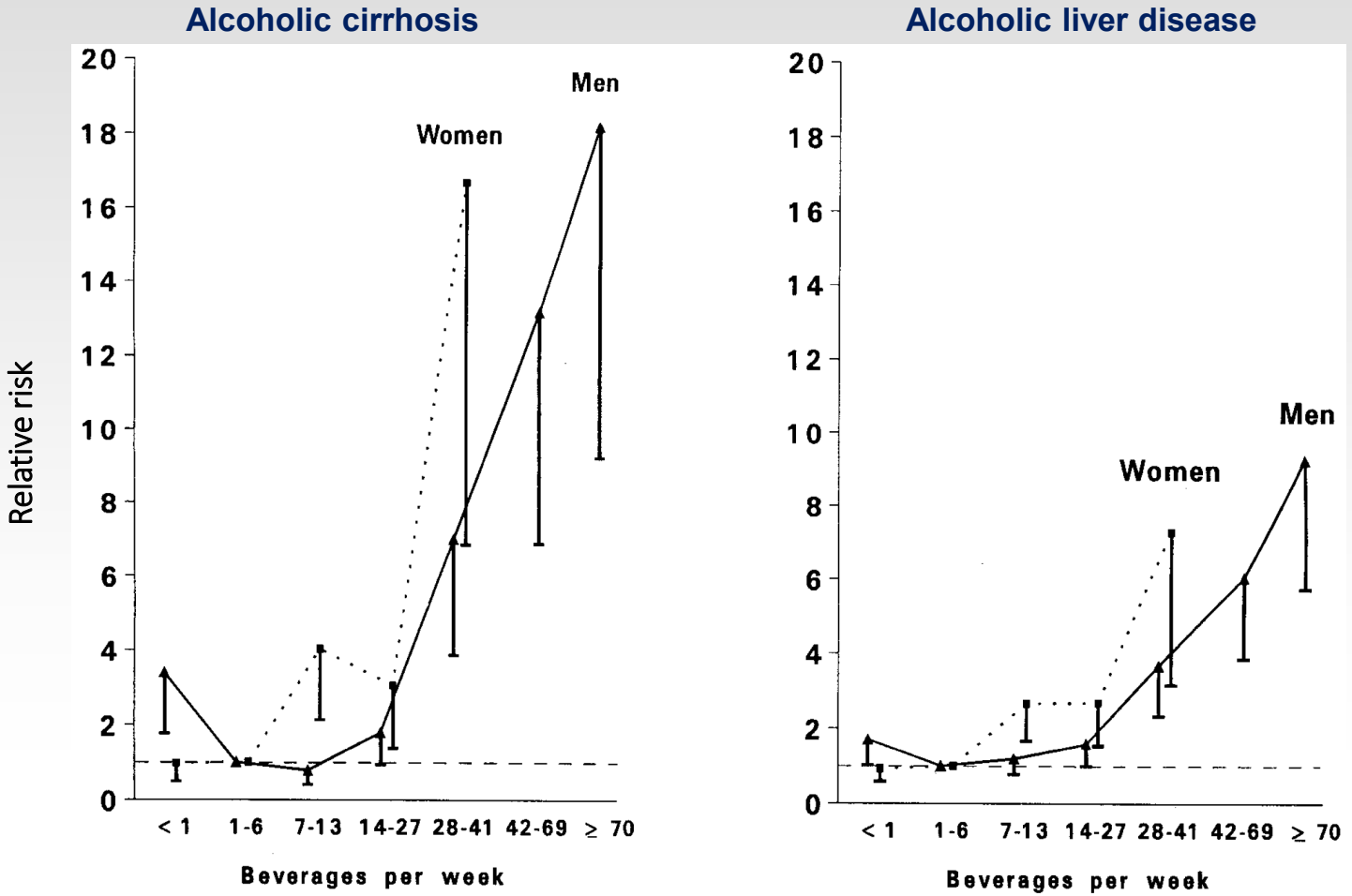
Rethinking harmful/hazardous alcohol use

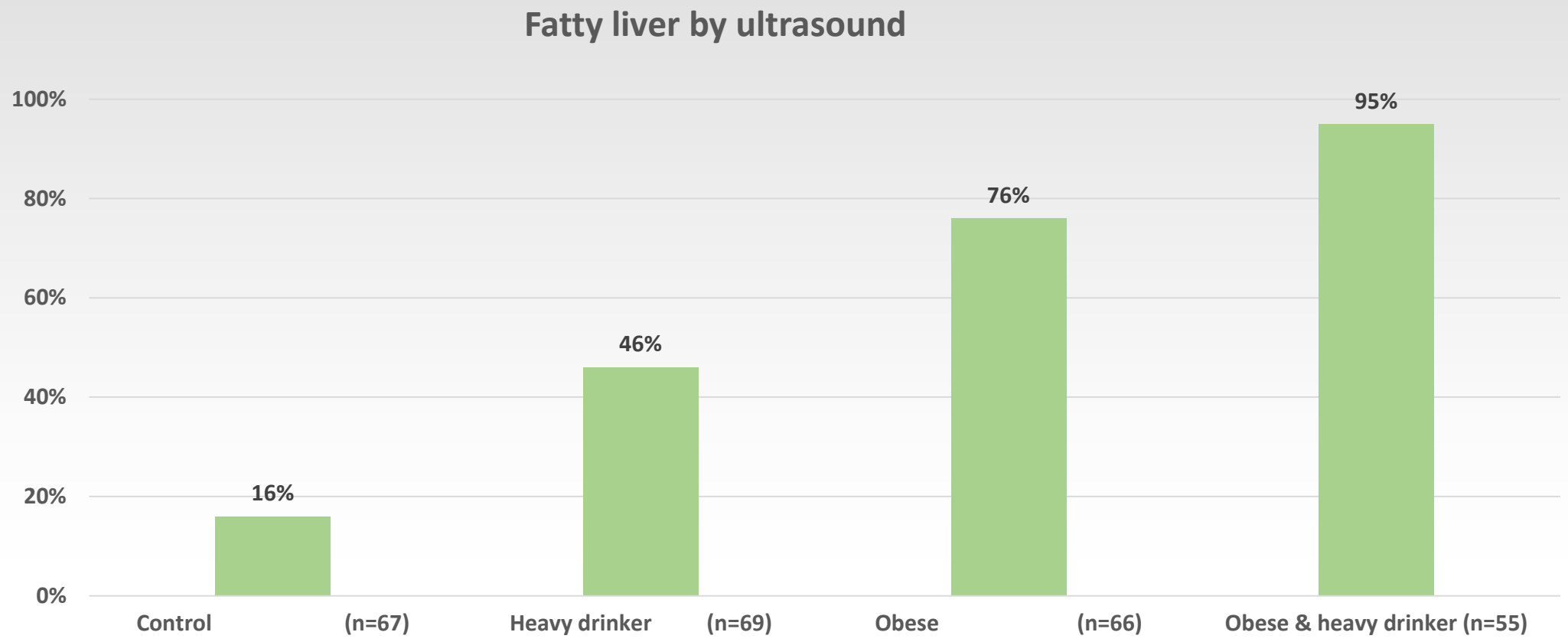
Women are at higher risk for alcohol associated liver disease at lower levels of consumption than men



Becker U et al. Hepatology 1996

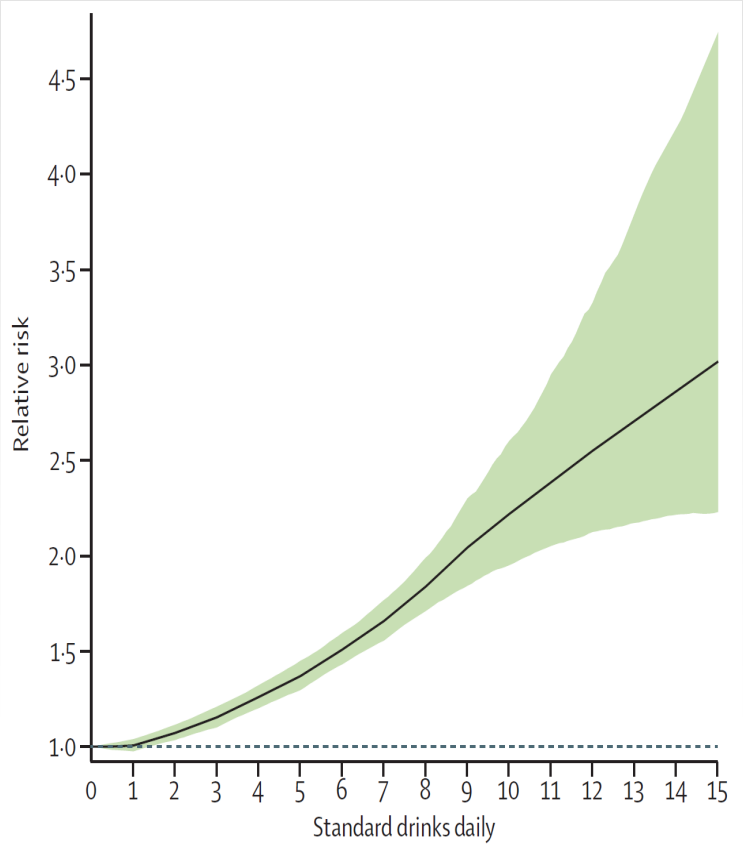
Alcohol synergy with obesity increases the risk of fatty liver

Metabolic dysfunction and alcohol-associated liver disease (MetALD)



Bellentani S et al. Ann Intern Med 2000

What's hazardous/harmful alcohol use?



> 1 drink for women

> 2 drinks for men

One standard drink:

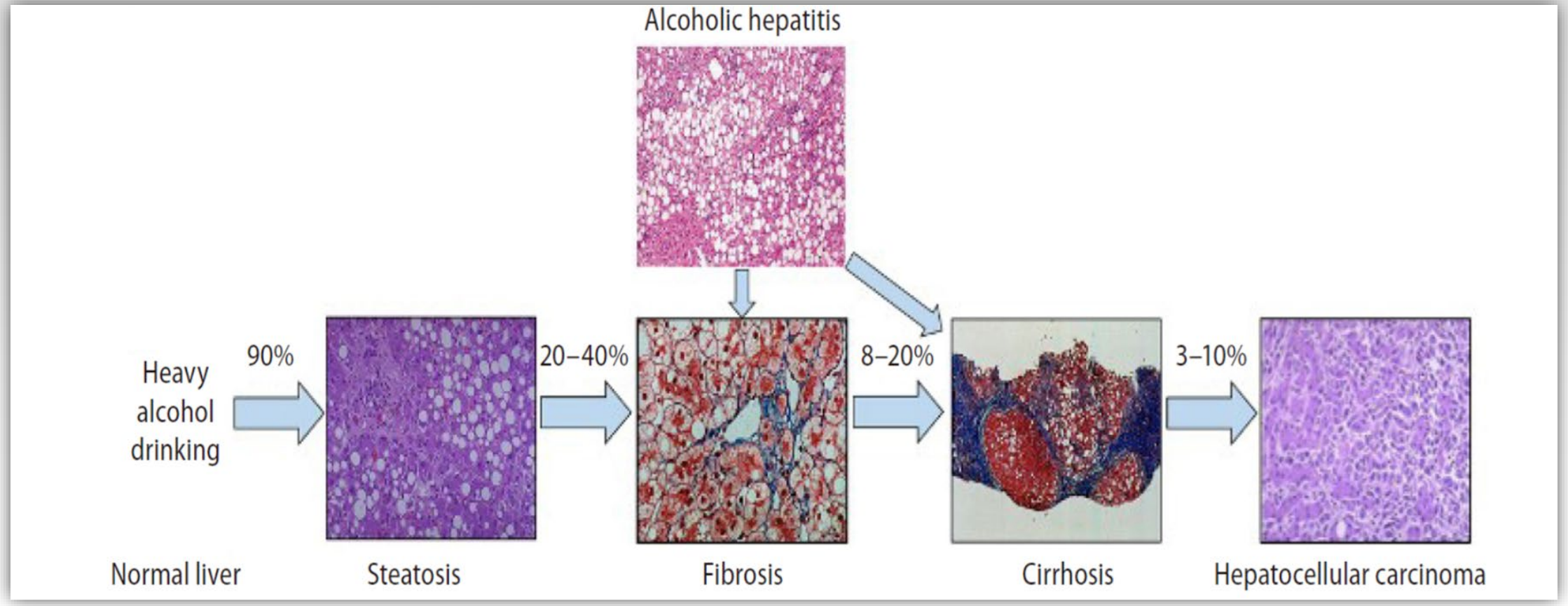
14 g of alcohol

GBD 2016 Alcohol Collaborators. Lancet 2018

Dietary Guidelines for Americans, 2020-2025. 9th Edition. 2020

Spectrum of ALD

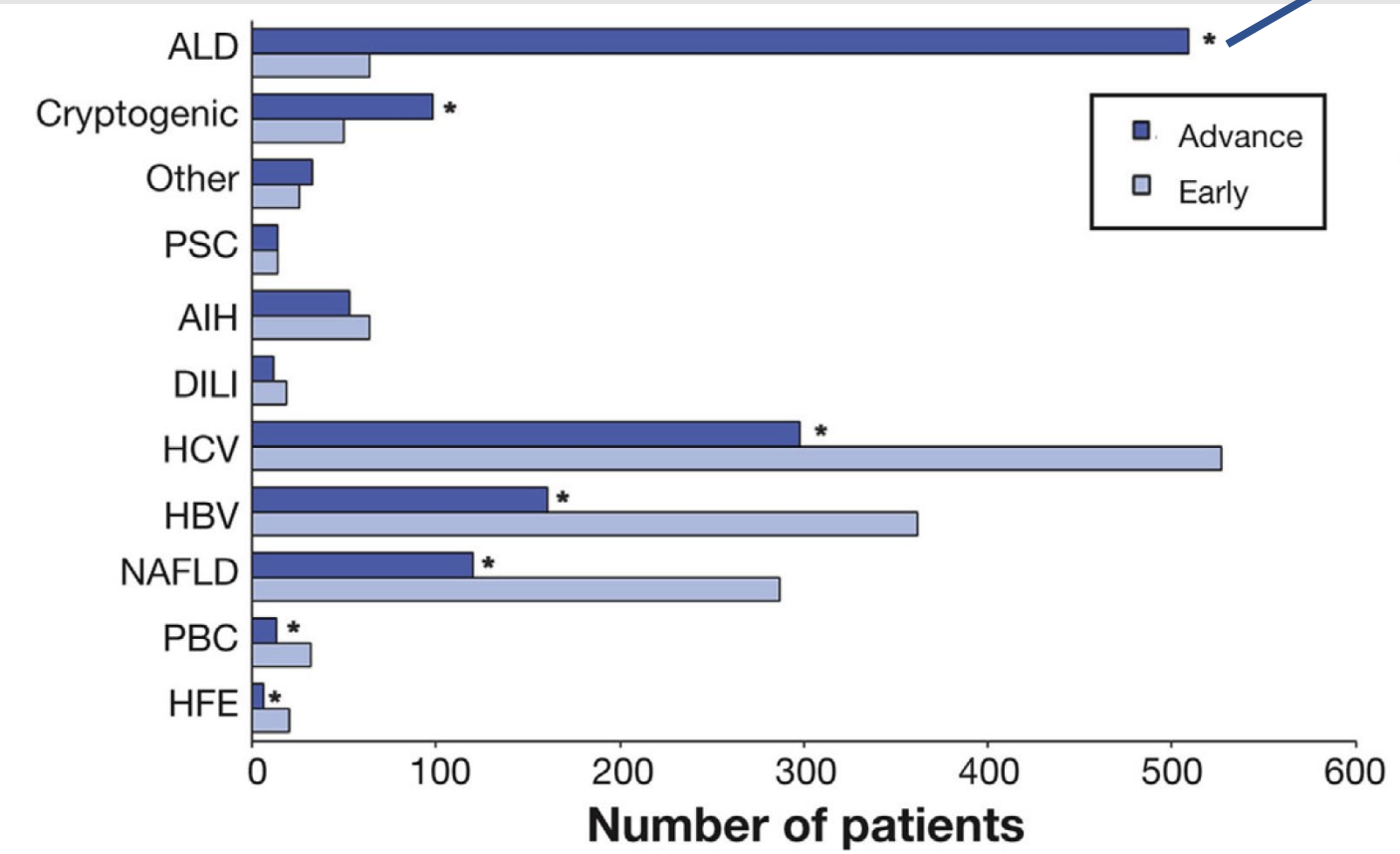
Asymptomatic/subclinical → Symptomatic



Gomez-Medina C et al. Clinical and Molecular Hepatology 2023

ALD is usually detected late compared to other liver diseases

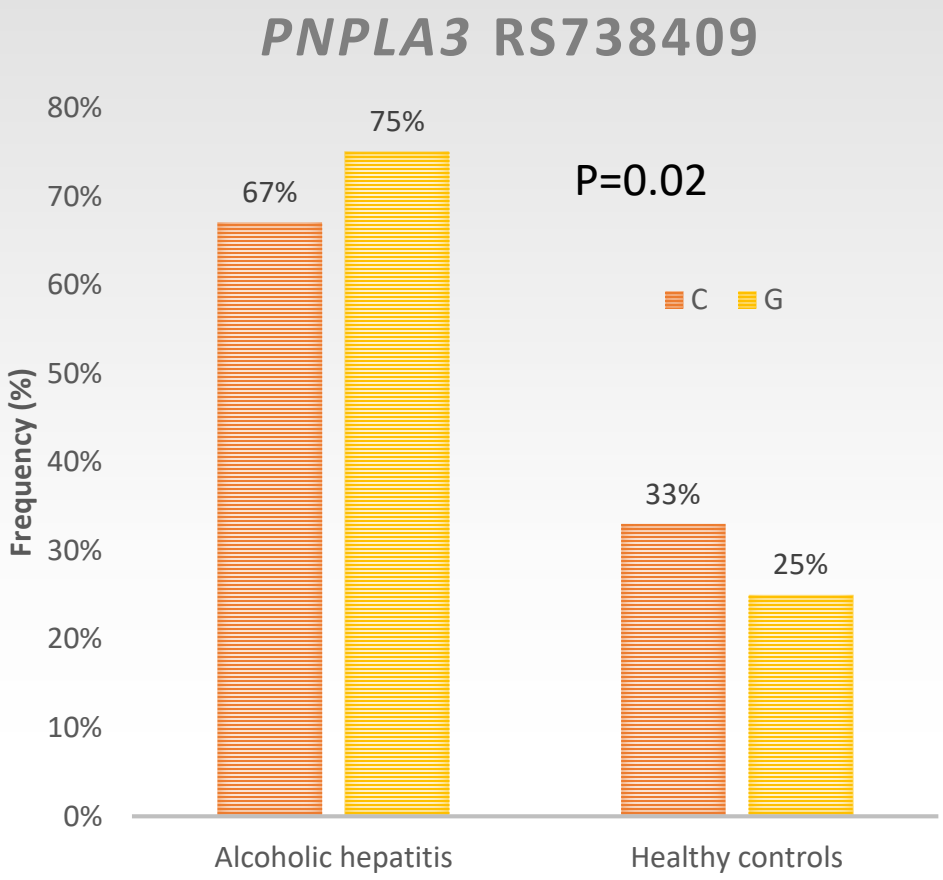
Aim for early screening in practice to detect early

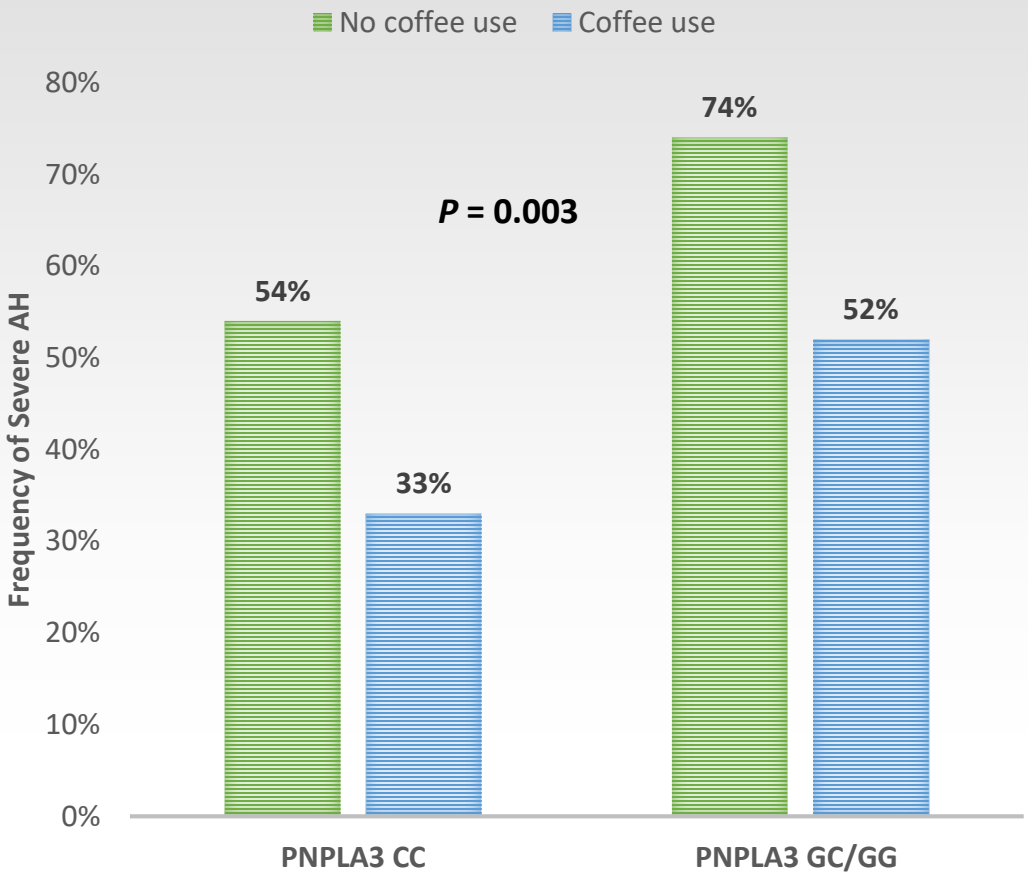


Shan ND et al. Clin Gastroenterol Hepatol. 2019

Factors affecting ALD risk

PNPLA3 and coffee influence risk and severity of AH





Beaudoin JJ. Alcohol Clin Exp Res 2021

Samala N et al. GastroHep 2019

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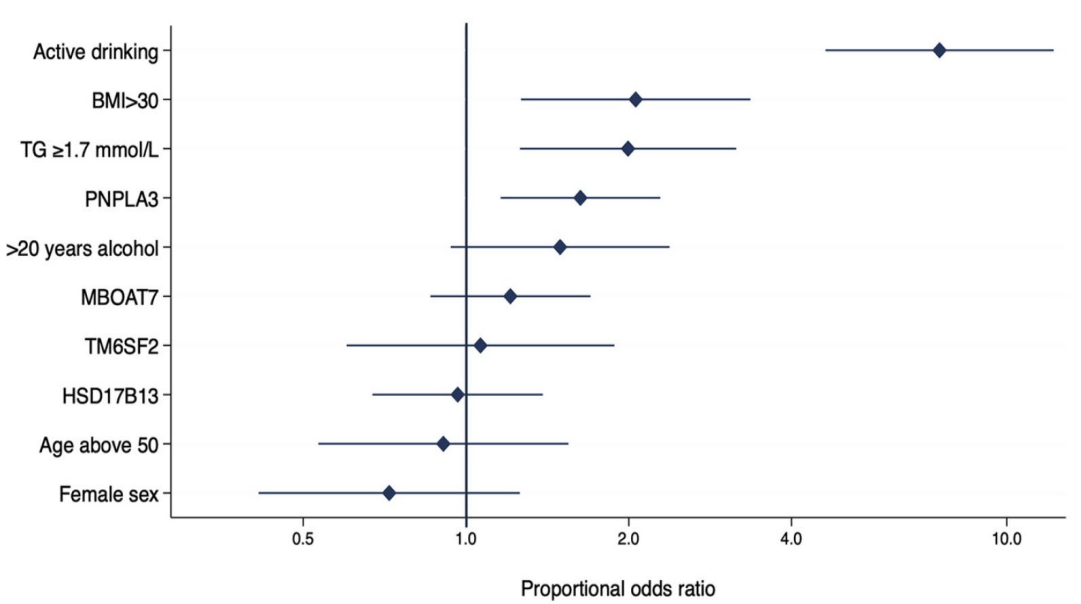
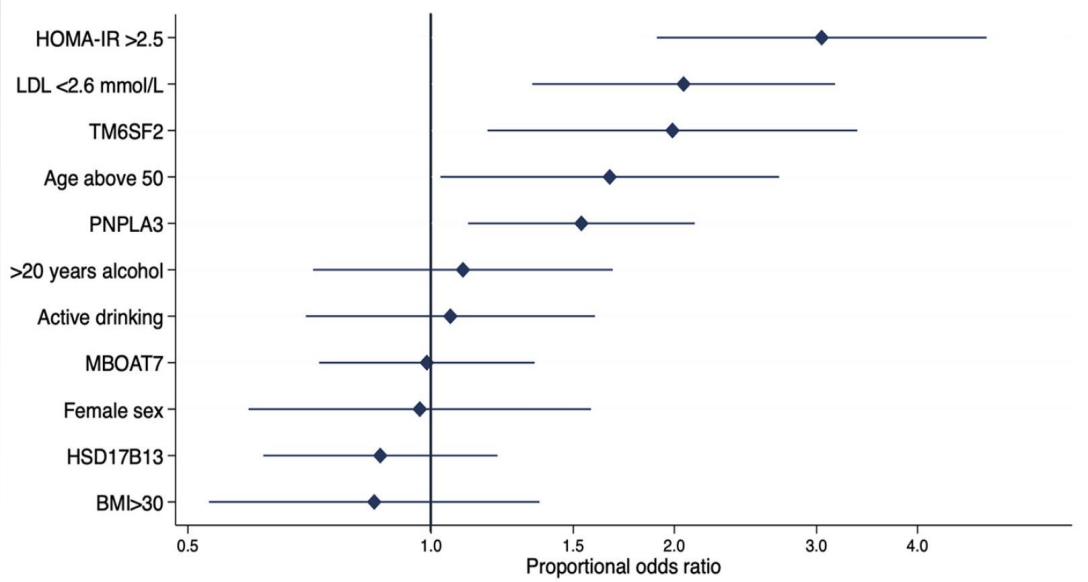
Metabolic and genetic risk factors are associated with severity of ALD

325 Danish patients with biopsy-proven ALD

Steatosis



Fibrosis



Israelsen M et al. Clin Gastroenterol Hepatol. 2022

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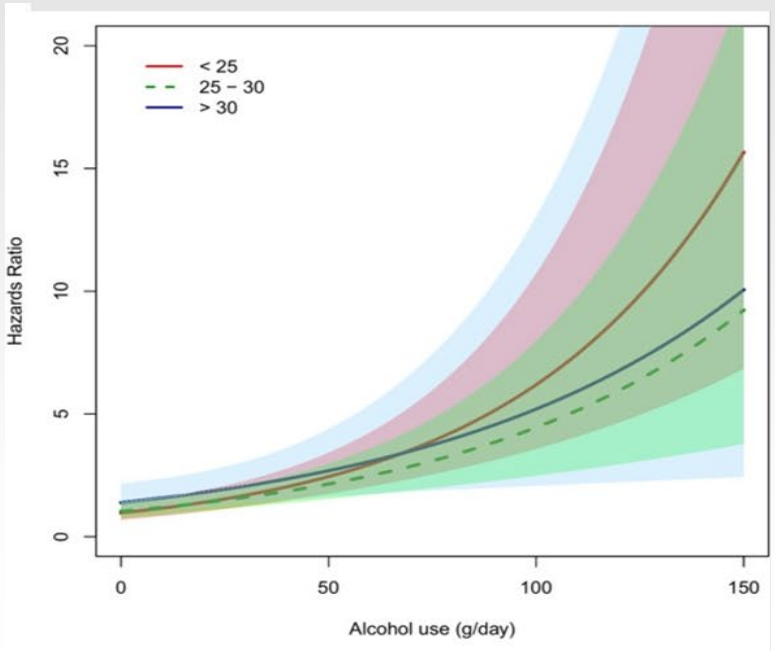
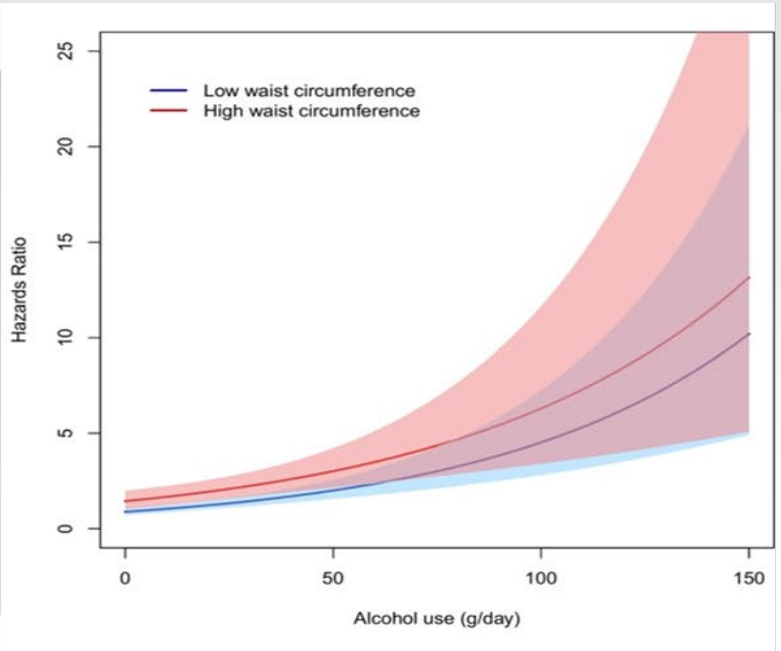
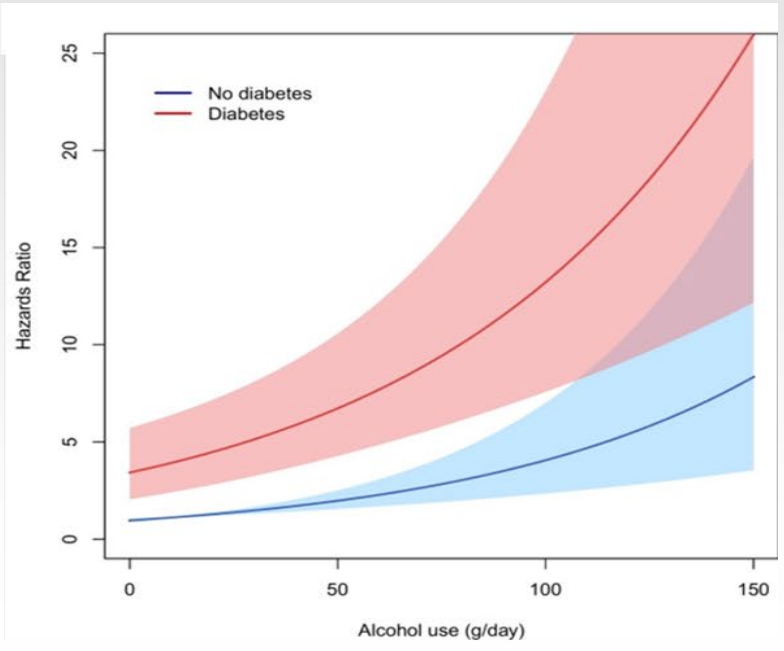
Synergy of alcohol and the metabolic syndrome increases the risk of incident severe liver disease*, even with MAC

6732 Finnish persons, no baseline liver disease. * Hospitalization, liver cancer, or death. Mean follow-up 11.4 years







Aberg F et al. Hepatology 2018

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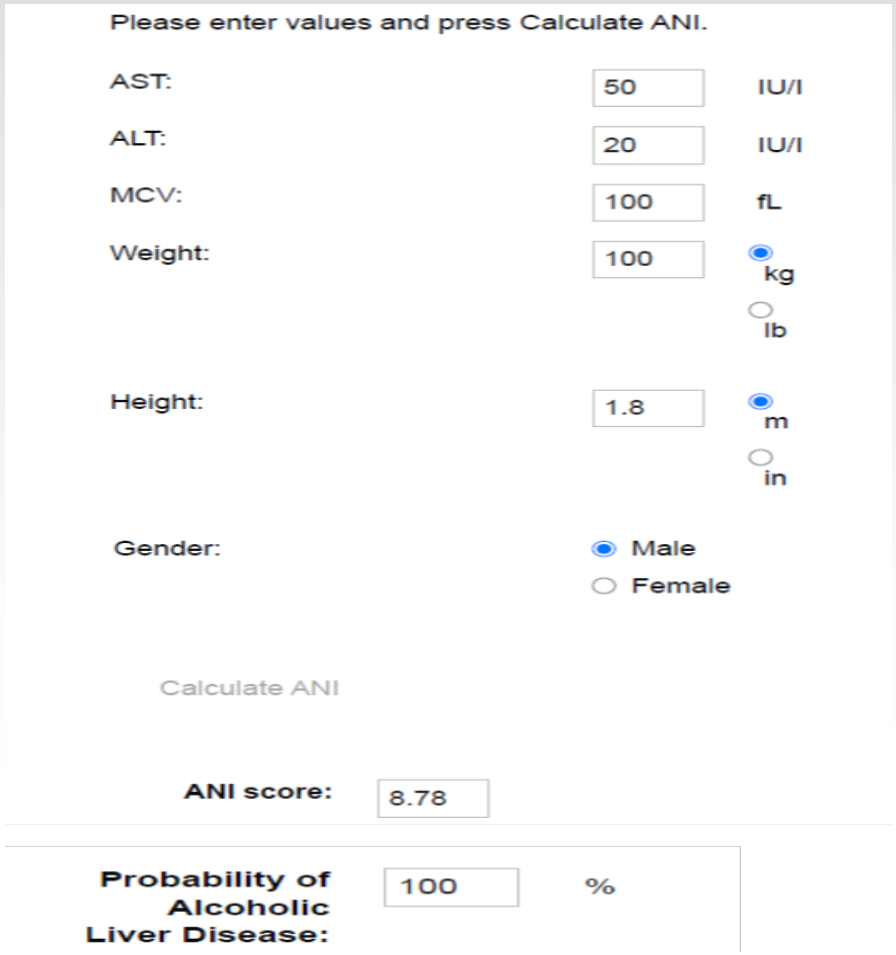
ALD-Diagnosis

Is steatostic (fatty) liver disease alcohol- related?

- Thorough alcohol use history
- Laboratory parameters (MCV, AST/ALT, GGT)
- Mayo's ALD/NAFLD Index (ANI)*



*Dunn W et al. Gastroenterology 2006

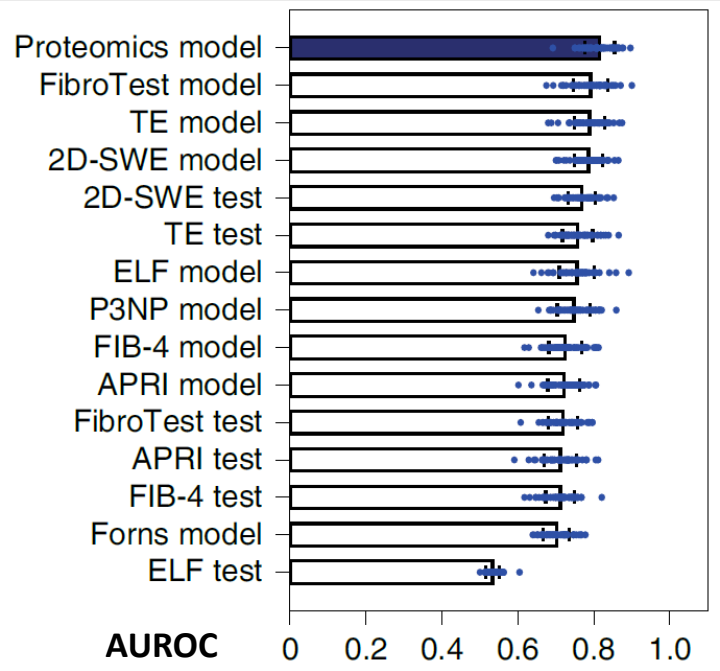
Biomarkers of alcohol use

Test	Source	Detection Time	Sensitivity	Specificity	PPV	NPV
CDT/%CDT*	Blood	2-3 weeks	21%-50%	50%-100%	64%-100%	86%-93%
EtG	Urine	3-7 days	76%-89%	93%-99%	81%-90%	91%-99%
EtG	Hair	Months	81%-100%	83%-98%	68%-95%	86%-100%
EtS	Urine	3 days	82%	86%	70%	93%
PEth	Blood	2-4 weeks	97%-100%	66%-96%	85%	100%

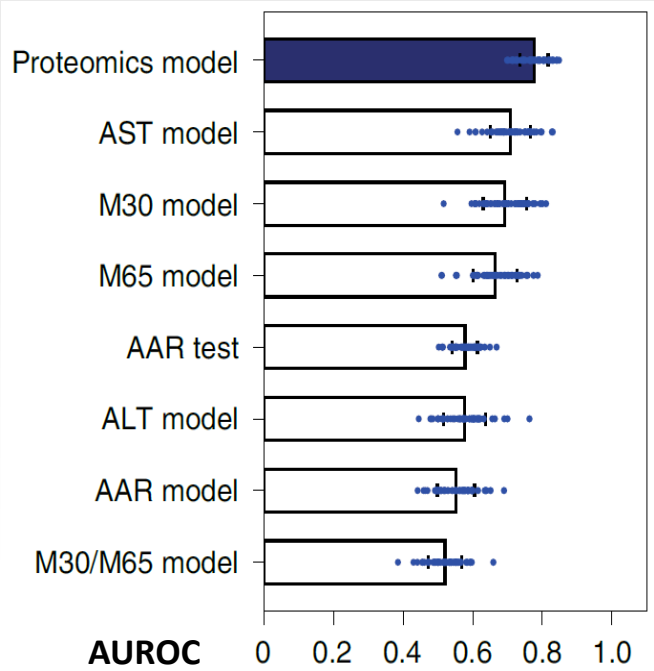
Modified from Crabb DW et al. Hepatology 2020

Non-invasive tests are useful for evaluation of significant fibrosis, inflammation and steatosis in asymptomatic ALD

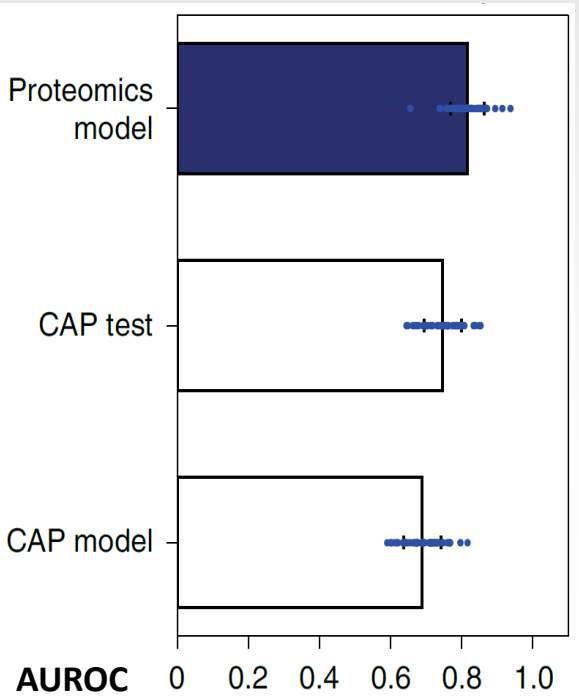
Significant fibrosis ≥F2



≥ mild inflammation



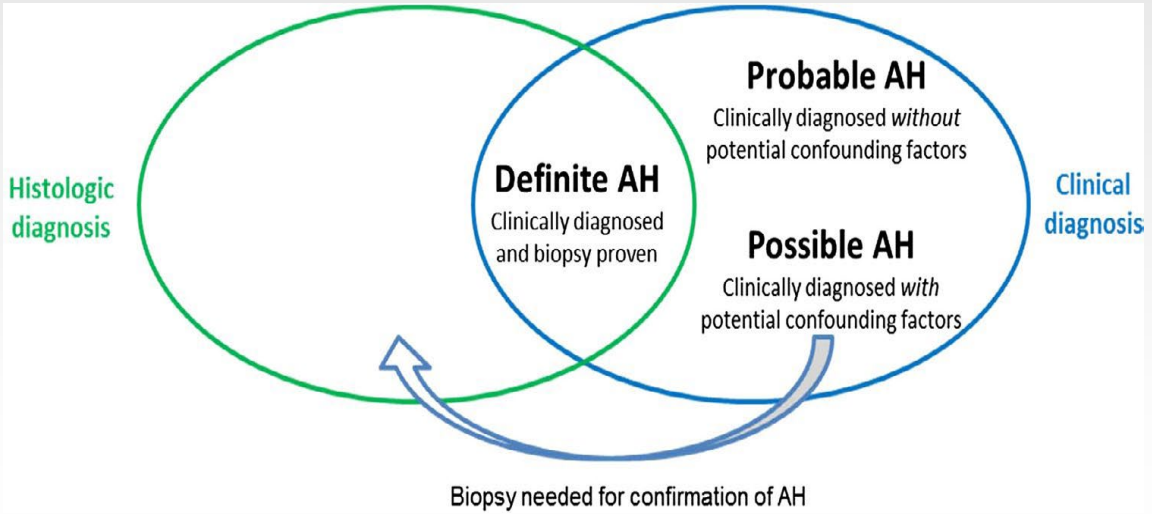
Mild steatosis ≥S1



Niu L et al. Nat Med 2022

Clinical diagnosis of AH: NIAAA definition

- Onset of jaundice within prior 8 weeks
- Ongoing consumption of >40 (female) or 60 (male) g alcohol/day for > 6 months, with <60 days of abstinence before the onset of jaundice
- AST >50, AST/ALT >1.5, and both values <400 IU/L Serum total bilirubin >3.0 mg/dl

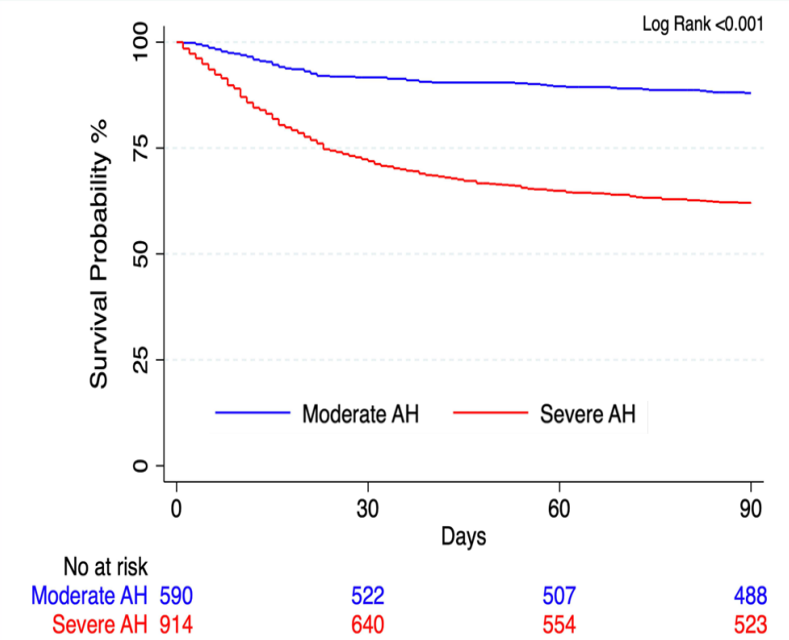


Crabb DW et al. Gastroenterology. 2016

ALD- Prognosis

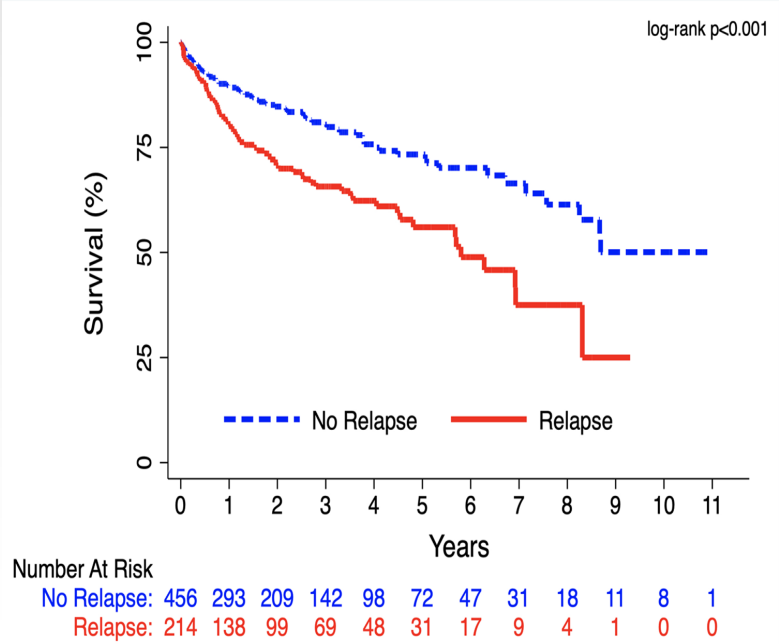
Major determinants of survival in patients with AH

Severity



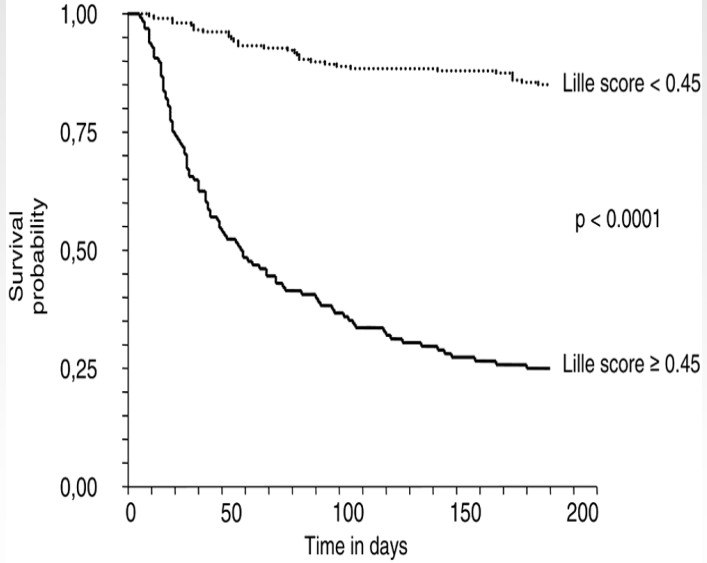
Gaurnizo-Ortiz M et al. Liver Int. 2024

Relapse to alcohol use



Patidar KR et al. Hepatol Commun. 2023

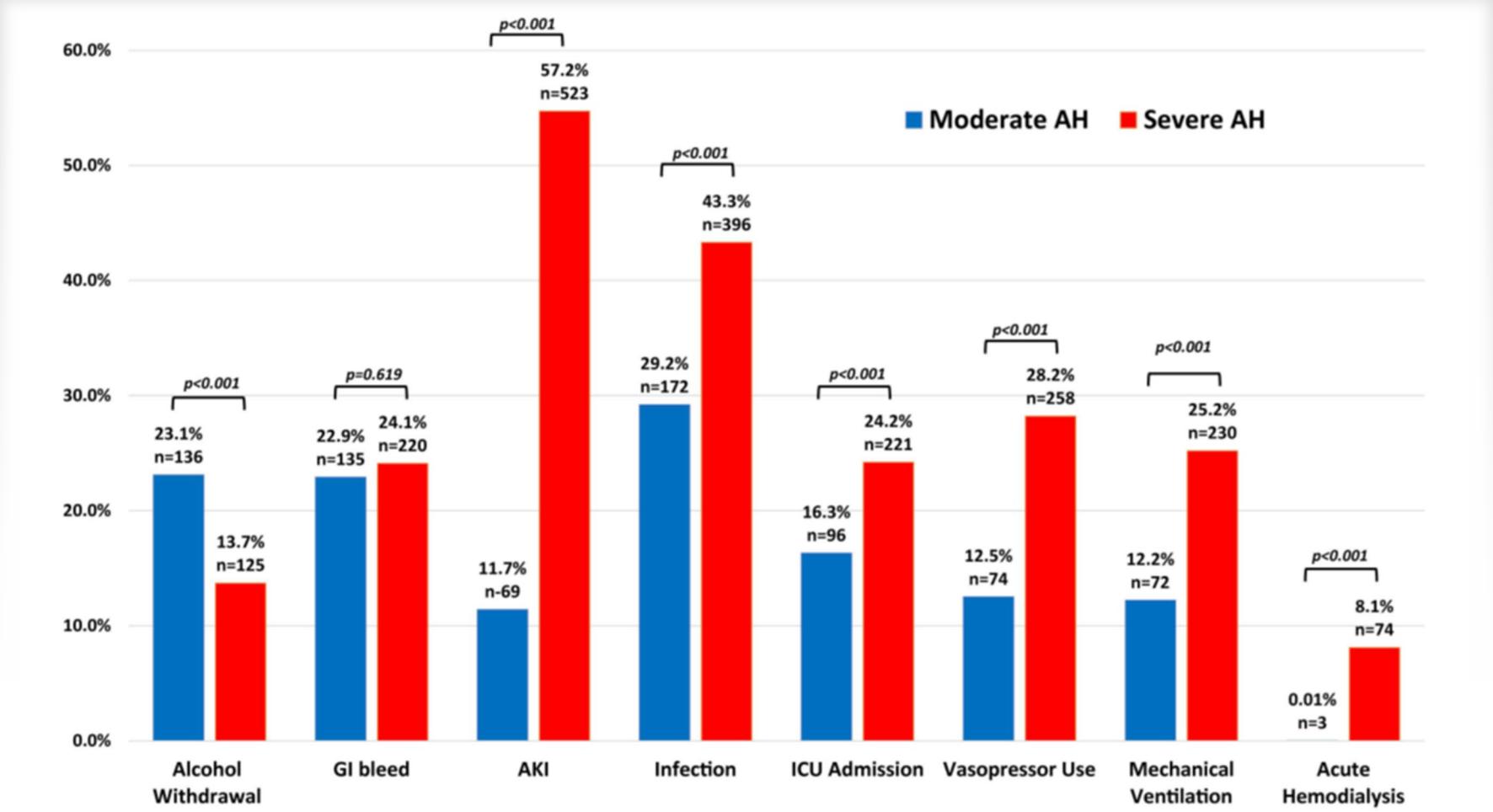
Lille response to steroids*



*Survival for US Lille non-responders is different

Louvet A et al. Hepatology 2007

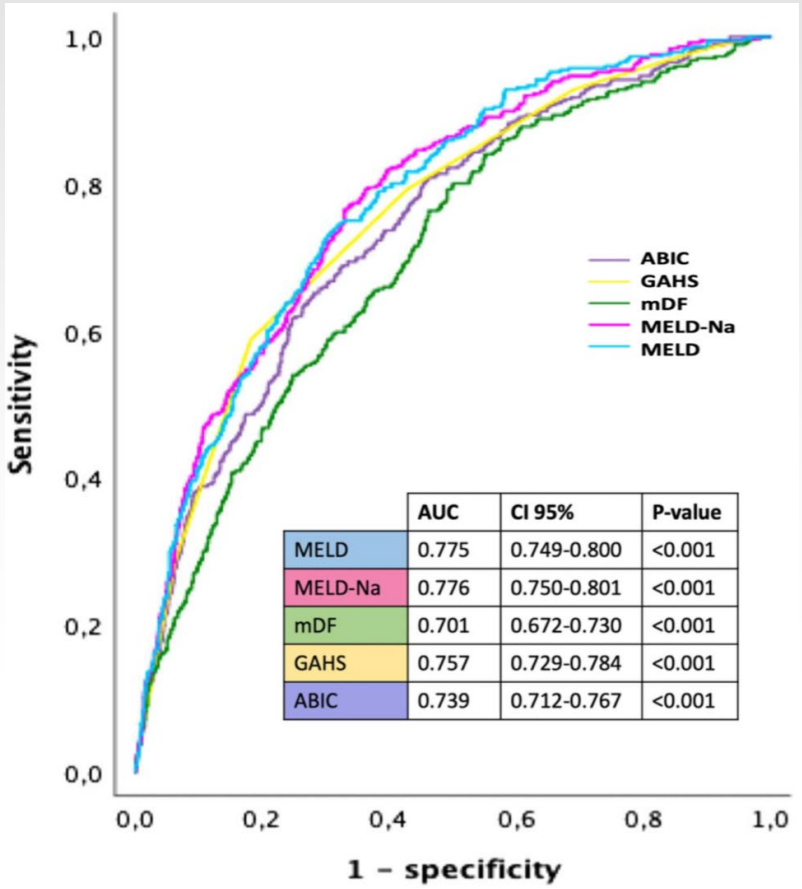
Causes of death in patients with AH



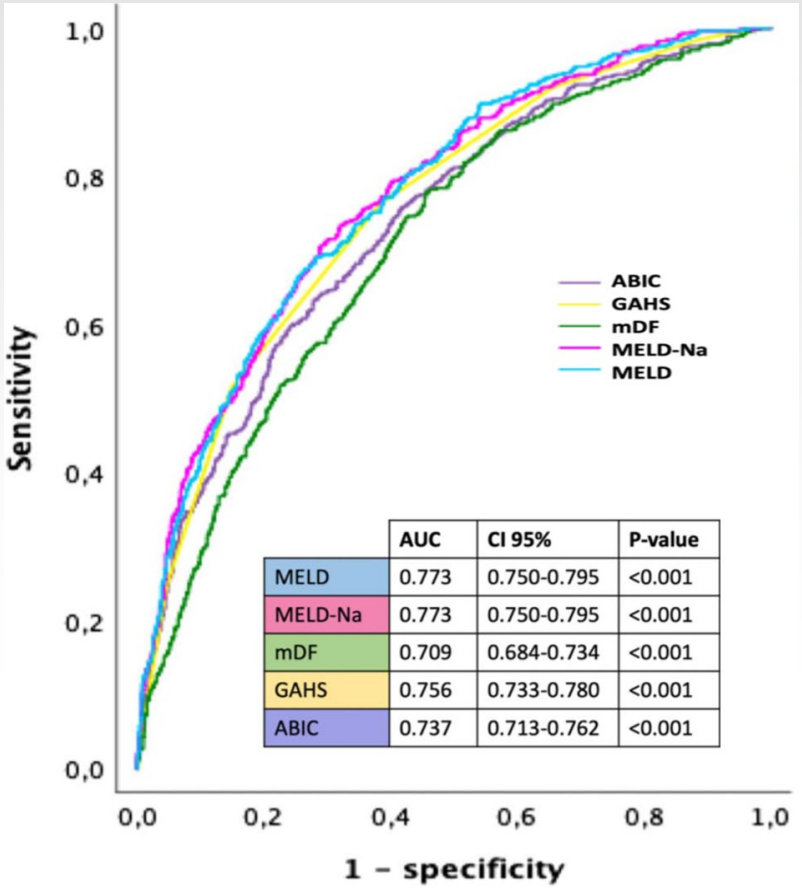
Gaurnizo-Ortiz M et al. Liver Int. 2024

Predicting AH severity and prognosis:
MELD superior to MDF and other scores

Mortality at 28 days & 90 days



	AUC	CI 95%	P-value
MELD	0.775	0.749-0.800	<0.001
MELD-Na	0.776	0.750-0.801	<0.001
mDF	0.701	0.672-0.730	<0.001
GAHS	0.757	0.729-0.784	<0.001
ABIC	0.739	0.712-0.767	<0.001



	AUC	CI 95%	P-value
MELD	0.773	0.750-0.795	<0.001
MELD-Na	0.773	0.750-0.795	<0.001
mDF	0.709	0.684-0.734	<0.001
GAHS	0.756	0.733-0.780	<0.001
ABIC	0.737	0.713-0.762	<0.001

Morales-Arráez D et al. Am J Gastroenterol. 2022

ALD-Management Rx

Integrated management of ALD and AUD

Screen for AUD at every encounter

Offer brief motivational interviewing

Manage cirrhosis complications similar to other liver diseases

Consider AUD Rx to prevent alcohol relapse for those with AUD

Involve AUD specialists in care of those with moderate-severe AUD

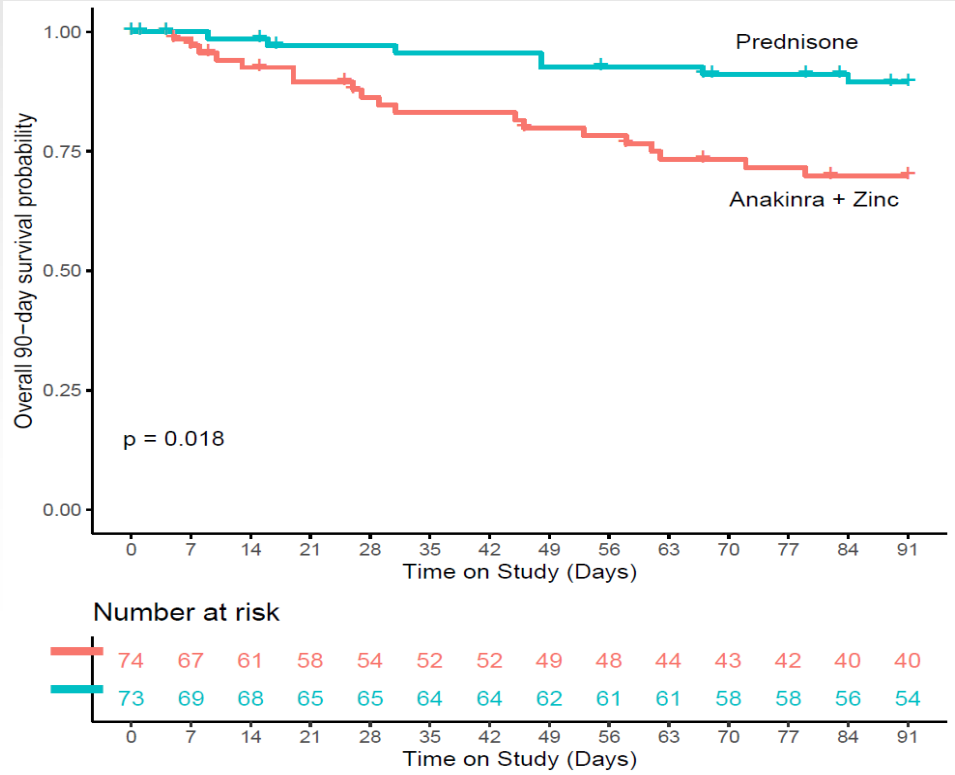
Refer eligible candidates to LT

Those with < 6 months of abstinence can be evaluated for early LT if at low risk for relapse and otherwise meet LT eligibility criteria

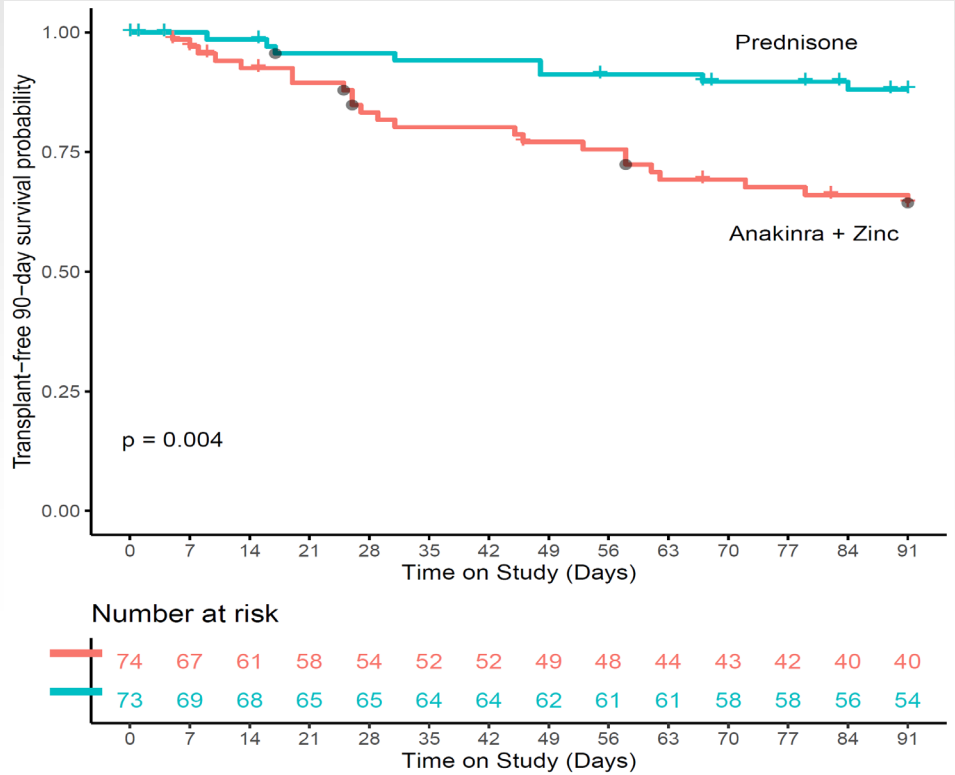
Based on ACG guidance. Jophlin LL et al. Am J Gastroenterol 2024

Steroids with Lille stopping rule result in superior survival to anakinra+zinc in patients with severe AH

Overall 90-day survival



Transplant free 90-day survival



Gawrieh S et al. In press, J Hepatol 2024

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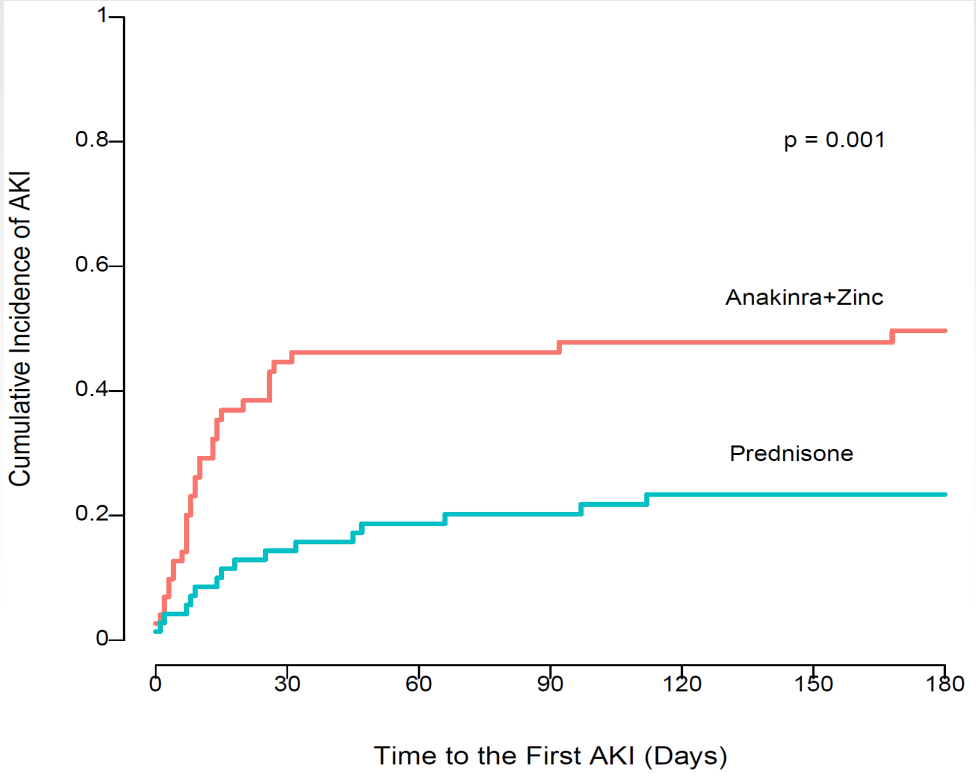
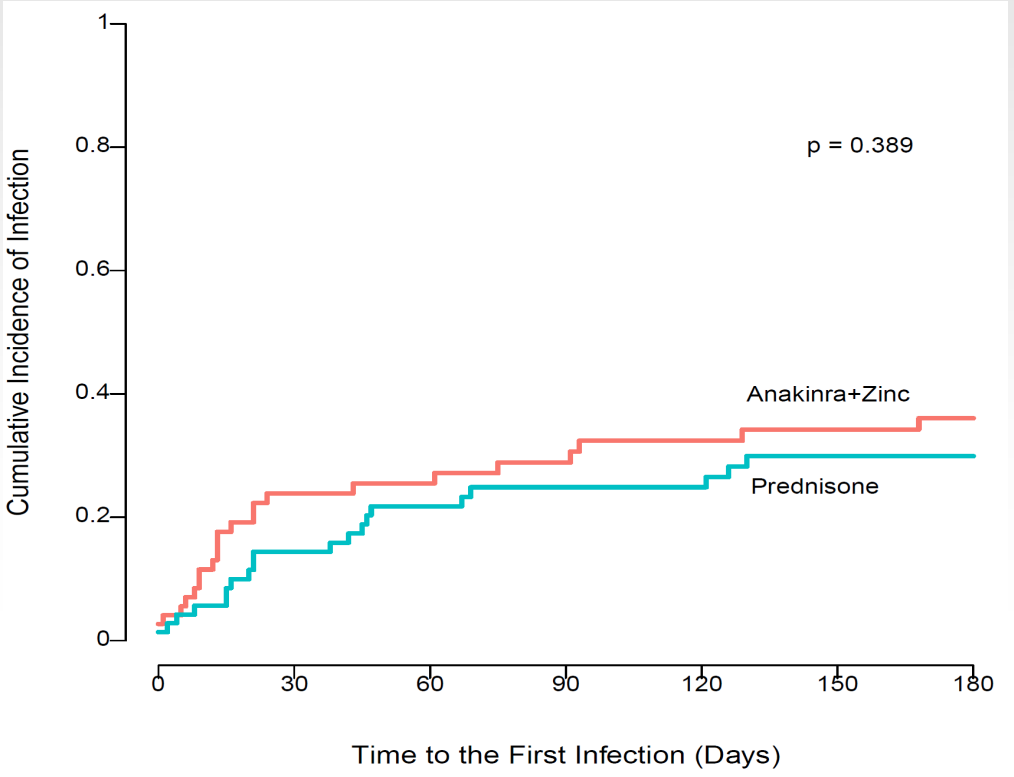
Steroids with Lille stopping rule result in lower rates of AKI to anakinra+zinc in patients with severe AH

Time to first AKI



Time to first infection



Gawrieh S et al. In press, J Hepatol 2024

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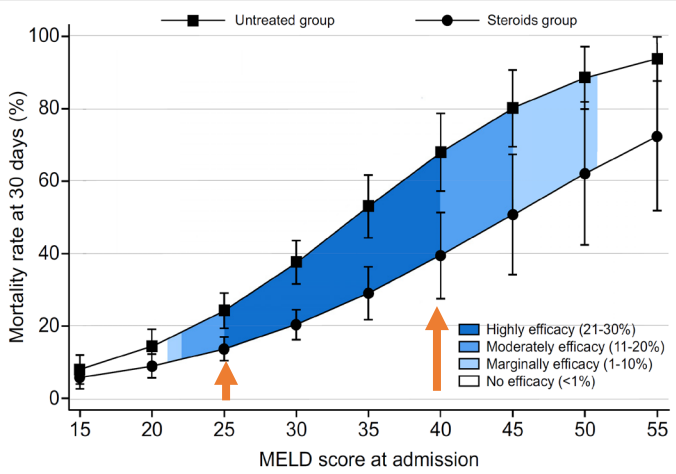
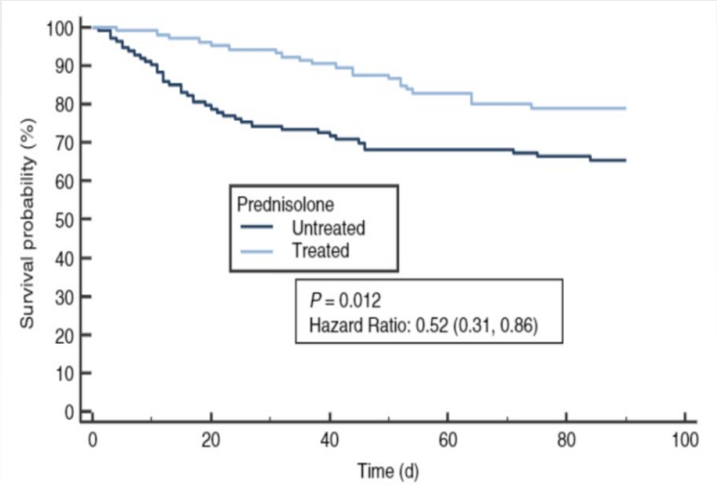
Who are the patients with severe AH most likely to respond to corticosteroids?

MELD 25-39



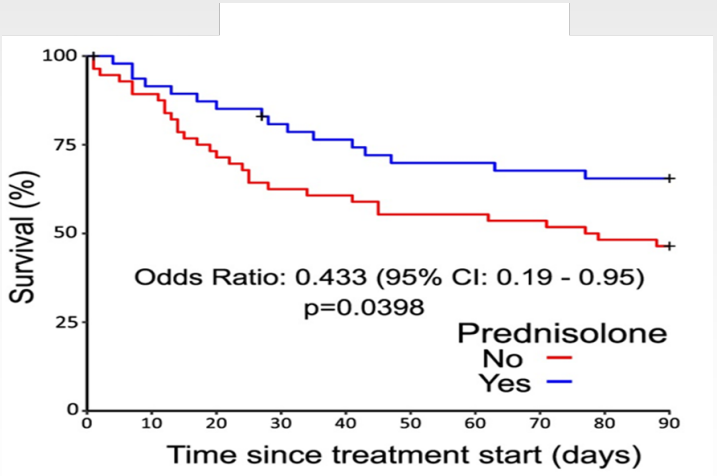
Arab JP et al. J Hepatol 2020

Baseline Neutrophil-to-Lymphocyte ratio 5-8



Forrest EW et al. Aliment Pharmacol Ther 2019

K18 fragments (M30) >5kIU/L



Atkinson SR et al. Am J Gastroenterol 2020

Validation in US studies is necessary

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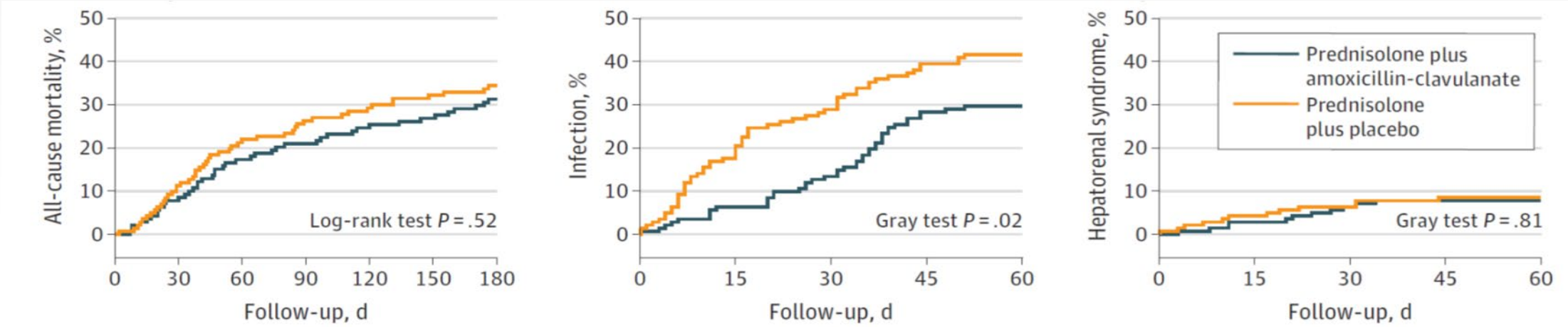
Infections and antibiotics use in patients with severe AH

- Infections are a major cause of death
- Screen for infection on admission
- Treat proven infections
- Controlled infections are generally not a contraindication to steroids use

Prophlactic antibiotics are not recommended

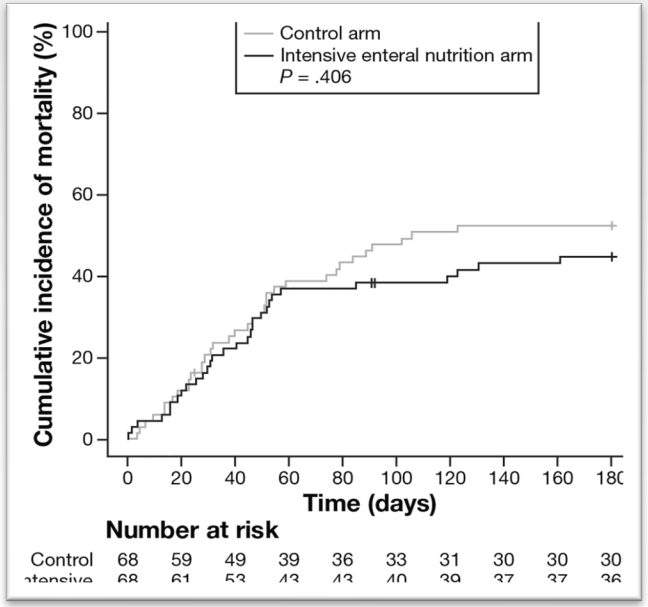
No effect on mortality | Lower infection rates | No effect of HRS

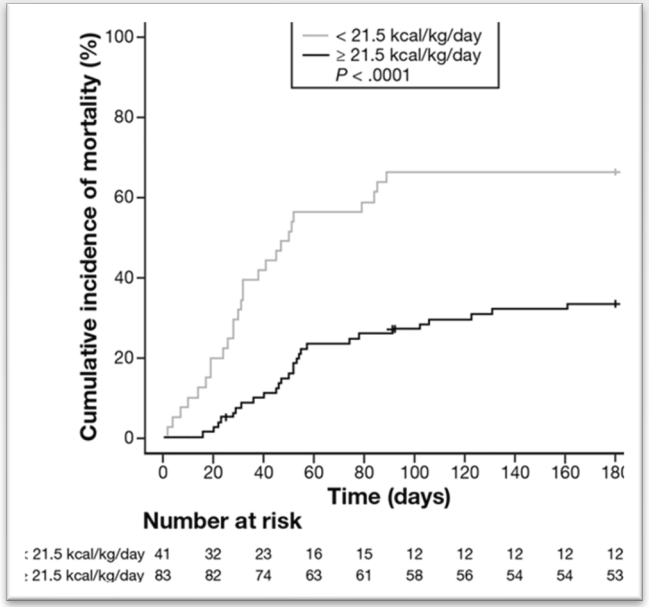


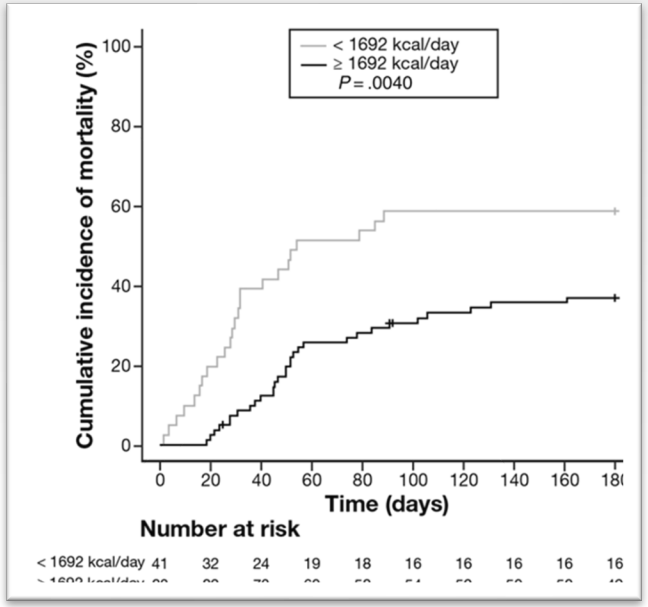
Louvet A et al. JAMA 2023

Effective nutrition is essential part of AH management

- Screen for adequacy of protein-calorie oral intake on admission
- Offer oral nutritional supplements when needed
- Place NJ for enteral feed early when needed



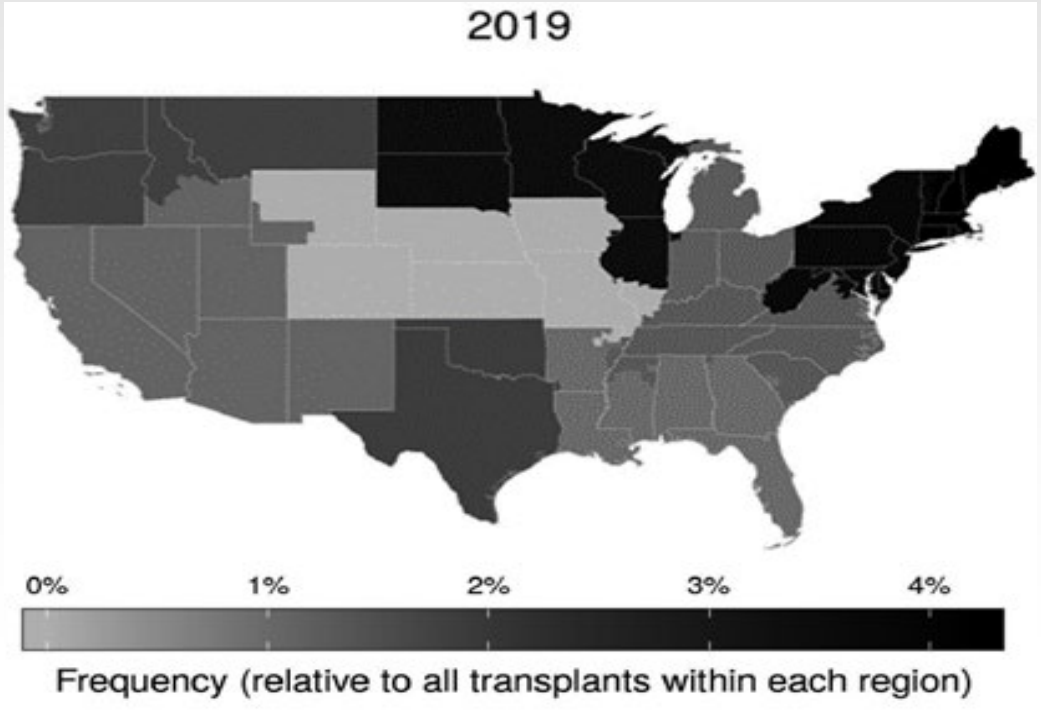




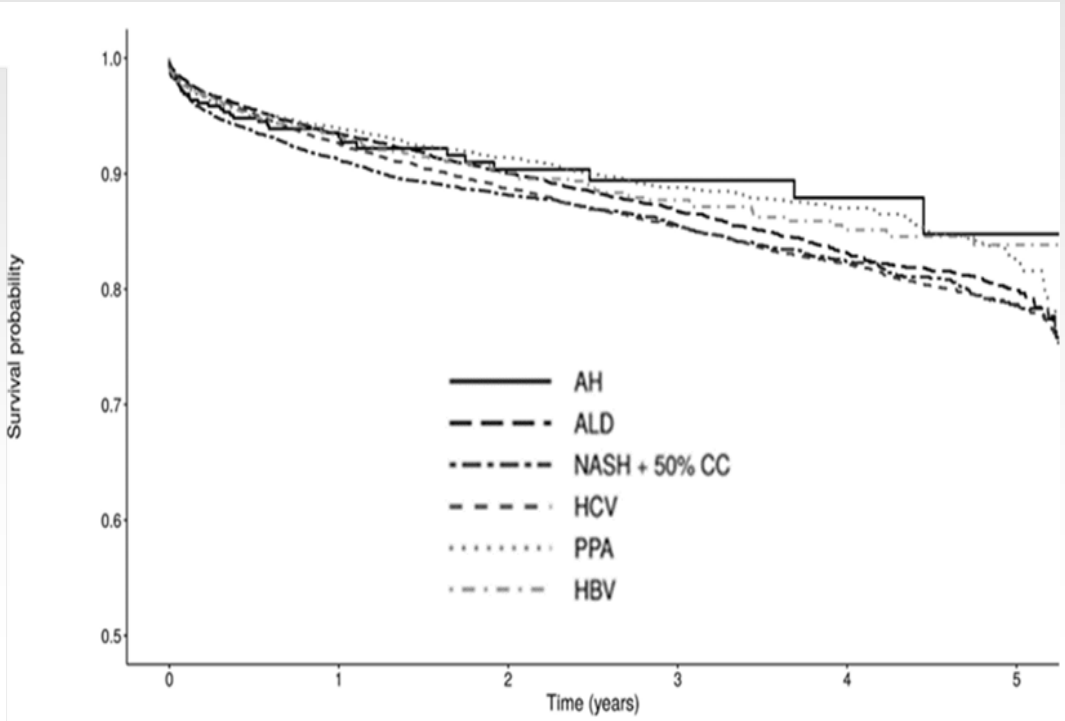
Moreno C et al. Gastroenterology 2016

Liver transplantation for alcohol-associated hepatitis in the US

Profound geographic variation in frequency



Excellent patients' outcomes



Cotter TG. Am J Transplantation 2021

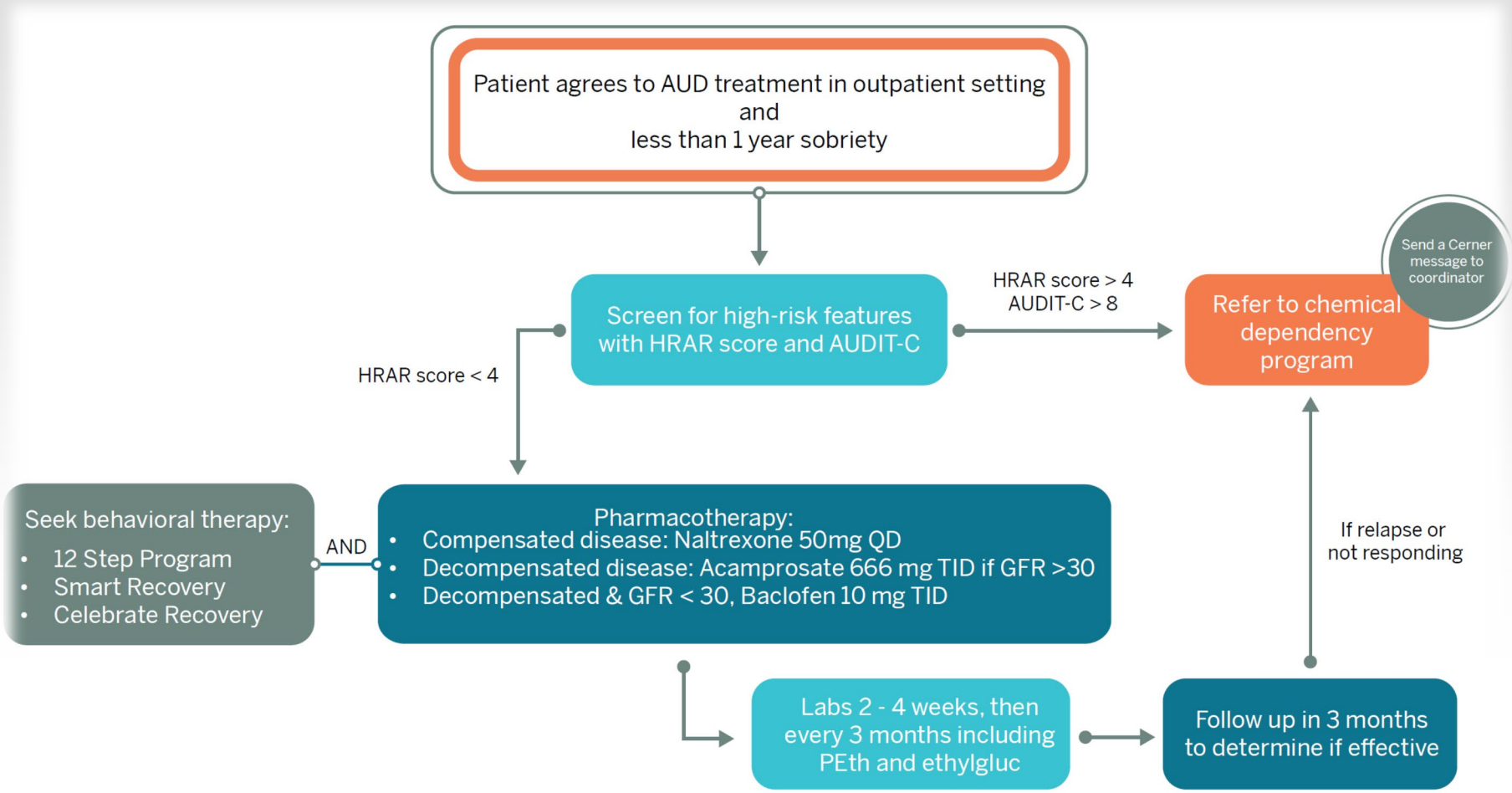
Relapse prevention therapy in patients with ALD & AUD

Medication	Dosing	Metabolism (M) and Excretion (E)	Mechanism of Action	ALD Considerations
Naltrexone*	50 mg/d orally or 380 mg monthly sq	M: Hepatic E: Mostly renal, fecal 2%-3%	Opioid receptor antagonist	1.Not studied in ALD 2.Hepatotoxicity concerns
Acamprosate*	666 mg tid	M: None E: Renal	NMDA receptor antagonist	1.Not studied in ALD 2.No reported instances of DILI
Gabapentin	600-1,800 mg/d	M: None E: Renal 75%, fecal 25%	Modulates GABA activity at presynaptic calcium channels	1.Not studied in ALD 2.Monitor closely for renal dysfunction and worsening mental status/sedation
Baclofen	30-60 mg/d	M: Hepatic, limited E: Renal	GABA-B receptor agonist	Single RCT in patients with ALD showed benefit
Topiramate	75-400 mg/d	M: Not extensively metabolized E: Renal	GABA action augmentation, glutamate antagonism	Not studied in ALD

Disulfiram is not included on this list because it is not recommended for use in patients with ALD.

Crabb DW et al. Hepatology 2020

Approach to AUD therapy in patients presenting with ALD to Indiana University



HRAR: High-Risk Alcohol Relapse score

Take-home messages

- ALD is a leading and rising cause of liver disease in the US
- Screen early for AUD
- Integrate AUD management with ALD management
- Offer steroids with Lille stopping rule for those with severe AH
- Nutritional support is essential part of ALD management
- Referral for early (< 6 months of abstinence) LT evaluation
  - Select patients with severe AH not responding to steroids
  - Patient with decompensated ALD-related cirrhosis and/or early HCC

Thank you