

Alcohol-Associated Liver Disease

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Disclosures

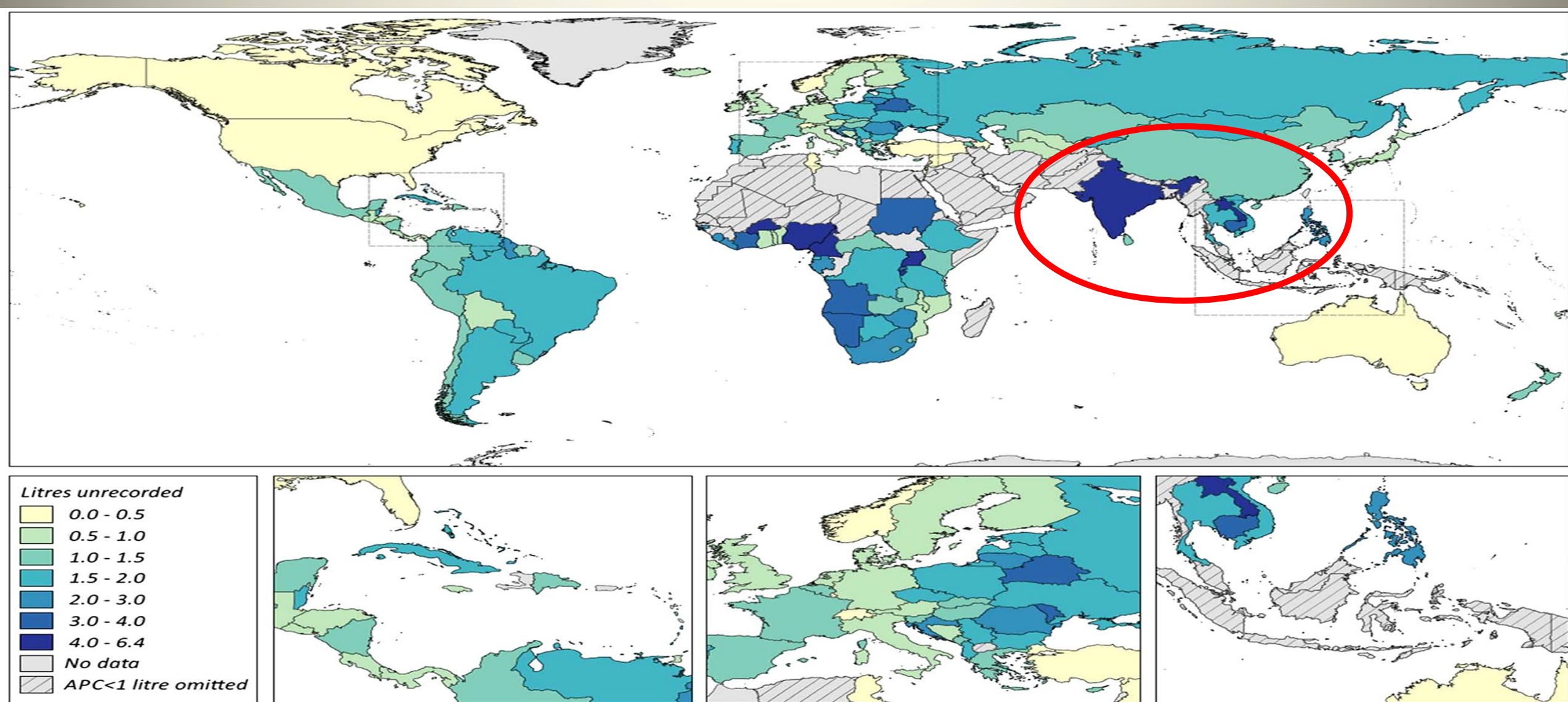
Type Support	With whom
Grants and Research Support	NIAAA, NIDDK, ACG, UAB, Industry
Chair ALD SIG	AASLD
Chair Portal HTN and HRS abstract review, member research awards panel and ALD abstracts review	AASLD
Member research awards panel and genetic / metabolic diseases abstracts	AGA
Member practice parameters committee and lead author practice guidelines ALD	ACG
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Advisory Board and Consultant	Gilead, APF, Guidepoint, CSL Behring
Royalties	Up-To-Date
Teaching and speaking	CLD Foundation, Medscape Gastroenterology
Honoraria	Gastroenterology Endoscopy News, CLD Foundation, Guidepoint, Medscape

Learning objectives

- ❖ Learn magnitude and healthcare burden of ALD
- ❖ Identify clinical spectrum, screening, and diagnosis of ALD
- ❖ Understand medical management of ALD
- ❖ Update on emerging targets and early LT in ALD
- ❖ Recognize alcohol use disorder as second pathology in ALD
- ❖ Determine short and long-term prognosis of ALD
- ❖ Review prevention of ALD and public health policies

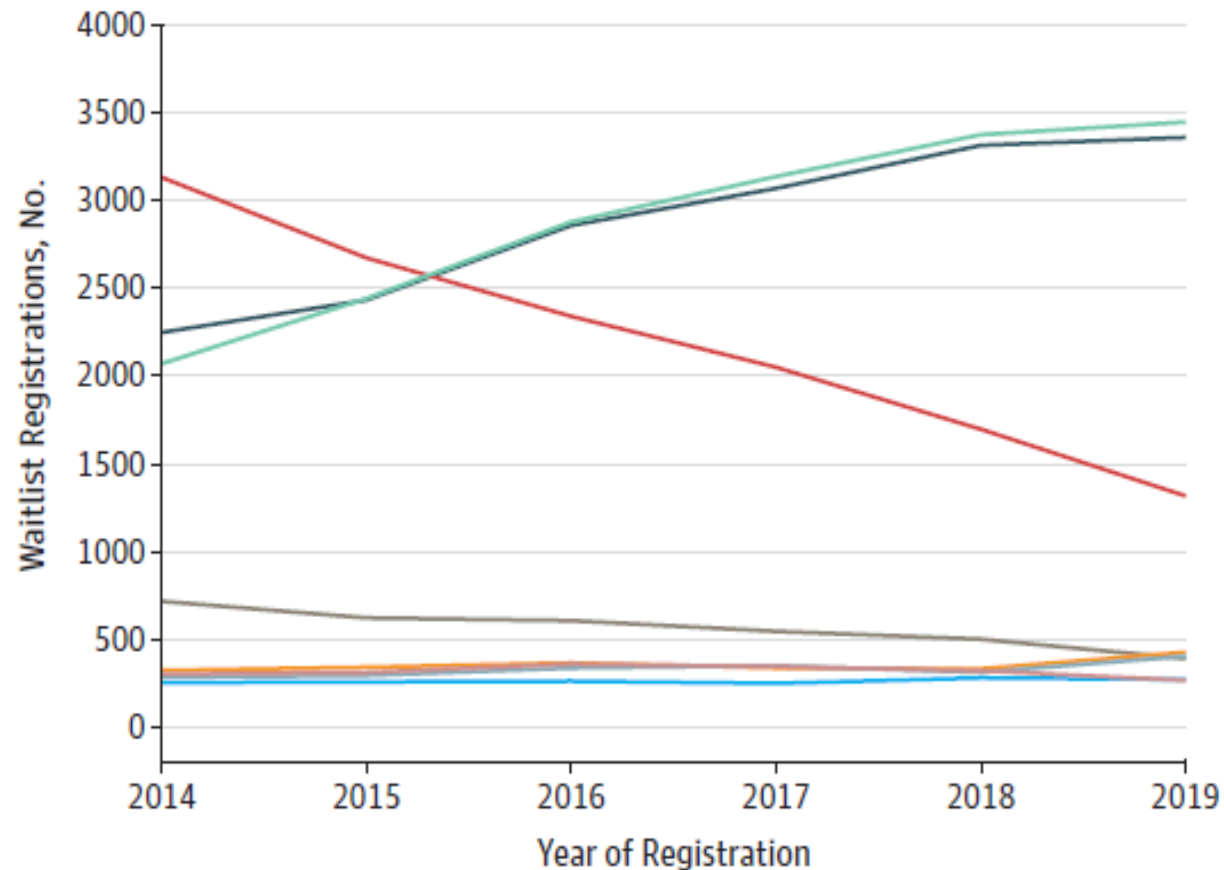
	Global	Distribution
Prevalence of alcohol use	31% (2.3 billion) people Per capita 6.4 liters in 2016* 45% spirits, 34% beer, and 12% wine	Highest in Europe ↑ in Asia, Middle East, Africa, Eastern Europe, ↓ in Southern Europe
Prevalence of alcohol use disorder	2.3%	4% Europe and 3.4% USA
Harmful alcohol use related healthcare burden (2016)	5.3% (3 million) of deaths 5.1% (132.6 million) of DALY	10.1% of deaths in Europe and 5.5% in US 10.8% of DALY in Europe and 6.7% in US
Alcohol-associated liver disease	27.3% (332,268) of cirrhosis related deaths \$22.7 billion hospitalization cost (2012-16)	ALD proportion of cirrhosis deaths: 35% Central and South America, 28% USA, 22% high income Asia Pacific, 42% Western Europe and 37% Eastern Europe

Over 50% of alcohol use is unrecorded

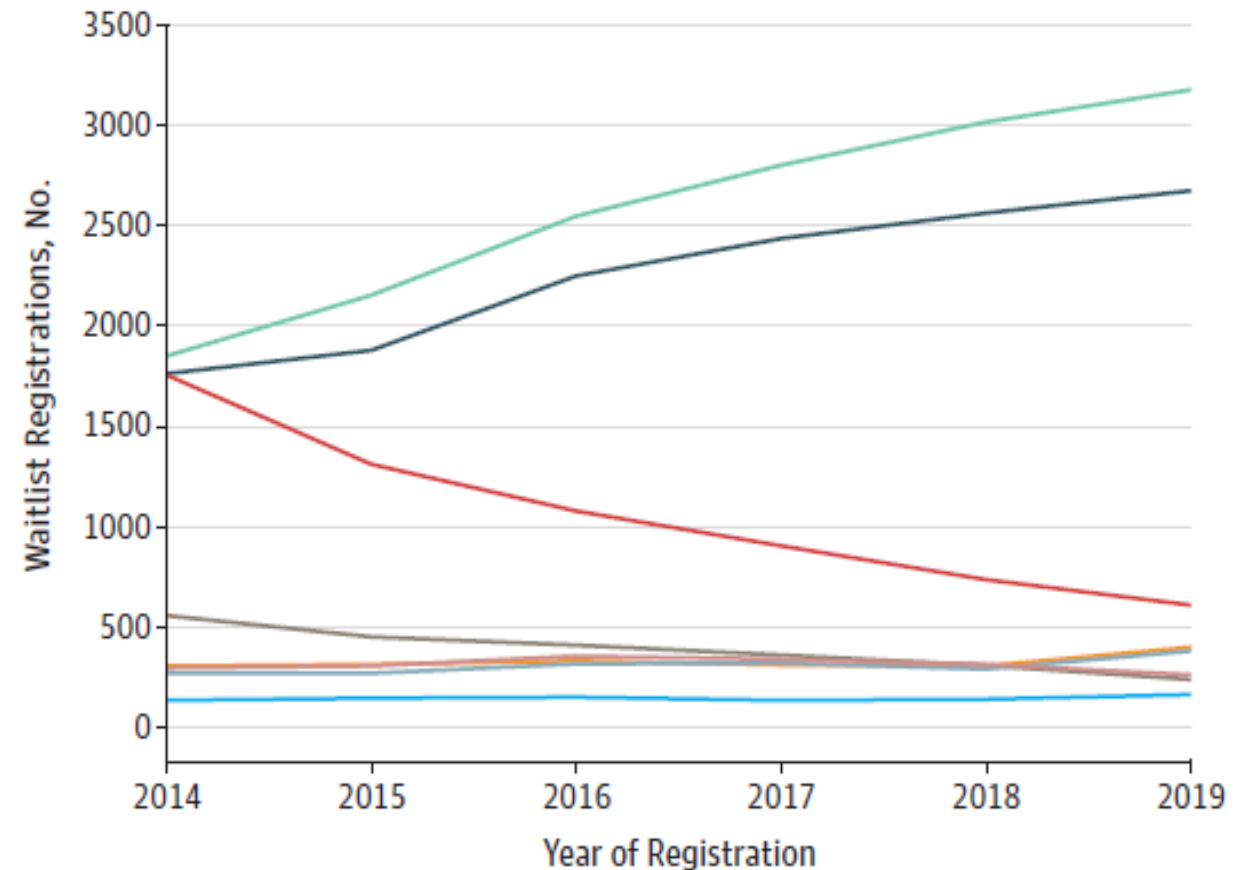


Alcohol-associated liver disease is the leading indication for liver transplant

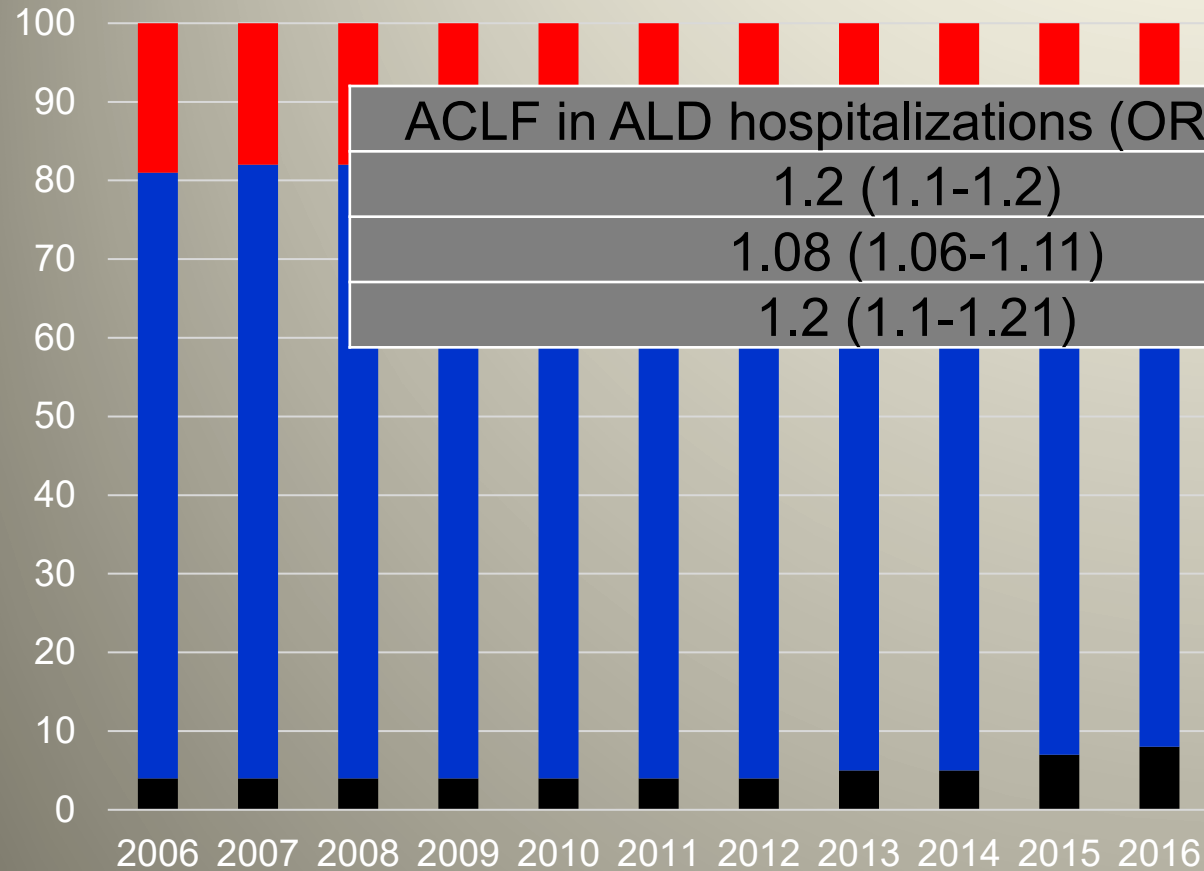
A All waitlist registrants



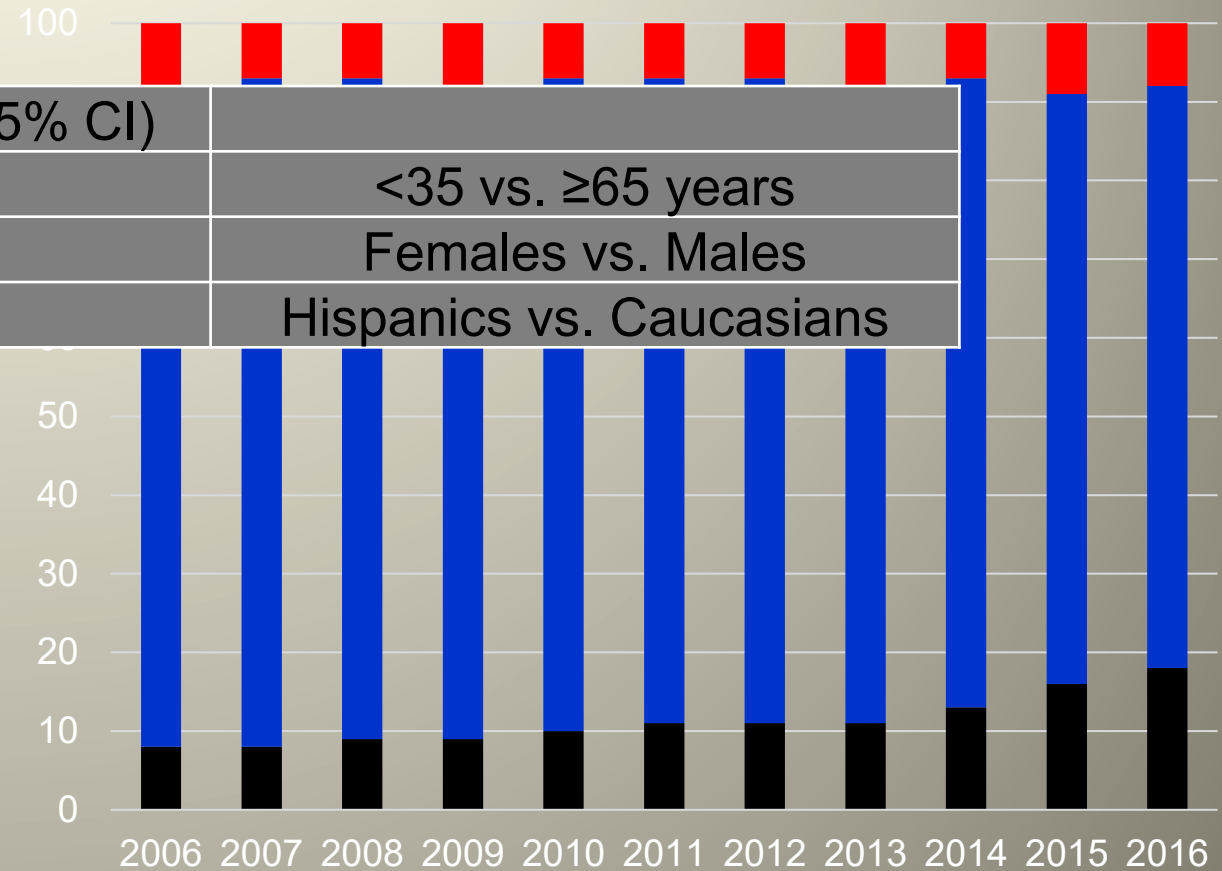
B Waitlist registrants without HCC



Increasing hospitalizations in the US for alcohol associated cirrhosis or for alcoholic hepatitis



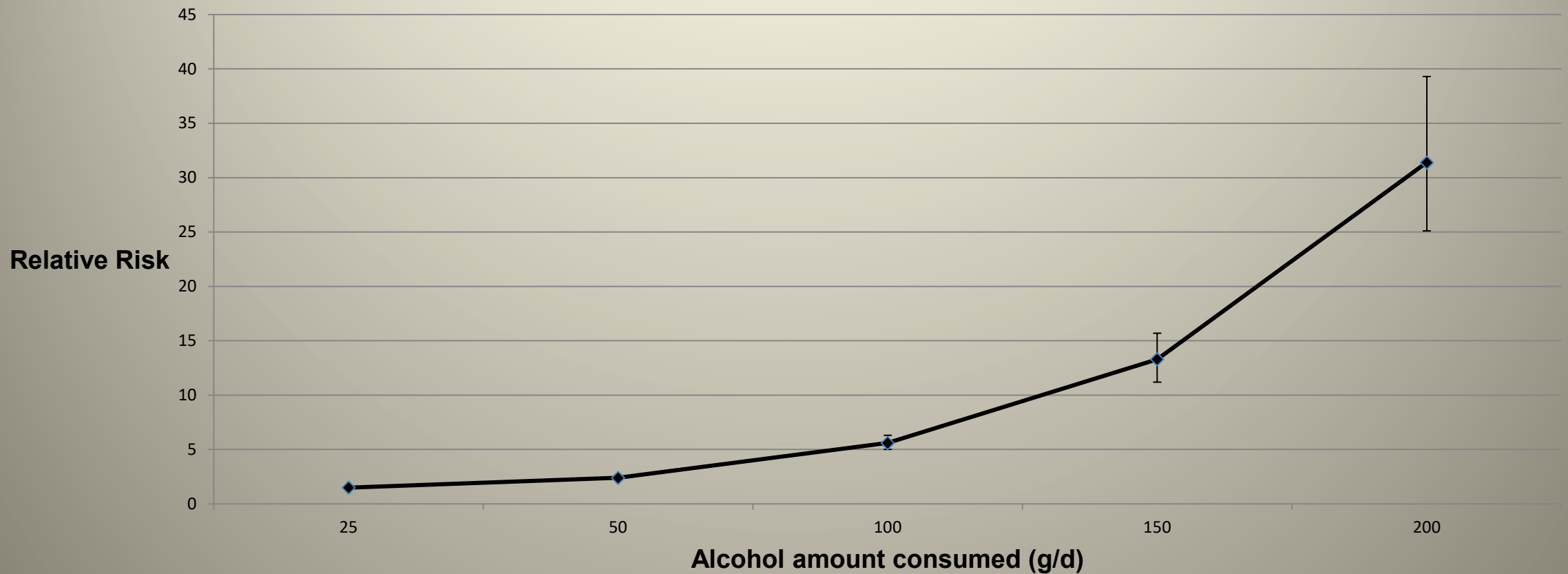
P<0.001



P<0.001

ACLF in ALD hospitalizations (OR, 95% CI)	
1.2 (1.1-1.2)	<35 vs. ≥65 years
1.08 (1.06-1.11)	Females vs. Males
1.2 (1.1-1.21)	Hispanics vs. Caucasians

Alcohol amount and alcohol-associated liver disease



Females are more susceptible to alcohol induced liver injury

- ❖ The risk of cirrhosis is 3.1% in men and 4.7% in women with drinking >10 drinks per day for >15 years¹
- ❖ *Higher blood levels of alcohol*²
- ❖ *Reduced gastric alcohol dehydrogenase activity*²
- ❖ *Increased body fat and reduced total body water*²
- ❖ *Reduced acetaldehyde dehydrogenase activity*³
- ❖ *Osteopontin induction and neutrophil recruitment*⁴

¹Delacote et al. Clin Gastroenterol Hepatol 2020; 18: 2315-23.

²Baraona and Lieber et al. ACER 2001; 25: 502-7.

³Ward and Coutelle. Arch Women Ment Health 2003; 6: 231-8.

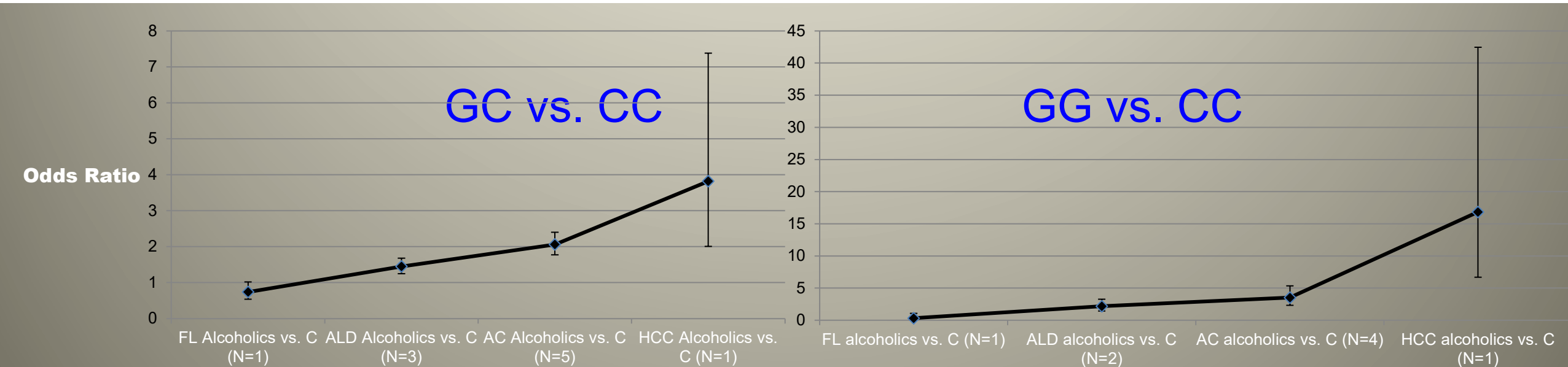
⁴Banerjee et al. J Pathology 2006; 208: 473-85.

Genetics and alcohol-associated liver disease

PNPLA3 Gene Polymorphism Is Associated With Predisposition to and Severity of Alcoholic Liver Disease

Am J Gastroenterol 2015; 110:846–856

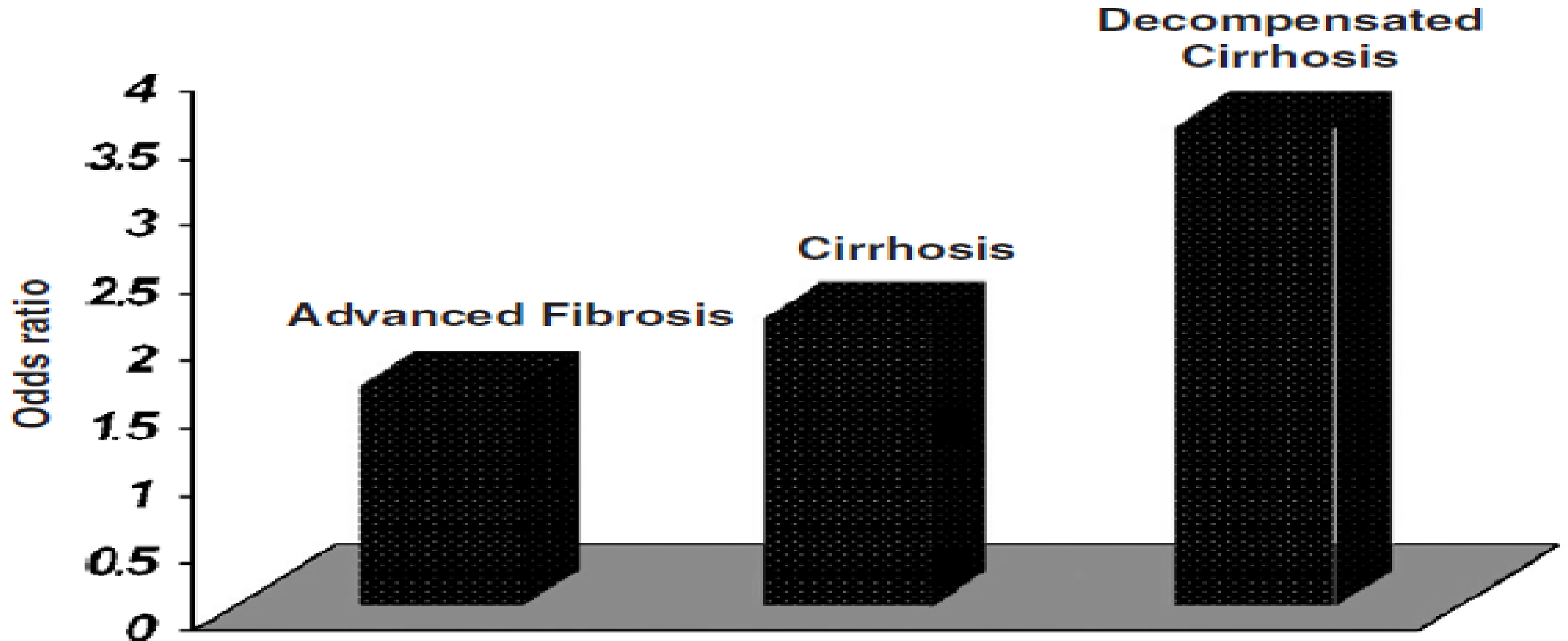
Habeeb Salameh, MD¹, Evan Raff, MD², Angelika Erwin, MD³, Devanshi Seth, PhD^{4,5,6}, Hans Dieter Nischalke, MD⁷, Edmondo Falletti, MD⁸, Maria Antonella Burza, PhD, MD⁹, Julian Leathert, M.Phil¹⁰, Stefano Romeo, MD, PhD^{9,11}, Antonio Molinaro, MD⁹, Stefano Ginanni Corradini, MD, PhD¹², Pierluigi Toniutto, MD¹³, Spengler Ulrich, MD⁷, Ann Daly, PhD¹⁴, Christopher P. Day, MD¹⁴, Yong-Fang Kuo, PhD¹⁵ and Ashwani K. Singal, MD, MS¹⁶



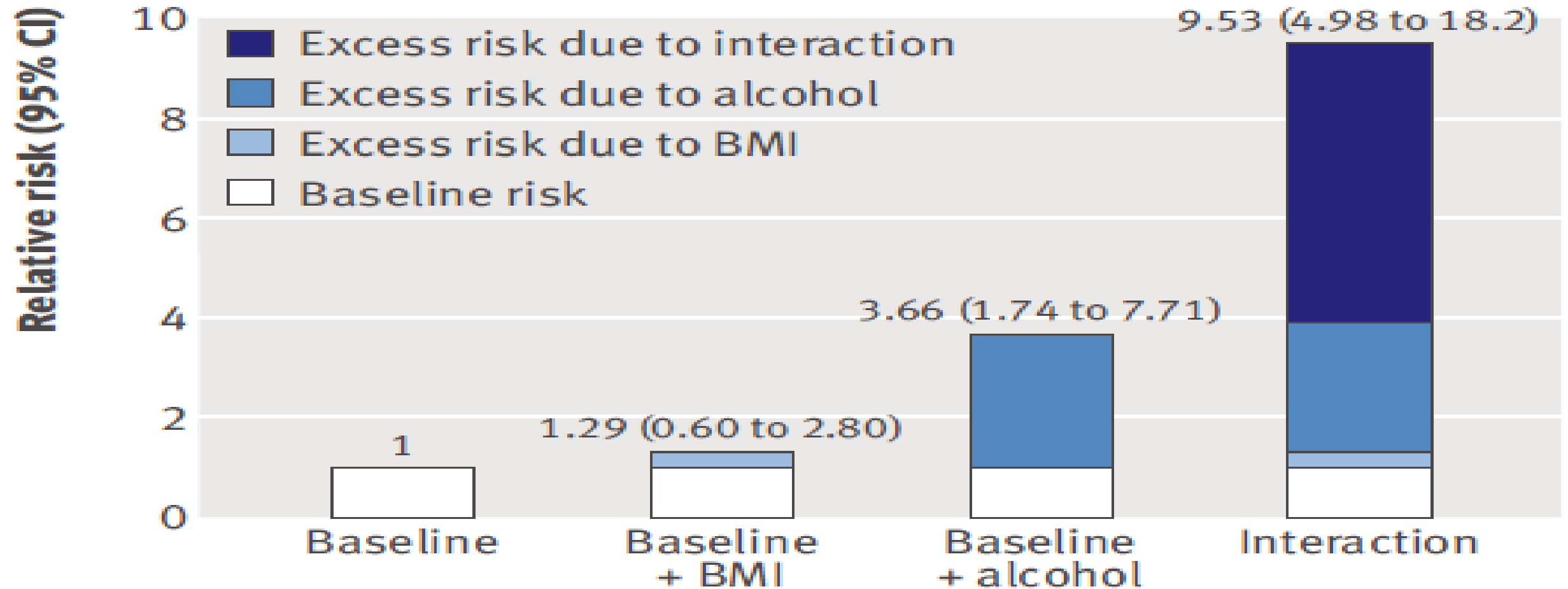
Frequency, pattern of use, alcohol type

- ❖ Odds for cirrhosis are about 4 fold higher among daily drinkers compared to 2-4 x/week
- ❖ Alcohol amount in recent years (after age 40) more relevant than early use of alcohol
- ❖ Wine drinking less harmful compared to beer and hard liquor
- ❖ Binge drinking: variable human data
- ❖ Drinking on empty stomach vs. after meals

Alcohol and chronic hepatitis C virus infection interact synergistically



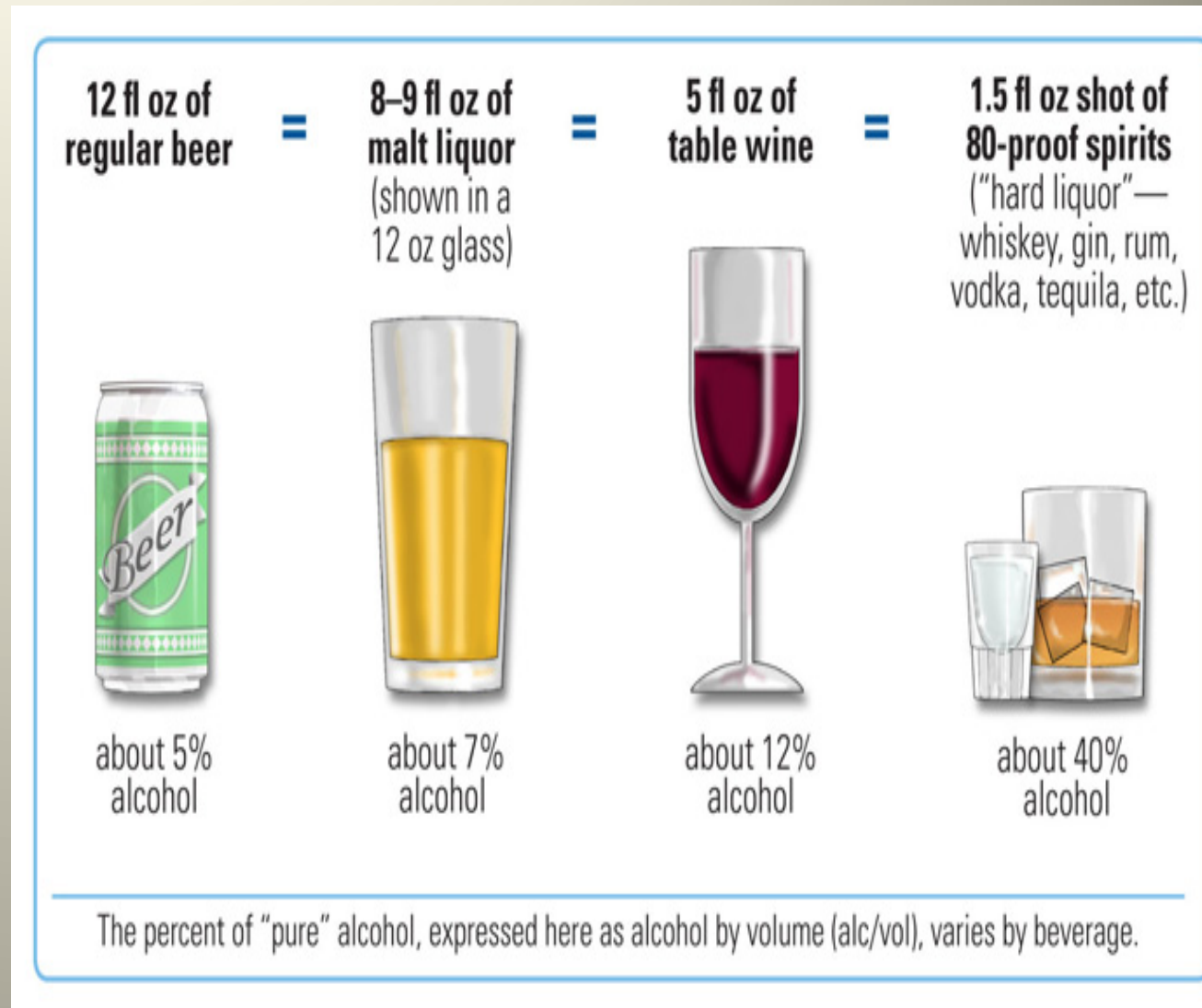
Body mass index and alcohol interaction



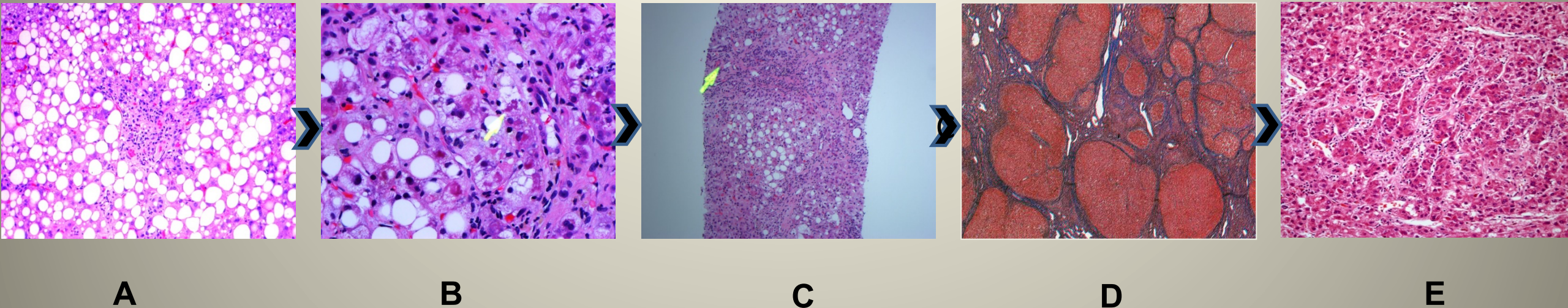
DIAGNOSIS AND SCREENING

Diagnosis of alcohol-associated liver disease

- ❖ Documentation of liver disease
- ❖ Harmful or heavy alcohol use (*>3 drinks/d in males and >2 in females*).
- ❖ Absence of other causes of liver disease
- ❖ >50 , $AST:ALT > 1.5$ and absolute values < 400



Histological spectrum of alcohol-associated liver disease



Early ALD*

- A. Steatosis or fatty liver and no fibrosis
- B. Alcoholic hepatitis and fibrosis stage 1

Advanced ALD*

- C. AH with advanced fibrosis (stage 3 fibrosis)
- D. Cirrhosis (stage 4 fibrosis)
- E. Hepatocellular carcinoma

Alcohol-associated vs. other liver disease presents at late stage and progresses faster

- ❖ In a retrospective cohort, 206 ALD compared to 365 NAFLD patients present with cirrhosis or complications (46 vs. 12%, $P < 0.001$).¹
- ❖ In a global cohort of 3453 individuals with liver disease, contribution of ALD was higher among 1754 with advanced versus 1699 with early disease (29 vs. 4%, $P < 0.001$).²
- ❖ Once present the progression over median follow up of 3-4 years was faster with lower transplant free survival (90 vs. 95%, $P < 0.04$).¹

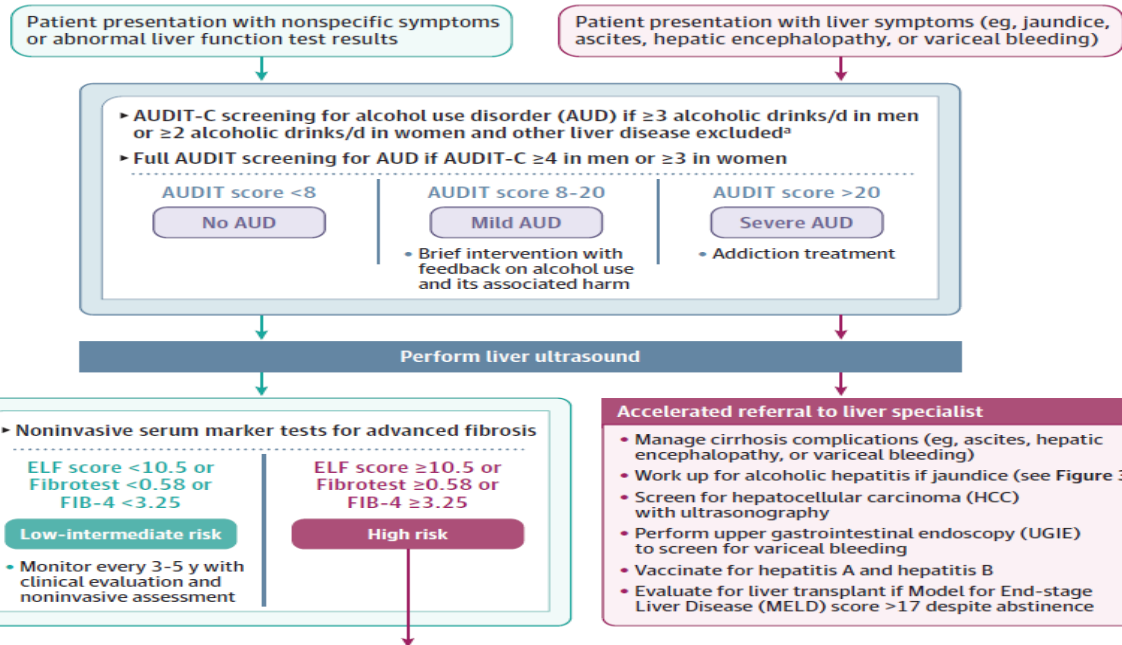
Identifying harmful alcohol use: AUDIT

Questions	0	1	2	3	4
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
3. How often do you have 5 or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year
10. Has a relative, friend, doctor or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year

At risk individuals should be screened for liver disease

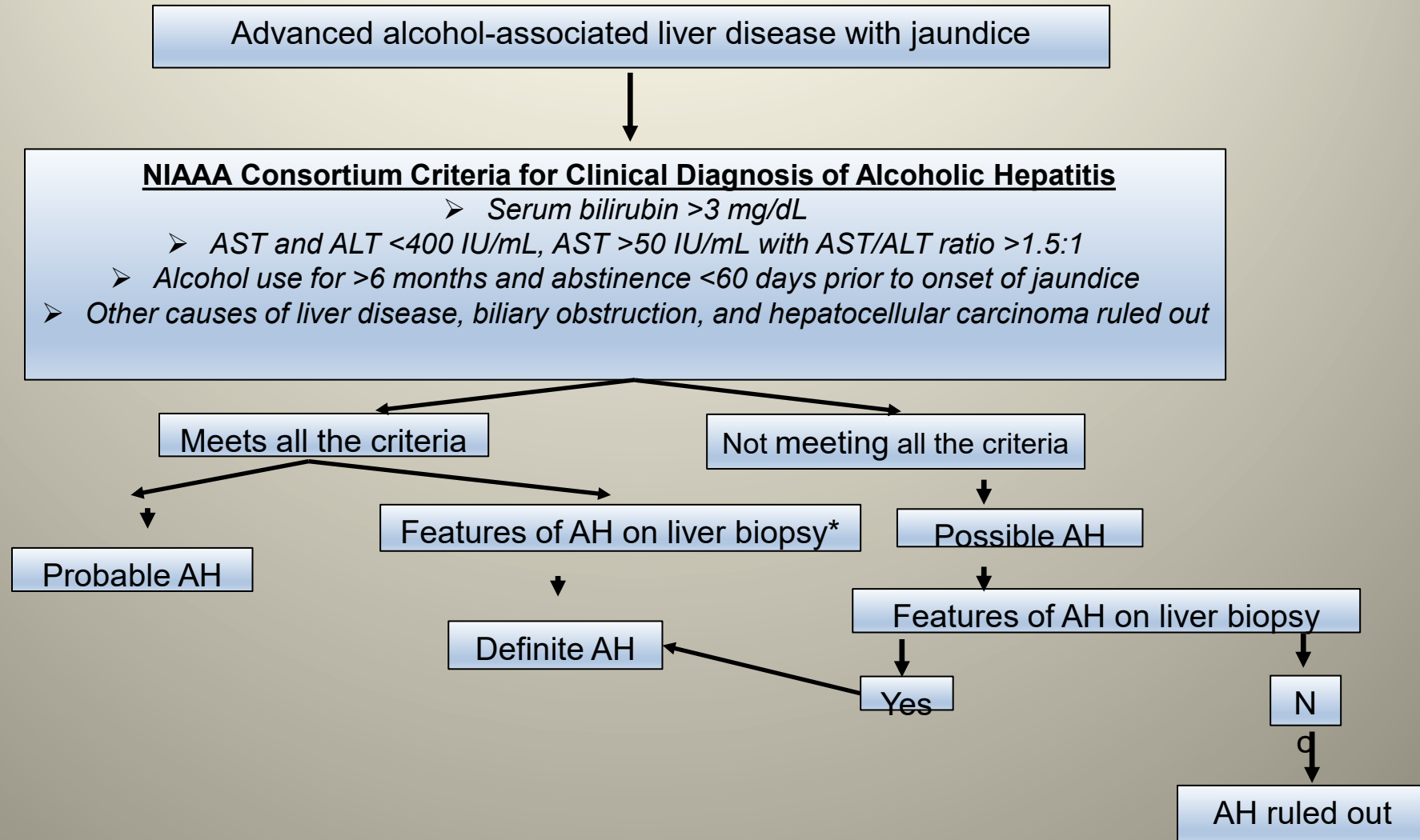
- ❖ Liver chemistry tests (AST, ALT, Bilirubin, albumin, INR)
- ❖ Complete blood count (white cell count, platelet count)
- ❖ Liver imaging with ultrasound

Patients with early alcohol-associated liver disease should be evaluated for fibrosis risk



Test for diagnosis of advanced fibrosis ($\geq$ stage 3)	Components	Cutoff value	Sensitivity (95% CI), %	Specificity (95% CI), %	Special considerations
Serum biomarkers					
FIB-4 (nonpatented) ⁴⁴	Age, AST, ALT, and platelets	≥ 3.25	58 (45-70)	91 (86-94)	When patented tests unavailable Cannot be used for patients with primary platelet disorders
ELF (patented) ⁴⁴	TIMP-1, PIINP, and hyaluronic acid	≥ 10.5	79 (67-88)	91 (86-94)	Needs specific radioimmunoassay equipment
FibroTest (patented) ⁴⁴	α -2 Macroglobulin, haptoglobin, bilirubin, apolipoprotein, GGT	≥ 0.58	67 (54-78)	89 (84-93)	Risk of misclassification in patients with hemolysis
Imaging techniques					
Transient elastography ⁴⁴	Ultrasonographic technique for LSM	≥ 15 kPa	86 (75-93)	94 (0-96)	Failure to measure liver stiffness in severe obesity or in patients with ascites
MR elastography ⁴⁵	MR imaging with low-frequency vibrations for LSM	≥ 3.31 kPa ^a	96 ^b	95.4 ^b	Availability limited to specialized centers Expensive

Diagnosis of alcoholic hepatitis



MANAGEMENT OF ALCOHOL ASSOCIATED LIVER DISEASE

Treating alcohol use disorder benefits alcohol-associated liver disease patients

- ❖ Benchmark of quality of care indicator¹
- ❖ Improves abstinence rates and reduce recidivism.²
- ❖ Reduction in new hepatic decompensation, 6.5 vs. 11.6% and long term mortality, 51 vs. 58%.³
- ❖ Reduced 30-d readmission, recidivism, and mortality among hospitalized patients with alcoholic hepatitis.⁴

¹Kanwal et al. CGH 2010; 8: 709-17; ²Khan et al. CGH 2016; 14: 191-202; ³Rogal et al. Hepatology 2020; 71: 2080-92; ⁴Peeraphatdit et al. CGH 2020; 18: 477-85.

Behavioral therapies for alcohol use disorder

➤ **Cognitive–Behavioral Therapy (CBT)**

- ❑ CBT approaches have among the highest level of empirical support for the treatment of alcohol and drug use disorders
- ❑ Evidence indicates a relatively durable effects, but limited diffusion in clinical practice

➤ **Motivational Interviewing (MI)**

- ❑ MI interventions have demonstrated efficacy in producing significant and durable effects and in contributing to counseling efforts
- ❑ Results with MI are influenced by participant and delivery factors

Table 6 US Food and Drug Administration (FDA)-Approved Medications and Others Tested in Alcohol Use Disorder Patients

Medication	Dosage	Pharmacologic Target	Possible Use in Alcohol Use Disorder Patients with Alcoholic Liver Disease?
FDA-Approved Medications for Alcohol Use Disorder			
Acamprosate	666 mg TID	Possibly NMDA receptor agonist	Yes (no hepatic metabolism)
Disulfiram	250-500 mg QD	Inhibition of acetaldehyde dehydrogenase	No (hepatic metabolism; cases of liver toxicity have been reported)
Naltrexone* PO or IM	PO: 50 mg QD IM: 380 mg monthly	Mu opiate receptor antagonist	With caution (perceptions of liver toxicity limit use in advanced alcoholic liver disease)
Not FDA-Approved Medications Tested for Alcohol Use Disorder			
Baclofen	10 mg TID; 80 mg QD max	GABA _B receptor agonist	Yes (minimal hepatic metabolism) Baclofen has been formally tested in clinical studies with alcohol use disorder patients with liver cirrhosis
Gabapentin	900-1800 mg QD	Unclear: modulates GABA transmission	Yes (no hepatic metabolism)
Ondansetron	1-16 µg/kg BID	5HT ₃ antagonist	Yes, but with caution because liver toxicity has been reported, albeit relationship to ondansetron administration is not determined
Topiramate	300 mg QD	Anticonvulsant multiple targets: —glutamate/+GABA	Yes (partial hepatic metabolism mostly by glucoronidation) In patients with hepatic encephalopathy, use with caution: topiramate-related cognitive side-effects may confound the clinical course and treatment of hepatic encephalopathy
Varenicline	2 mg QD	Nicotinic acetylcholine receptor partial agonist	Yes (minimal hepatic metabolism)

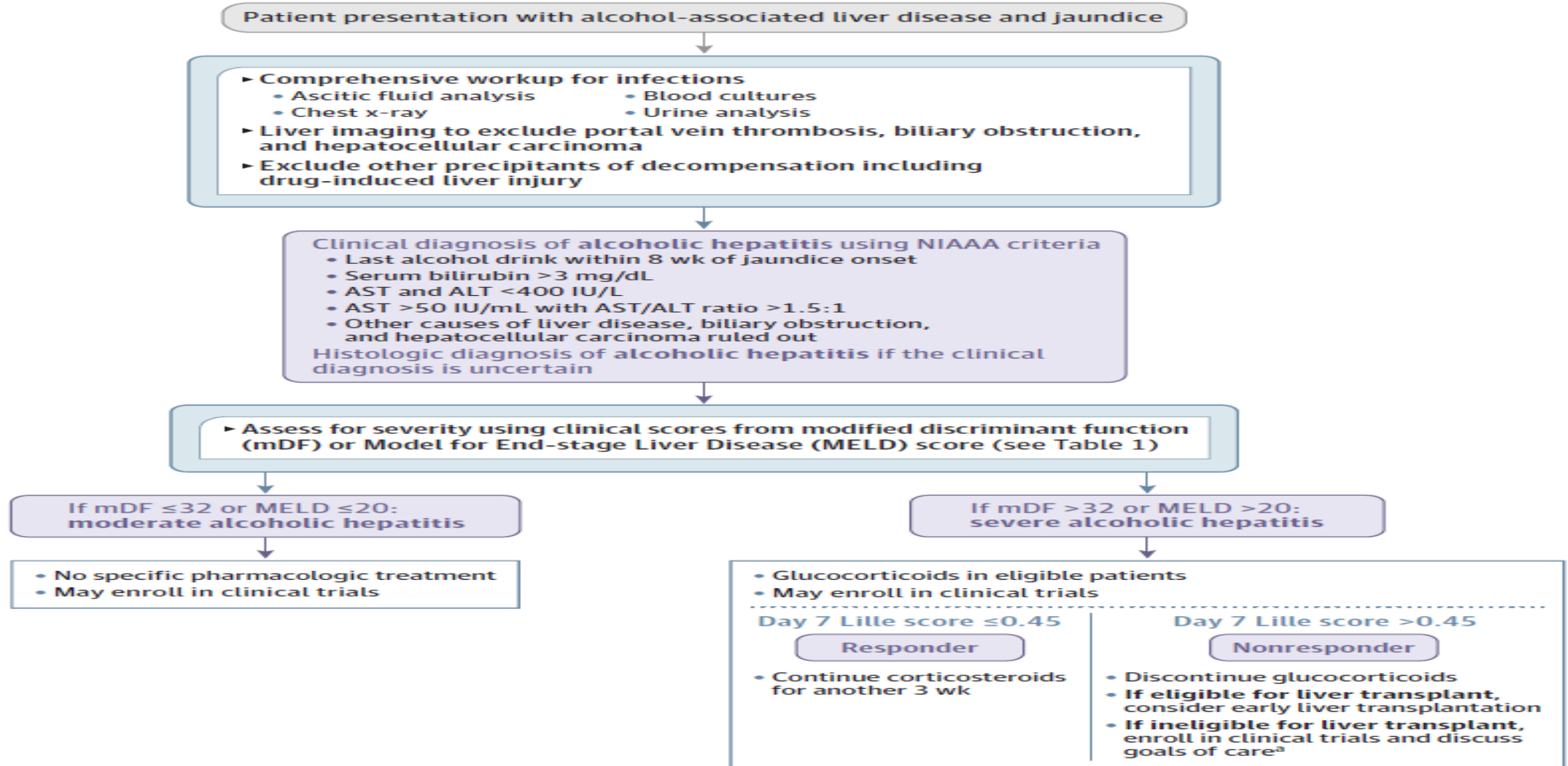
Post-transplant graft & patient survival

TABLE 2. Graft and patient survival at 1, 3, 5, and 10 years after transplantation for various indications

	Graft survival				Patient survival			
	1 yr	3 yr	5 yr	10 yr	1 yr	3 yr	5 yr	10 yr
PBC (n=3052)	85	80.5	78.1	71.9	90.2	86.7	84.4	79
PSC (n=3854)	86.5	81.4	78	71.5	93.4	89.7	87.4	83.2
HCV (n=15,147)	82.2	73.3	68.5	62.7	87.2	79.9	75.9	70.8
AC (n=8940)	84.1	77.8	73.8	67.6	88.6	83	79.4	73.2
ALD+HCV (n=6066)	83.8	74.8	69.6	62.3	88.4	80.1	76.2	69.9
NASH (n=1368)	85.6	81.9	80.1	80.4	88.8	85.4	84.1	83.9
CC (n=5856)	82	76.7	72.7	66	86.9	82.4	78.6	72.1
HBV (n=1816)	84.1	78.3	75.8	71.6	89.5	84.5	82.4	78.5
HCC (n=8588)	84.1	73.4	69	66.2	88.1	78.3	74.3	71.7

AC, alcoholic cirrhosis; ALD, alcohol liver disease; CC, cryptogenic cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

Current treatment of alcoholic hepatitis

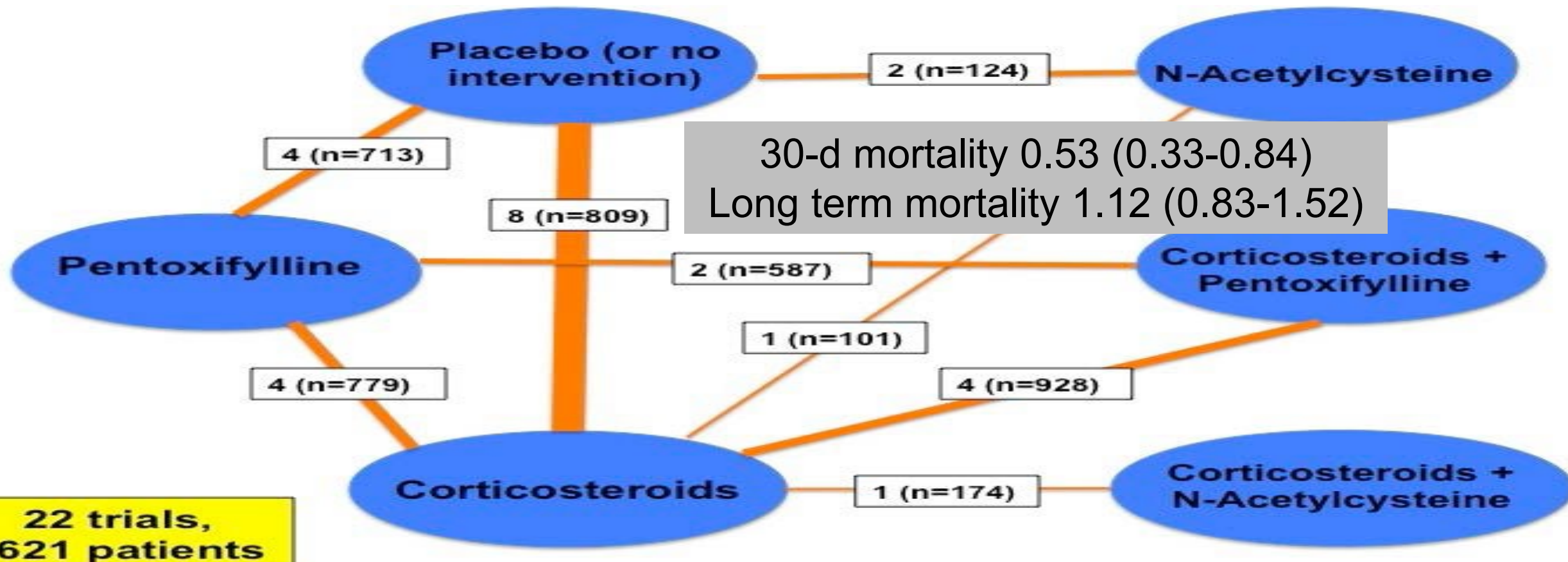




CLINICAL—LIVER

Comparative Effectiveness of Pharmacological Interventions for Severe Alcoholic Hepatitis: A Systematic Review and Network Meta-analysis

Siddharth Singh,¹ Mohammad Hassan Murad,² Apoorva K. Chandar,³ Connie M. Bongiorno,⁴ Ashwani K. Singal,⁵ Stephen R. Atkinson,⁶ Mark R. Thursz,⁶ Rohit Loomba,⁷ and Vijay H. Shah⁸



- ❖ Patients with severe AH should be treated with corticosteroids in eligible patients (moderate evidence, strong)
- ❖ Pentoxifylline has no role in treatment of severe AH (moderate evidence, strong)

ACG Clinical Guideline: Alcoholic Liver Disease

Ashwani K. Singal, MD, MS, FACG¹, Ramon Bataller, MD, PhD, FACG², Joseph Ahn, MD, MS, FACG (GRADE Methodologist)³,
Patrick S. Kamath, MD⁴ and Vijay H. Shah, MD, FACG⁴

Contraindications for corticosteroids

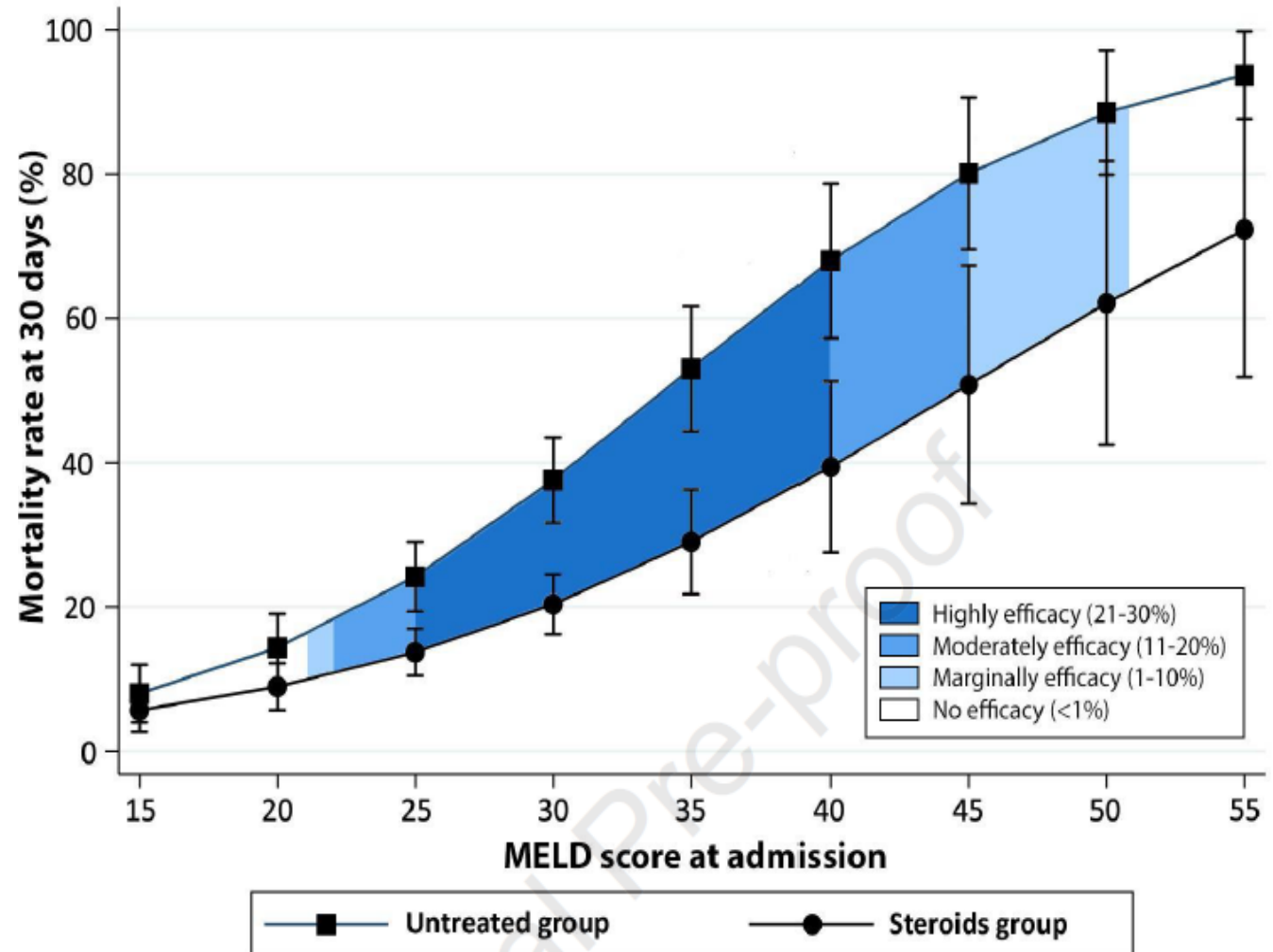
- ❖ Active infection
- ❖ Poorly controlled diabetes
- ❖ GI Bleeding
- ❖ Acute pancreatitis
- ❖ Concomitant HCV infection
- ❖ Hepatorenal syndrome

Therapeutic window for use of corticosteroids in alcoholic hepatitis

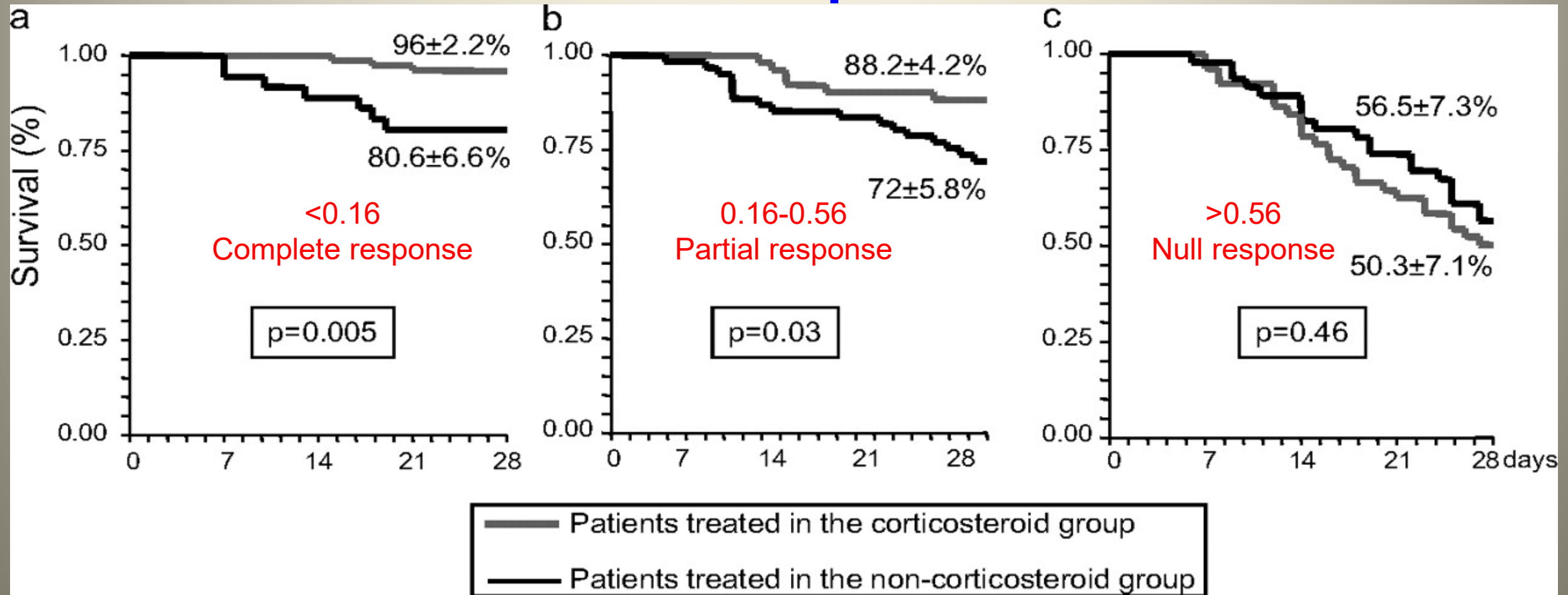
Journal Pre-proof

IDENTIFICATION OF OPTIMAL THERAPEUTIC WINDOW FOR STEROID USE IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS: A WORLDWIDE STUDY

Juan Pablo Arab, Luis Antonio Díaz, Natalia Baeza, Francisco Idalsoaga, Eduardo Fuentes-López, Jorge Arnold, Carolina A. Ramírez, Dalia Morales-Arraez, Meritxell Ventura-Cots, Edilmar Alvarado-Tapias, Wei Zhang, Virginia Clark, Douglas Simonetto, Joseph C. Ahn, Seth Buryska, Tej I. Mehta, Horia Stefanescu, Adelina Horhat, Andreea Bumbu, Winston Dunn, Bashar Attar, Rohit Agrawal, Zohaib Syed Haque, Muhammad Majeed, Joaquín Cabezas, Inés García-Carrera, Richard Parker, Berta Cuyàs, Maria Poca, German Soriano, Shiv K. Sarin, Rakhi Maiwall, Prasun K. Jalal, Saba Abdulsada, María Fátima Higuera-de la Tijera, Anand V. Kulkarni, P Nagaraja Rao, Patricia Guerra Salazar, Lubomir Skladaný, Natália Bystrianska, Veronica Prado, Ana Clemente-Sanchez, Diego Rincón, Tehseen Haider, Kristina R. Chacko, Fernando Cairo, Marcela de Sousa Coelho, Gustavo A. Romero, Florencia D. Pollarsky, Juan Carlos Restrepo, Susana Castro-Sanchez, Luis G. Toro, Pamela Yaquich, Manuel Mendizabal, Maria Laura Garrido, Adrián Narvaez, Fernando Bessone, Julio Santiago Marcelo, Diego Piombino, Melisa Dirchwolf, Juan Pablo Arancibia, José Altamirano, Won Kim, Roberta C. Araujo, Andrés Duarte Rojo, Victor Vargas, Pierre-Emmanuel Rautou, Tazime Issoufaly, Felipe Zamarripa, Aldo Torre, Michael R. Lucey, Philippe Mathurin, Alexandre Louvet, Guadalupe García-Tsao, José Alberto González, Elizabeth Verna, Robert S. Brown, Juan Pablo Roblero, Juan G. Abalde, Marco Arrese, Vijay H. Shah, Patrick S. Kamath, Ashwani K. Singal, Ramon Bataller

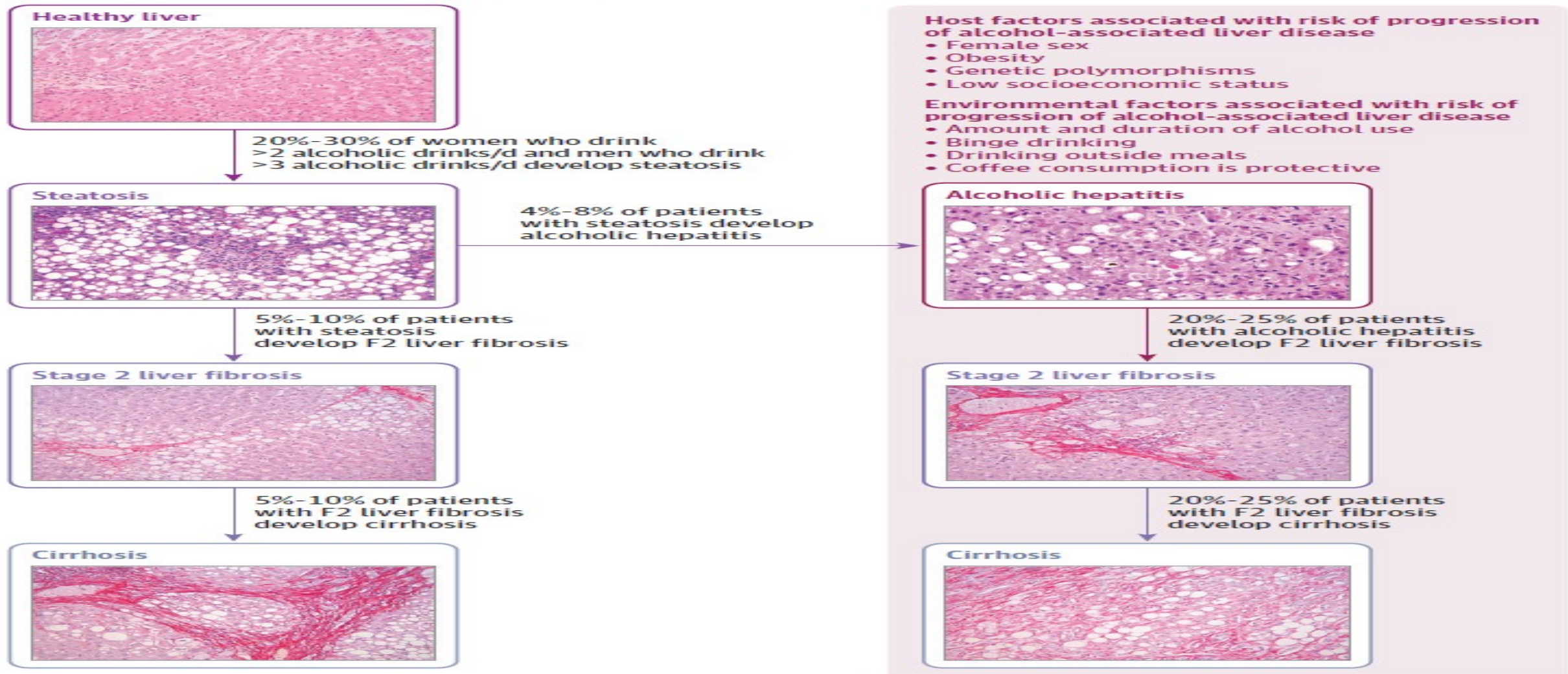


Lille score at 1 week predicts response to treatment and patient survival



PROGNOSIS OF ALCOHOL- ASSOCIATED LIVER DISEASE

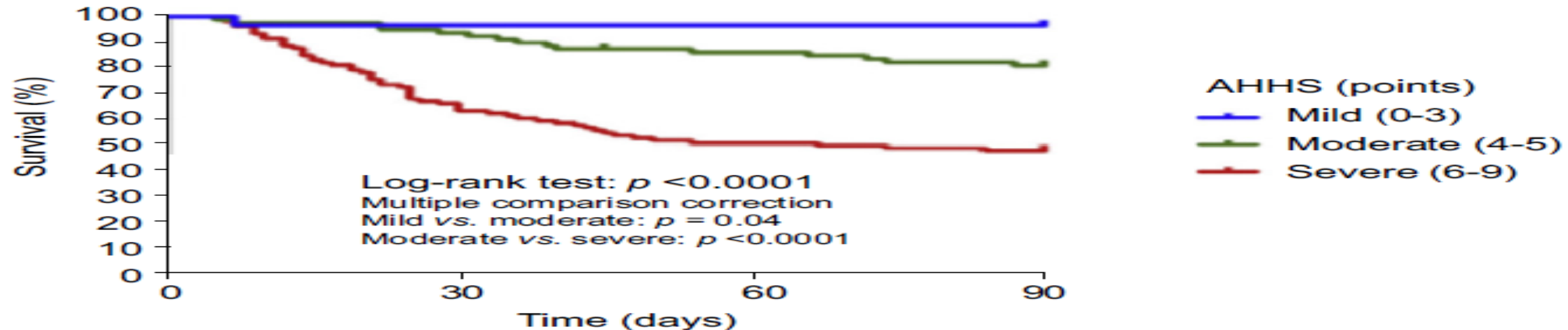
Prognosis of alcohol-associated liver disease



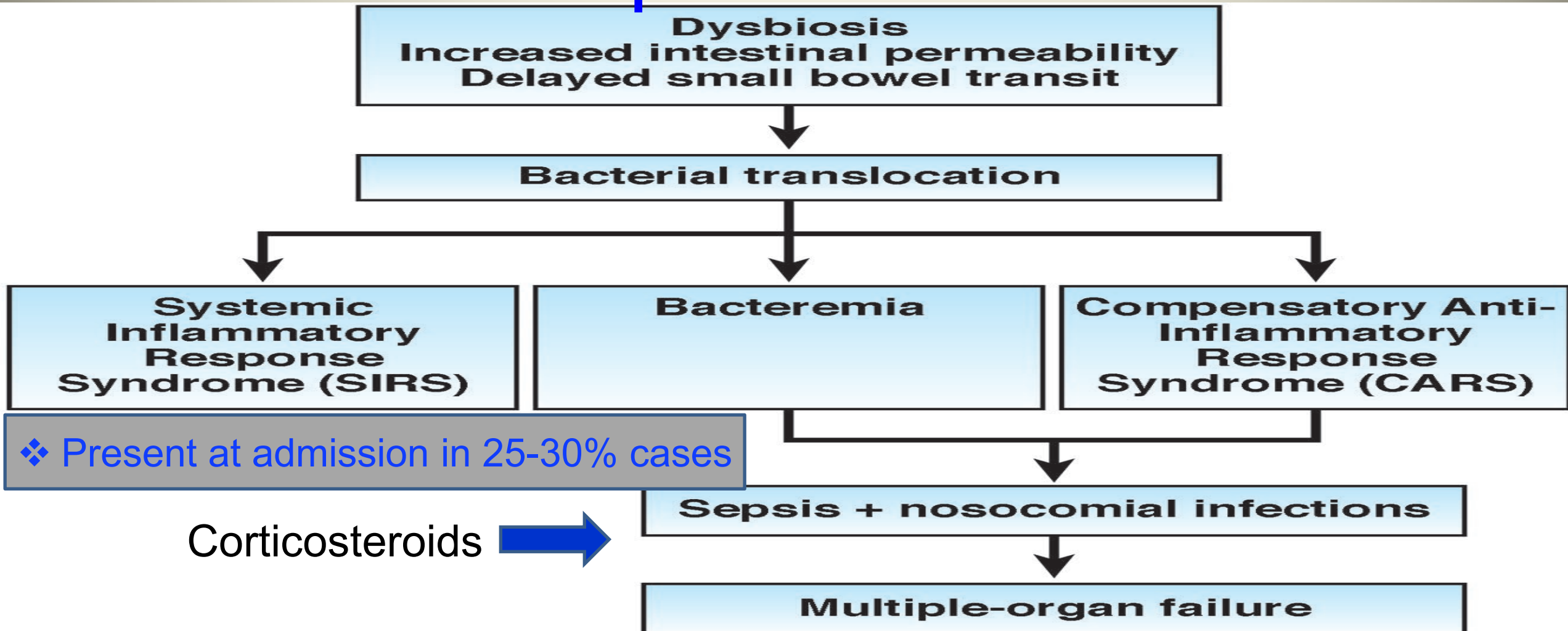
Alcoholic hepatitis histologic score

AHHS for prognostic stratification of AH

	Points
Stage of fibrosis	
No fibrosis or portal fibrosis	0
Expansive fibrosis	0
Bridging fibrosis or cirrhosis	+3
Bilirubinostasis	
No	0
Hepatocellular only	0
Canalicular or ductular	+1
Canalicular or ductular plus hepatocellular	+2
PMN infiltration	
No/mild	+2
Severe	0
Megamitochondria	
No megamitochondria	+2
Megamitochondria	0

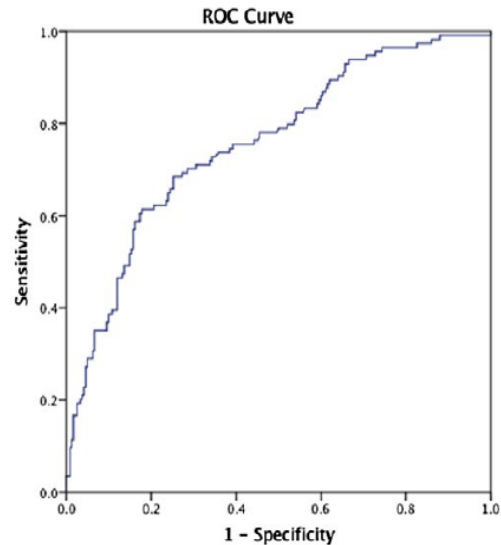


Infections shadow alcoholic hepatitis patients

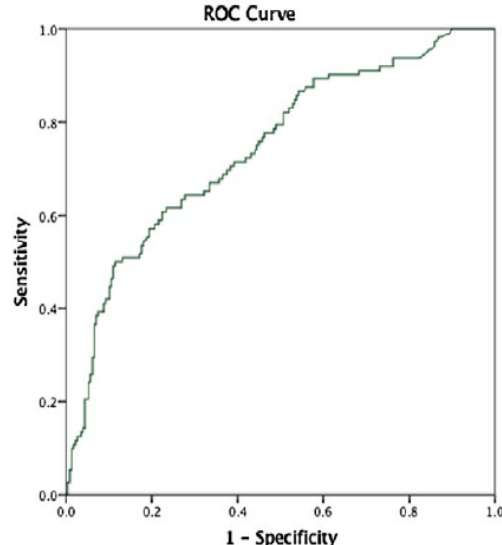


Acute kidney injury in alcoholic hepatitis worsens outcome and is predictable at admission

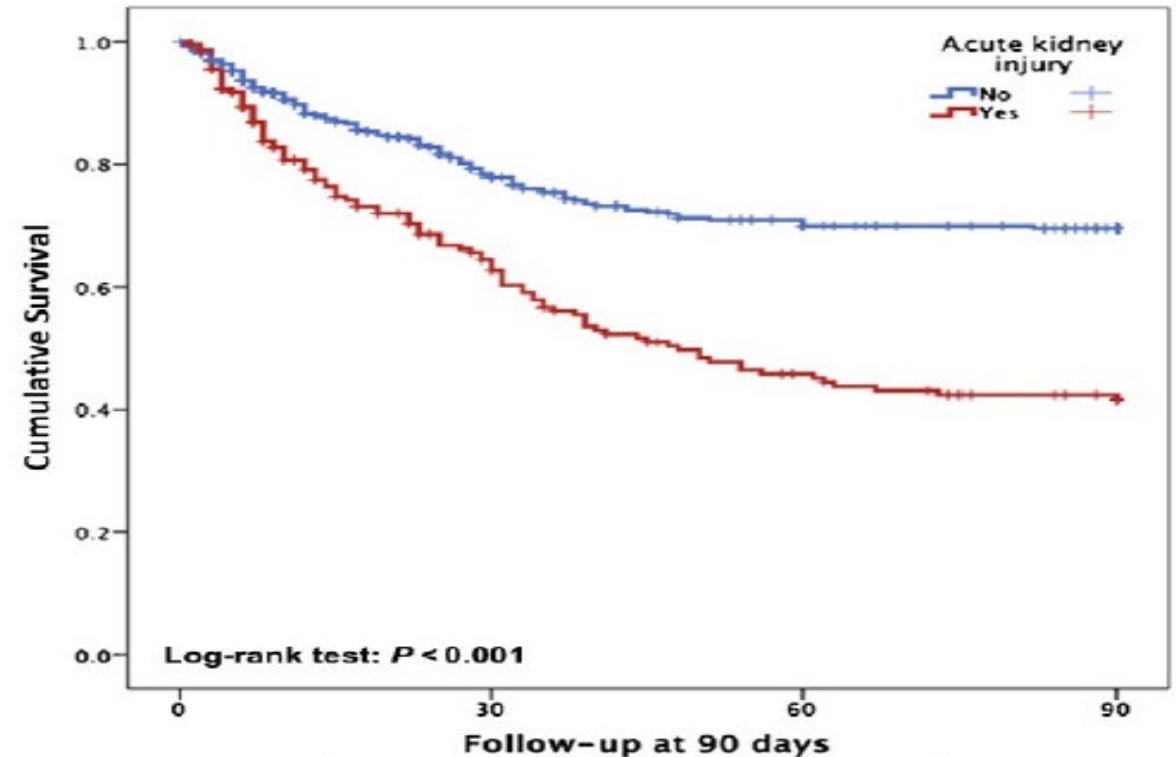
AKI-AH Risk Score = MELD*(LN[1.109]) + HE*(LN[2.775]) + SIRS*(LN[1.993])



Test cohort, n = 390
AUROC 0.76, 95% CI 0.70-0.81
 $P < 0.001$



Validation cohort, n = 383
AUROC 0.74, 95% CI 0.69-0.80
 $P < 0.001$



Moderate alcoholic hepatitis has significant short term mortality

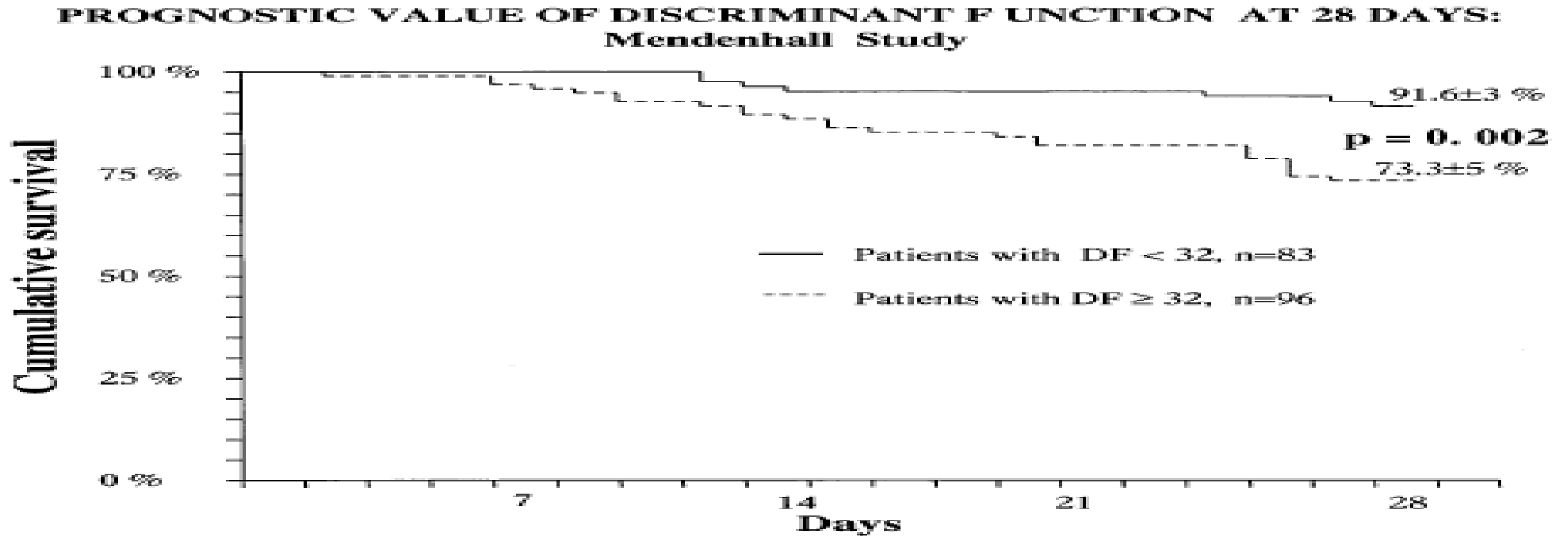


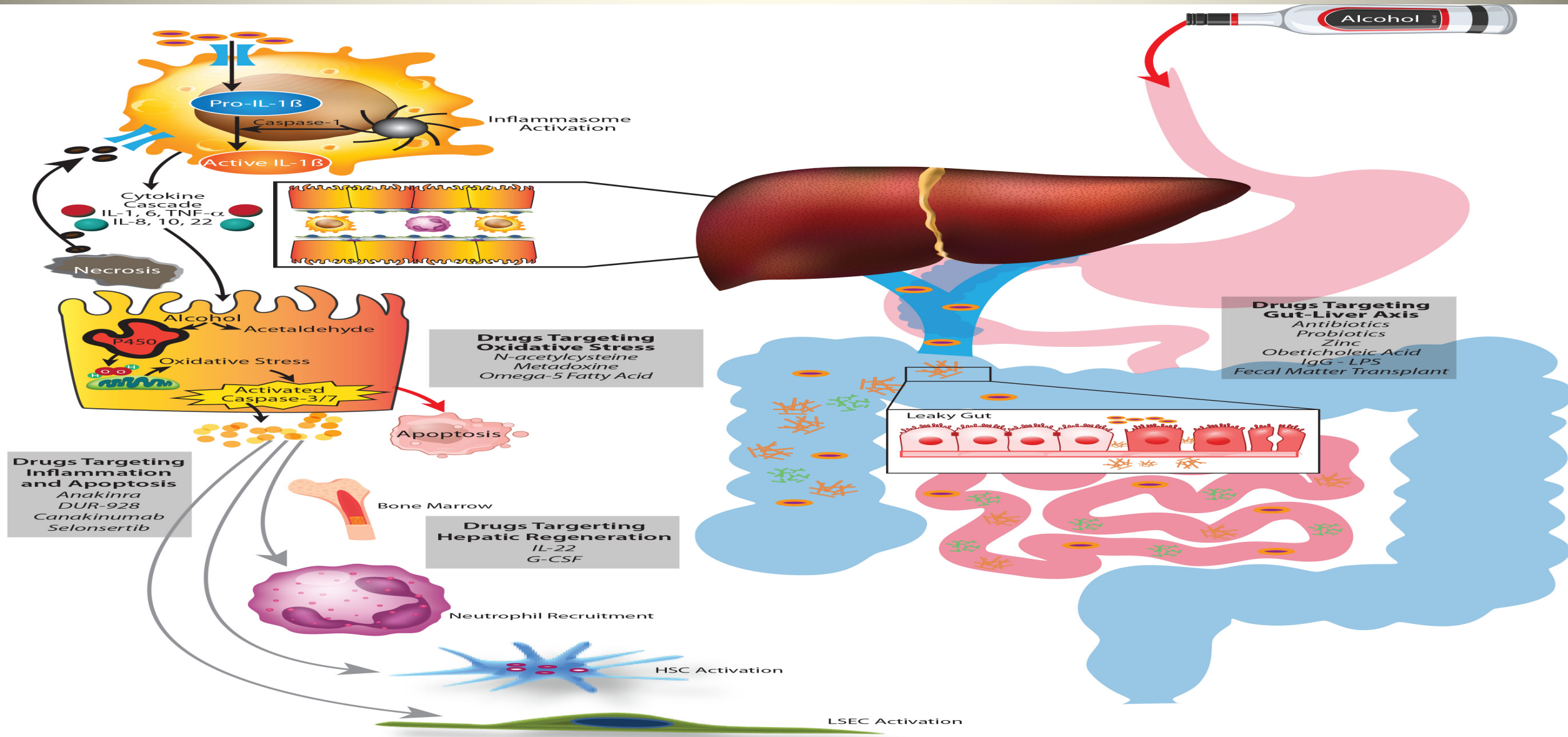
Fig. 1. Survival at 28 days of patients with a DF ≥ 32 ($n = 96$) and patients with DF < 32 ($n = 83$) in Mendenhall's study.

Corticosteroid is suboptimal treatment for severe alcoholic hepatitis

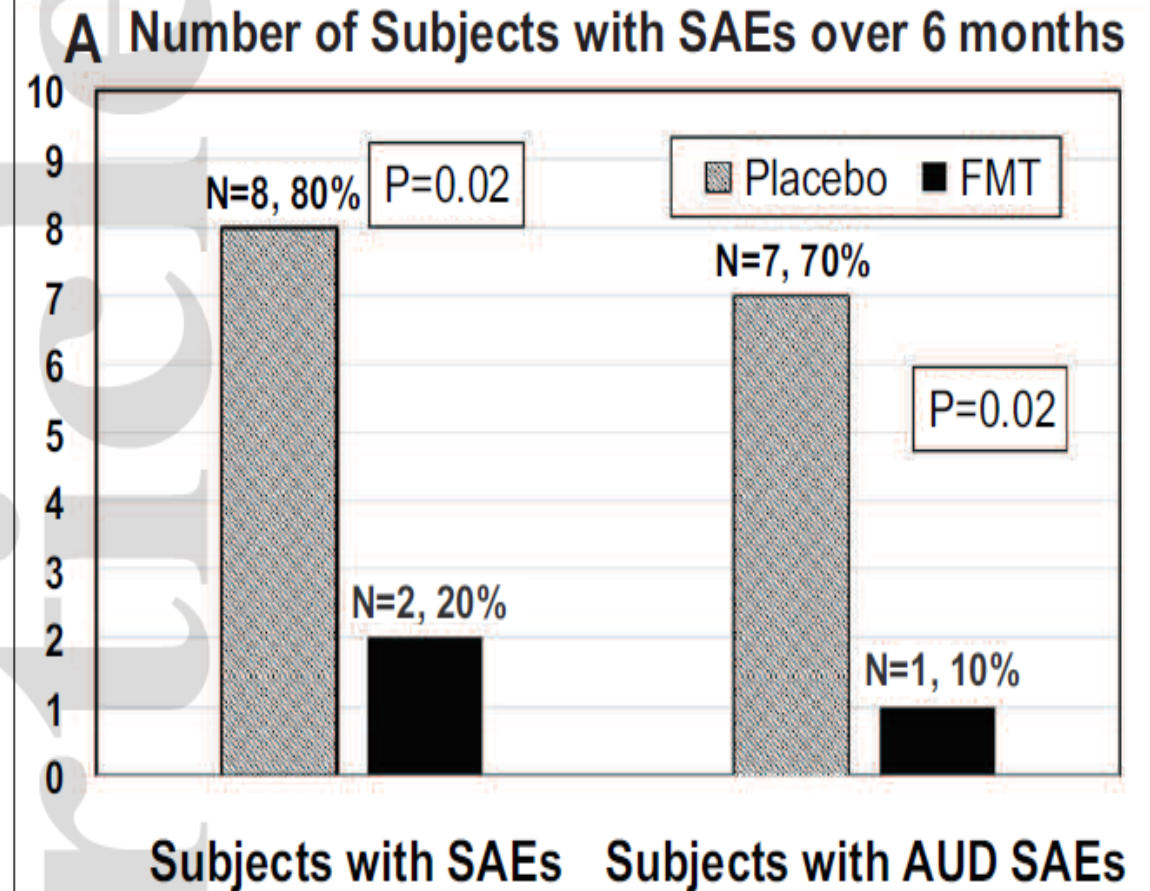
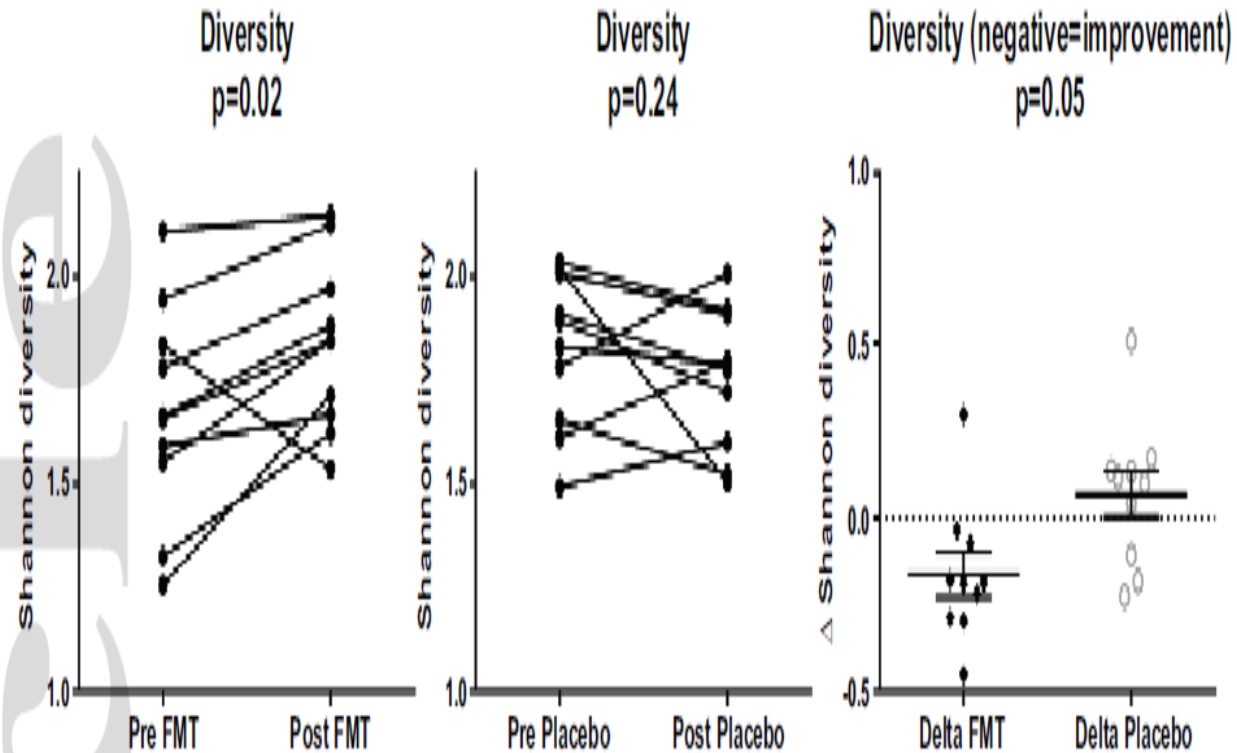
- ❖ Only 60-70% patients are eligible for corticosteroids
- ❖ Response rate only 50-60% which can only be predicted at 4-7 days of treatment
- ❖ Provider heterogeneity for fear of adverse effects
- ❖ Survival benefit for only one month

EMERGING TARGETS FOR ALCOHOL-ASSOCIATED LIVER DISEASE AND ALCOHOLIC HEPATITIS

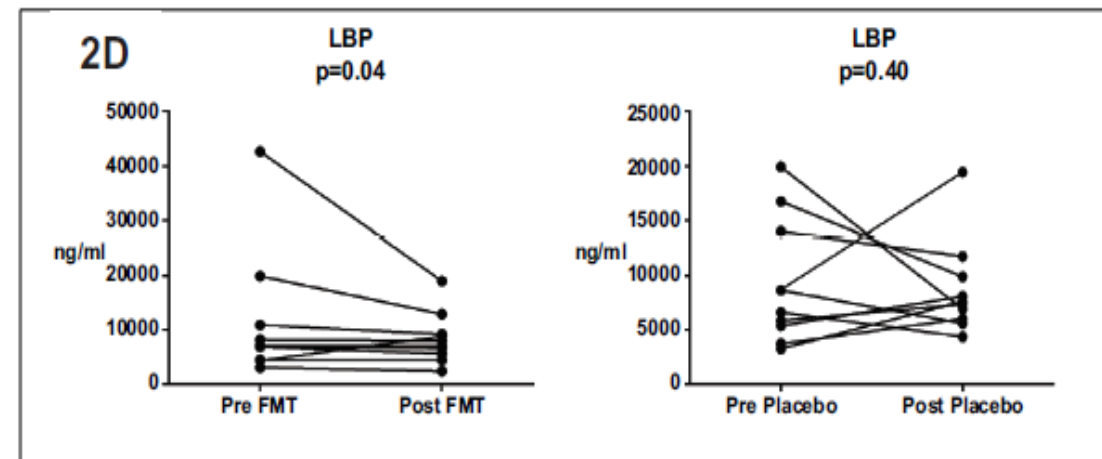
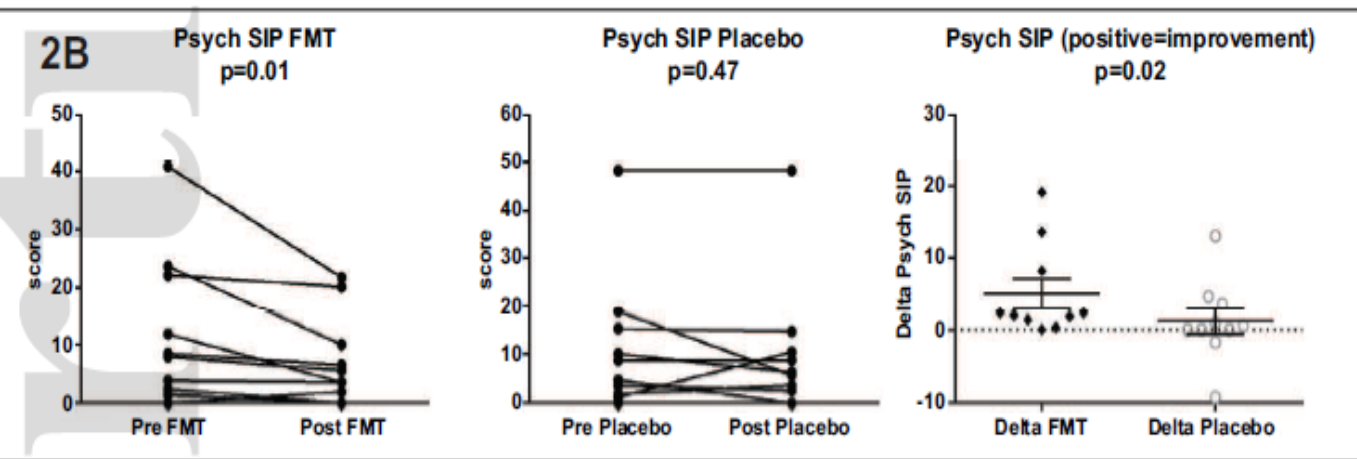
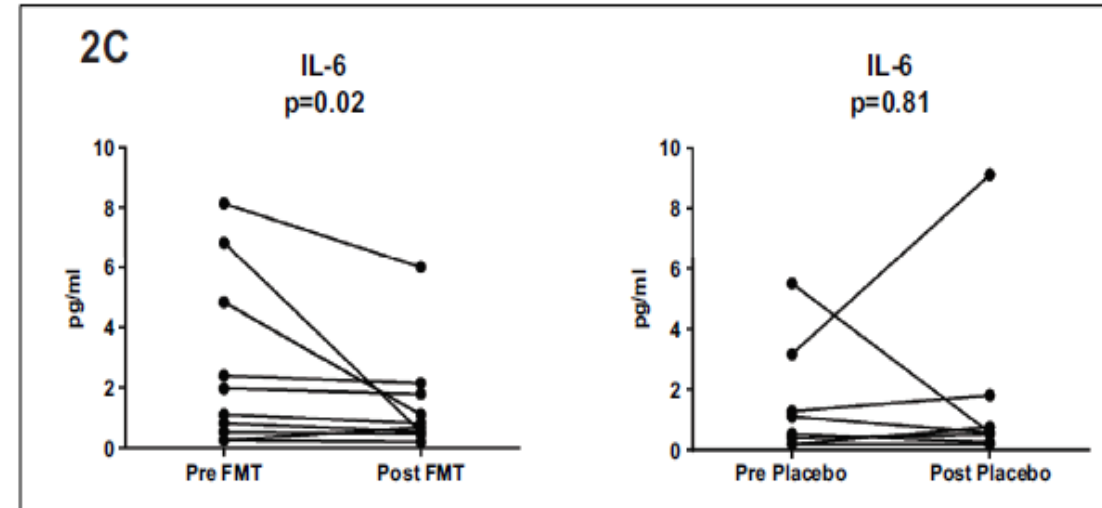
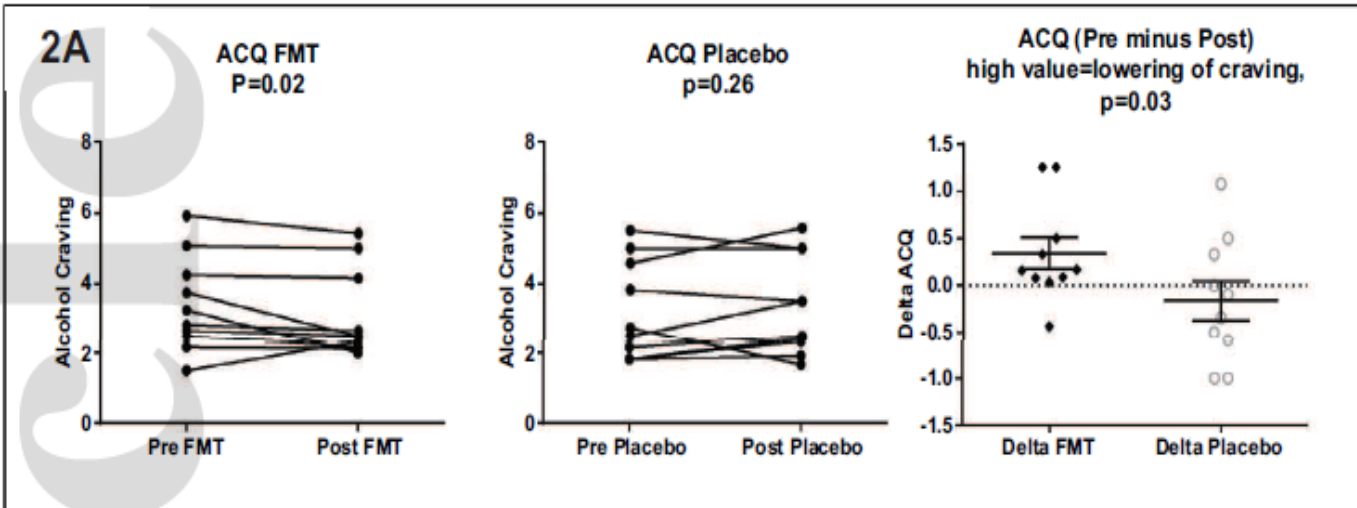
Newer targets for alcoholic hepatitis



Fecal microbiota transplant is safe and improves gut microbiome diversity



Improved diversity is associated with decreased inflammation and craving



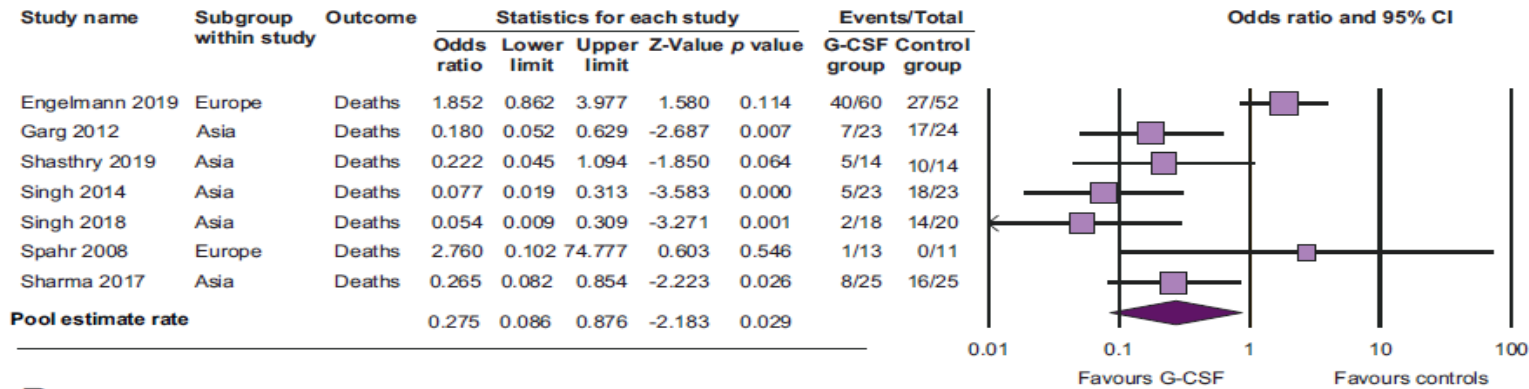
IL-22 in alcoholic hepatitis

Phase-2 dose escalating study

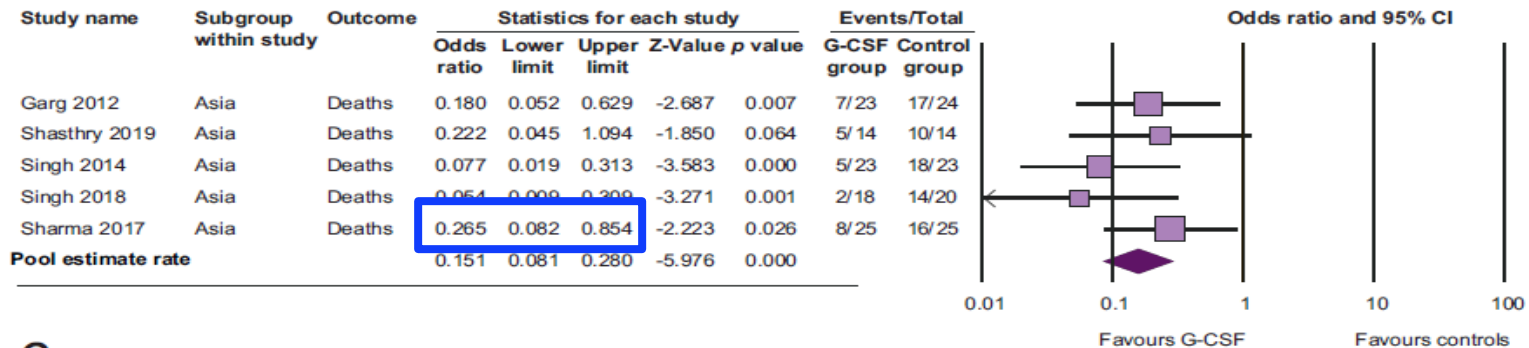
- ❖ 10, 30, or 45 mcg/kg on days 1 and 7
- ❖ N=18, 3 patients each with moderate (MELD 11-20) and severe (MELD 21-28) AH
- ❖ No serious adverse events
- ❖ 83% responders compared to 56% in prospective steroid treatment and 6-12% historical controls
- ❖ EV count and markers of inflammation decreased at day 28
- ❖ Markers of regeneration increased at days 28 and 42

G-CSF remains controversial in treatment of AH

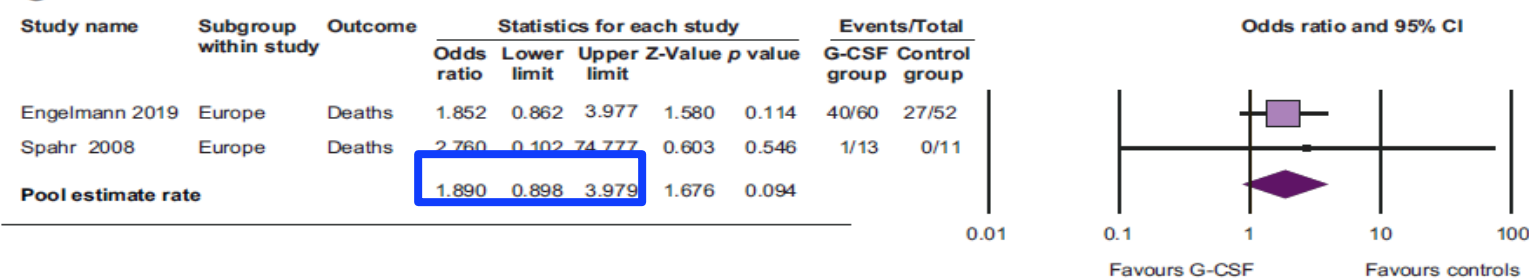
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B



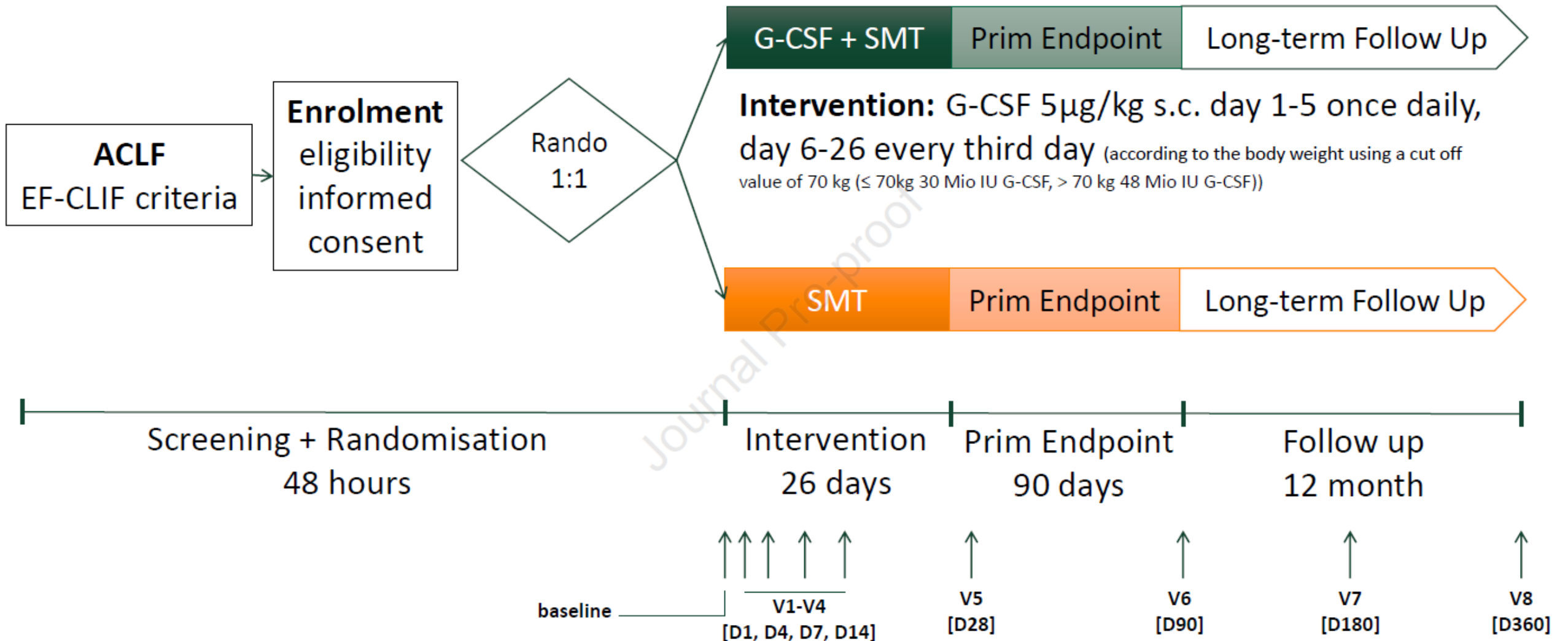
C



- ❖ Meta-analysis of 7 RCT (n=396, 199 G-CSF)
- ❖ Improved 90-d survival
- ❖ Heterogeneous data
- ❖ Benefit in Asia but not in European studies

Marot, Singal, Moreno, Deltenre. JHEP Reports 2020; Jun 12 Epub

Multicenter randomized trial in acute on chronic liver failure (GRAFT study)



G-CSF not associated with improved complications or organ failures

Complication	Treatment group (G-CSF + SMT)	Control group (SMT)	Level of significance
ACLF remission observed ¹	33/87 ² (37.9%)	30/86 ² (34.9%)	p=0.68 ⁵
ACLF re-episode ³	15/87 (17.2%)	8/86 ² (9.3%)	p=0.13 ⁴
Ascites	87 (98.9%)	87 (98.9%)	p=1.000
Hepatic encephalopathy	64 (72.7%)	67 (76.1%)	p=0.730
Hepatorenal syndrome	71 (80.7%)	69 (78.4%)	p=0.852
Bacterial infections	71 (80.8%)	69 (78.4%)	p=0.709
Variceal Bleeding	7 (8%)	7 (8%)	p=1.000

EARLY LIVER
TRANSPLANTATION IN
ALCOHOL ASSOCIATED LIVER
DISEASE

Guidelines on liver transplantation for alcohol-associated liver disease

- ❖ Appropriate patients with alcoholic cirrhosis should be considered for liver transplantation, after careful evaluation of medical and psychosocial candidacy (*AASLD 2010*).
- ❖ The decision on liver transplant evaluation should not be based solely on six mo. of abstinence and other criteria should be considered (*ACG 2018*).
- ❖ The selection of patients with alcohol use disorder should not be based on the six month criterion alone (*EASL 2018*).
- ❖ Candidate selection for liver transplantation in alcohol-associated cirrhosis should not be based solely on a fixed interval of abstinence (*AASLD 2020*).

Six months abstinence is not the best predictor of relapse to alcohol use

Criterion to predict relapse	Total studies	Predicted	Did not predict
Six months of pre-LT abstinence	11	2	9
Polysubstance abuse	5	3	2
Social instability	7	6	1
Family history of alcoholism	4	3	1
Younger age	3	2	1
Co-existing mental disorders	5	3	2
Failed previous treatment	3	2	1
Lack of insight	7	0	7
Contract non-compliance	4	3	1

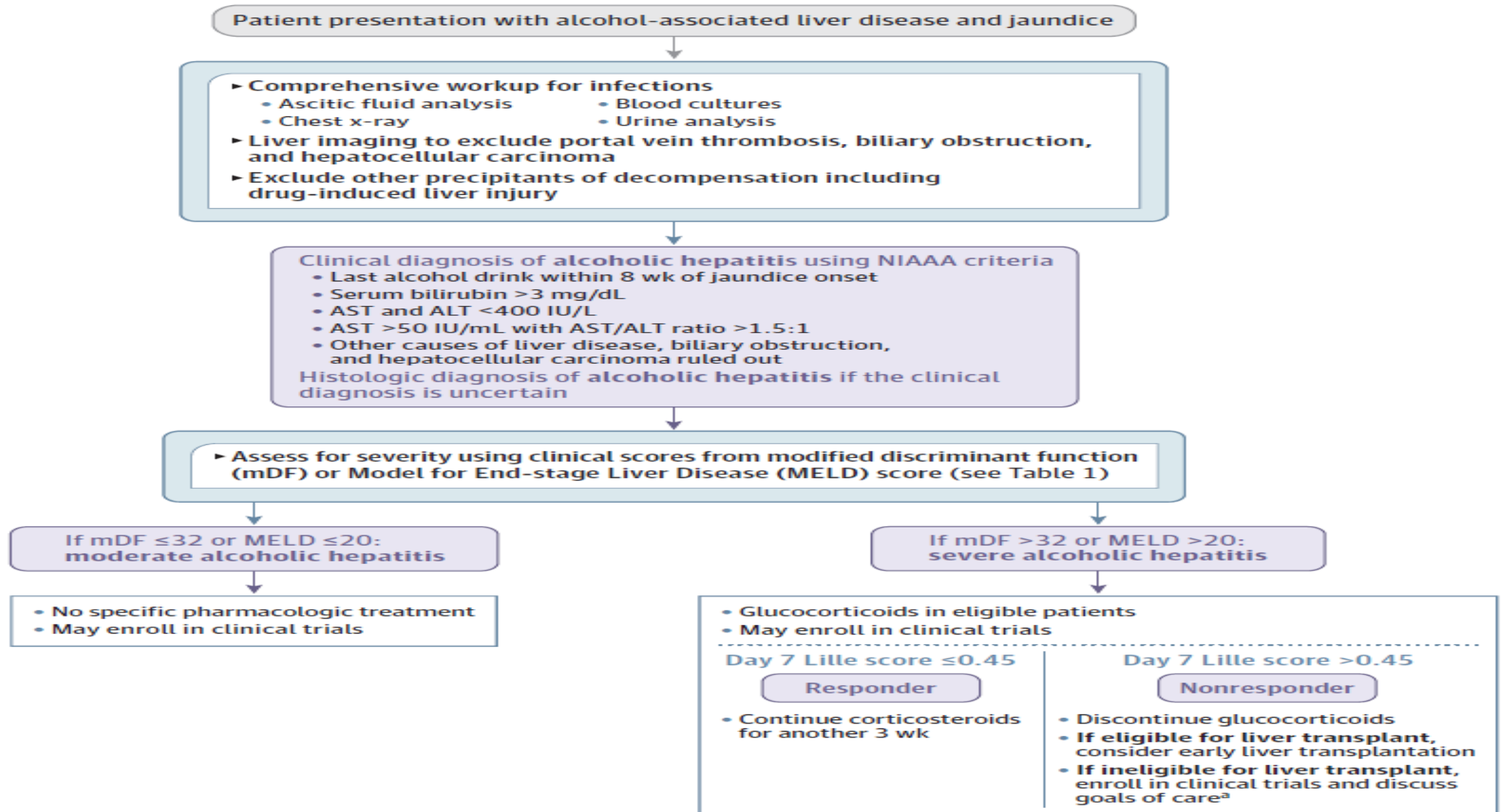
Early liver transplant for alcoholic hepatitis improves patient survival

Group	Effect size (95% CI)	Heterogeneity P
Relapse to alcohol use		
Harmful use of alcohol	0.14 (0.08-0.23)	0.6
AH vs. AC	1.68 (0.79-2.36)	0.3
Six months survival		
AH with stringent criteria	0.80 (0.69-0.88)	0.2
AH vs. AC within six months	2.00 (0.95-4.23)	0.7
Early LT for AH vs. no LT	16.7 (6.2-44.8)	0.3

Guidelines recommend early liver transplant for select ALD patients

- ❖ Early LT may be considered for highly selected patients with severe alcoholic hepatitis (*ACG 2018*).
- ❖ Early LT should be proposed to a minority of patients with severe AH not responding to medical therapy after a careful selection process (*EASL 2018*).
- ❖ Liver transplantation may be considered in carefully selected patients with favorable psychosocial profiles in severe AH not responding to medical therapy (*AASLD 2020*).

Current management of alcoholic hepatitis



Barriers to early liver transplantation in alcoholic hepatitis

	Centers with LT for AH (N=12)	Centers without LT for AH (N=33)
Insurance approval	3	1
Lack of supporting evidence	0	2
Socio-cultural factors	0	5
Concern for recidivism	1	2
Limited social support	0	2
Organ shortage	0	1
Center policy / protocol	2	9
No challenges	6	11*

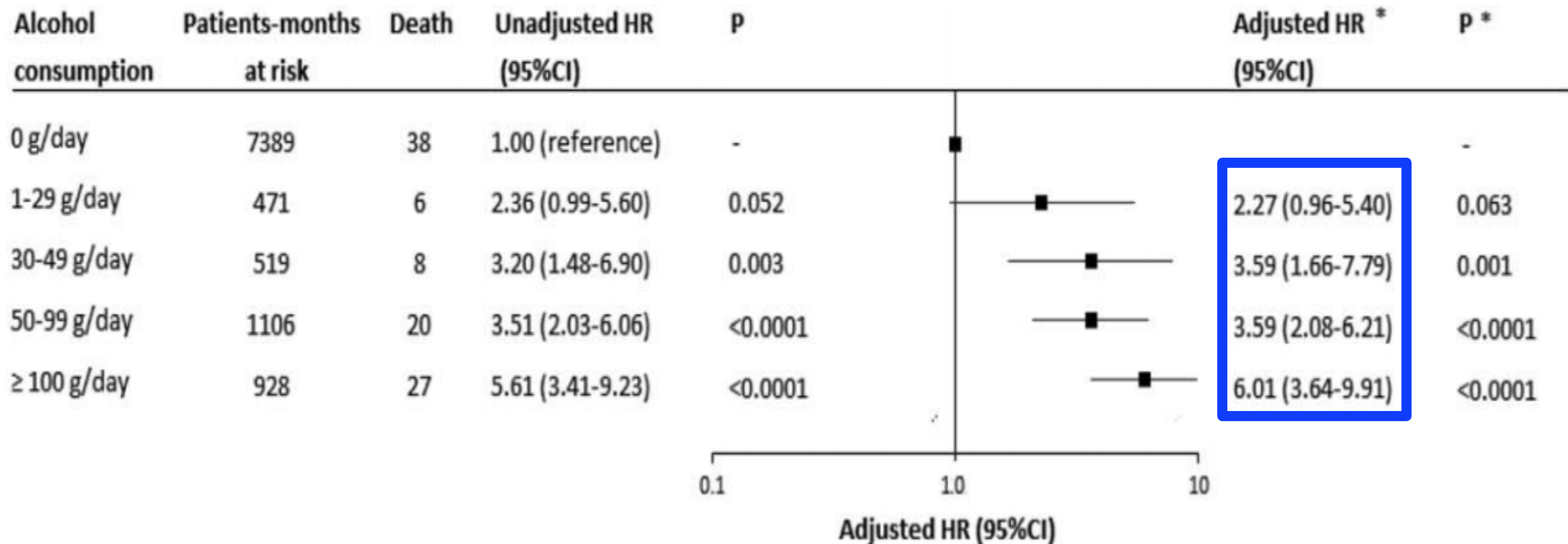
**Two centers reported that they are planning on liver transplantation for alcoholic hepatitis (AH)*

Hasanin et al. Liver Transpl 2015; 21: 1449-52.

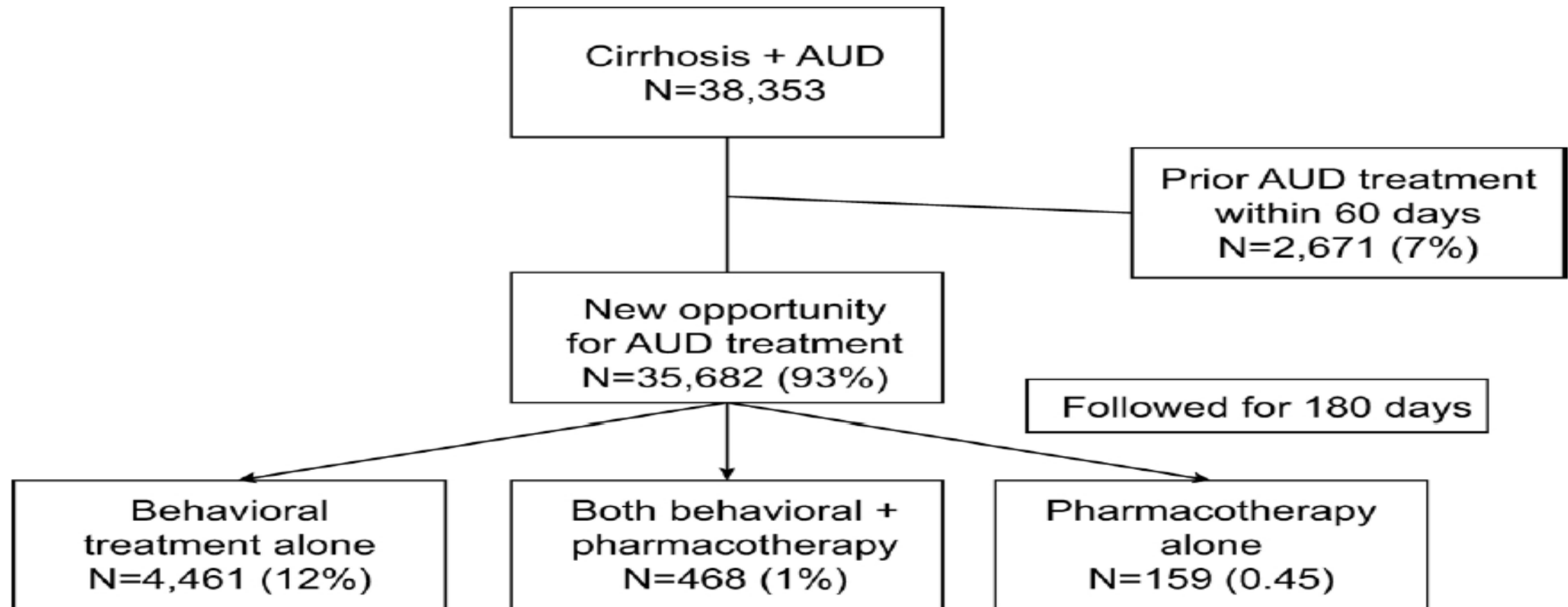
Alcohol relapse negatively impacts long-term post-transplant outcomes

- ❖ Steatohepatitis and cirrhosis are 9 and 8 folds ↑ among harmful alcohol users.¹
- ❖ Recurrent alcoholic cirrhosis 2% of all recipients and 9% of 141 biopsied.¹
- ❖ Harmful alcohol relapse associated with about 4 folds ↓ patient survival at 10 years.¹
- ❖ Increased risk of malignancy of the aero-digestive tract, especially in smokers.²
- ❖ TAC to everolimus change improves long-term outcome in those with malignancy.³

Alcohol use determines long-term outcome in alcoholic hepatitis patients



Treatment for alcohol use disorder is used rarely in cirrhosis patients



Clinician level barriers in implementing integrated care model in practice

- | | |
|--|--|
| <ul style="list-style-type: none">• Lack of recognition of AUD screening• Lack of awareness and experience on AUD treatment• Lack of screening for ALD in at risk asymptomatic individuals | <ul style="list-style-type: none">• Education and awareness about AUD• Training of hepatologists on addiction medicine• Education to develop positive attitude towards patients with AUD |
|--|--|

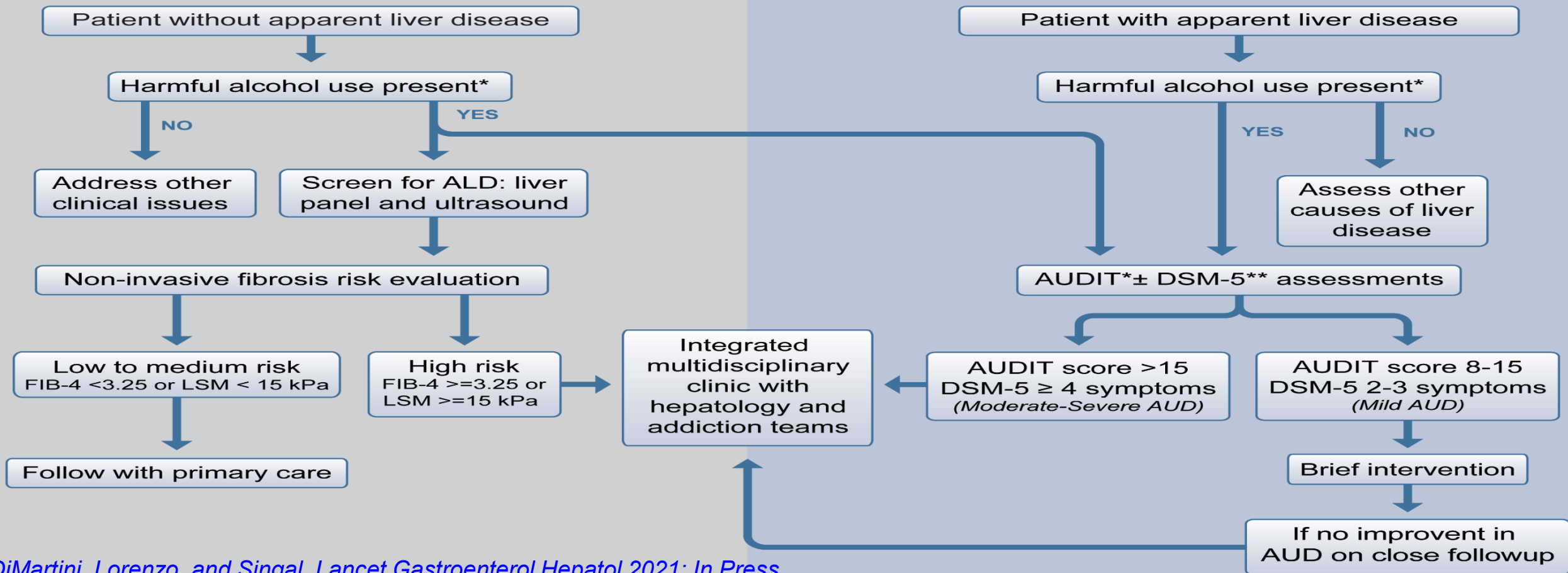
Patient level barriers in implementing integrated care model in practice

- | | |
|--|---|
| <ul style="list-style-type: none">• Lack of awareness and education• Lack of insight and acceptance of diagnosis of AUD• Lack of willingness to undergo AUD treatment• Too sick or other issues to undergo treatment sessions | <ul style="list-style-type: none">• Changing to alcohol-associated to avoid stigma of “Alcoholic”• Address AUD as a disease and in a non-threatening way• Patient education and briefing on alcohol related harms• Frequent monitoring (digital/smart phone Apps / random BAC / wearable alcohol biosensors) |
|--|---|

System level barriers in implementing integrated care model in practice

- | | |
|---|--|
| <ul style="list-style-type: none">• Lack of insurance coverage for AUD treatment• Lack of adequate mental health resources and manpower• Difficulty in combined billing by two specialists• Siloed practices of addiction specialists and hepatologists• Lack of specific protocols for AUD monitoring and care | <ul style="list-style-type: none">• National policies to increase federal and state level funding for mental health care• Collaborative administrative policies to establish combined billing process and cost sharing• Development of uniform protocols on use of alcohol biomarkers and definition of relapse of alcohol use after LT. |
|---|--|

Integrated multidisciplinary care model for management of dual pathology in patients with ALD



HEALTH CARE POLICIES AND PREVENTION OF ALCOHOL ASSOCIATED LIVER DISEASE

Impact of public health policies on alcohol-associated liver disease in Latin America: An ecological multi-national study

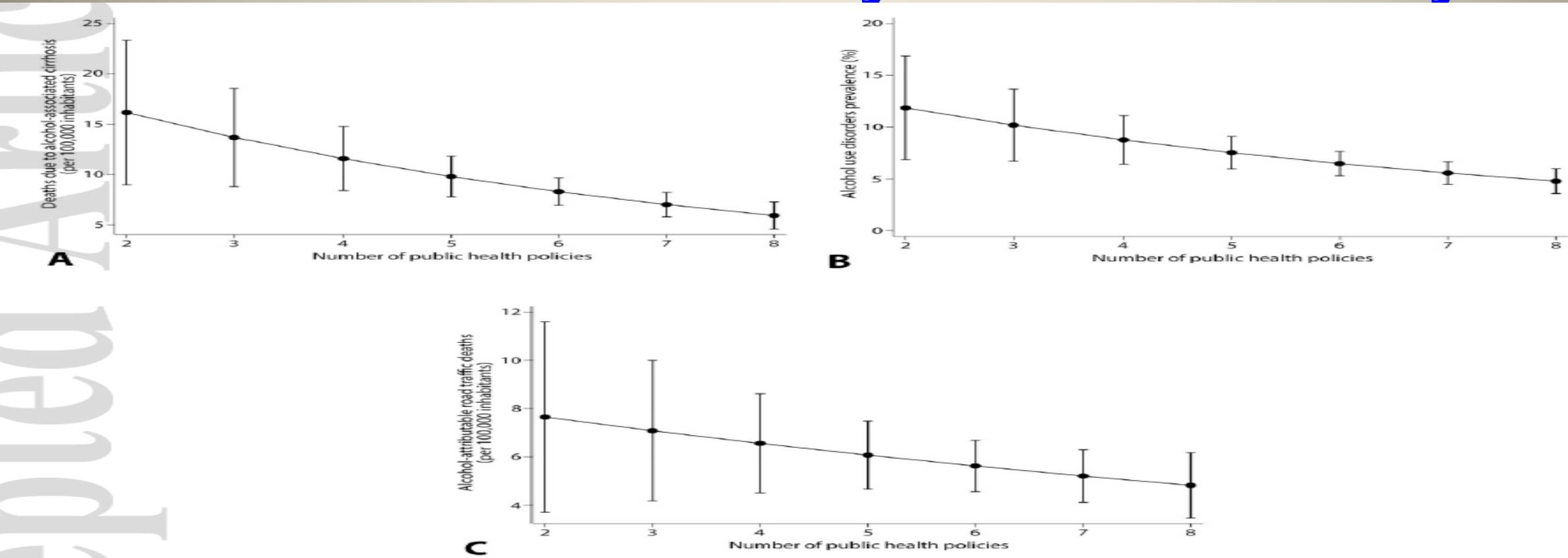
Luis Antonio Díaz¹, Francisco Idalsoaga¹, Eduardo Fuentes-López², Andrea Márquez-Lomas³, Carolina A Ramírez⁴, Juan Pablo Roblero⁵, Roberta C Araujo⁶, Fátima Higuera-de-la-Tijera⁷, Luis Guillermo Toro⁸, Galo Pazmiño⁹, Pedro Montes¹⁰, Nelia Hernandez¹¹, Manuel Mendizabal¹², Oscar Corsi¹³, Catterina Ferreccio¹⁴, Mariana Lazo¹⁵, Mayur Brahmanian¹⁶, Ashwani K Singal¹⁷, Ramon Bataller¹⁸, Marco Arrese¹, Juan Pablo Arab¹

Hepatology 2021; Jun 16, Epub ahead of print.

Public policies	Deaths due to alcohol-associated cirrhosis*			Alcohol use disorders**			Alcohol-attributable deaths due to road traffic injuries**		
	PR	95%CI	p-value	PR	95%CI	p-value	PR	95%CI	p-value
1. National plan to fight harmful consequences of alcohol consumption	0.13	0.05-0.32	<0.001	0.17	0.06-0.48	0.001	0.22	0.09-0.60	0.003
2. Taxes control & pricing policies	0.90	0.27-3.02	0.865	0.71	0.17-2.95	0.640	0.89	0.20-4.00	0.877
3. Drinking age and youth focus policies	0.28	0.09-0.81	0.019	0.63	0.22-1.96	0.424	0.42	0.15-1.19	0.101
4. Driving-related alcohol policies	0.31	0.12-0.83	0.020	0.35	0.15-0.83	0.016	0.33	0.12-0.89	0.029
5. Control over advertising and promotion	0.44	0.17-1.10	0.080	0.44	0.12-1.81	0.268	0.55	0.15-2.07	0.378
6. Government monitoring systems	0.49	0.18-1.38	0.177	0.48	0.20-1.19	0.113	0.39	0.16-0.96	0.040
7. Restrictions to alcohol access	0.25	0.09-0.67	0.006	0.34	0.13-0.91	0.032	0.90	0.26-3.01	0.850
8. National license, production, and selling control	2.24	0.51-9.95	0.288	1.46	0.35-6.01	0.604	1.73	0.45-6.71	0.428
Prevalence difference (PD) >20 10-20 -X to 10 PD with p<0.05									

*Model adjusted by obesity and diabetes. **Model adjusted by the Gini index. PR: Prevalence ratio; CI: Confidence interval.

Number of public health policies is associated with reducing alcohol related morbidity and mortality



Key take home points

- ❖ ALD is one of the most common liver diseases worldwide.
- ❖ Need for diagnosis of ALD in its early stage.
- ❖ Low threshold for suspecting AH among decompensated ALD patients with jaundice.
- ❖ Clinical diagnosis of AH and liver biopsy if uncertain.
- ❖ Corticosteroid for severe AH is a suboptimal treatment.

Key take home points

- ❖ Clinical unmet need of newer therapies for alcoholic hepatitis.
- ❖ FMT, G-CSF, IL-22, and DUR-928 seem promising.
- ❖ Complete abstinence determines long-term outcome in ALD patients.
- ❖ Need to overcome barriers to implement integrated care model for the management of ALD patients.
- ❖ Need for public health policies to reduce alcohol use in population and prevent ALD related healthcare burden

