2020 Annual Update in Medical Hepatology

How to Effectively Treat Alcohol-Related Liver Disease

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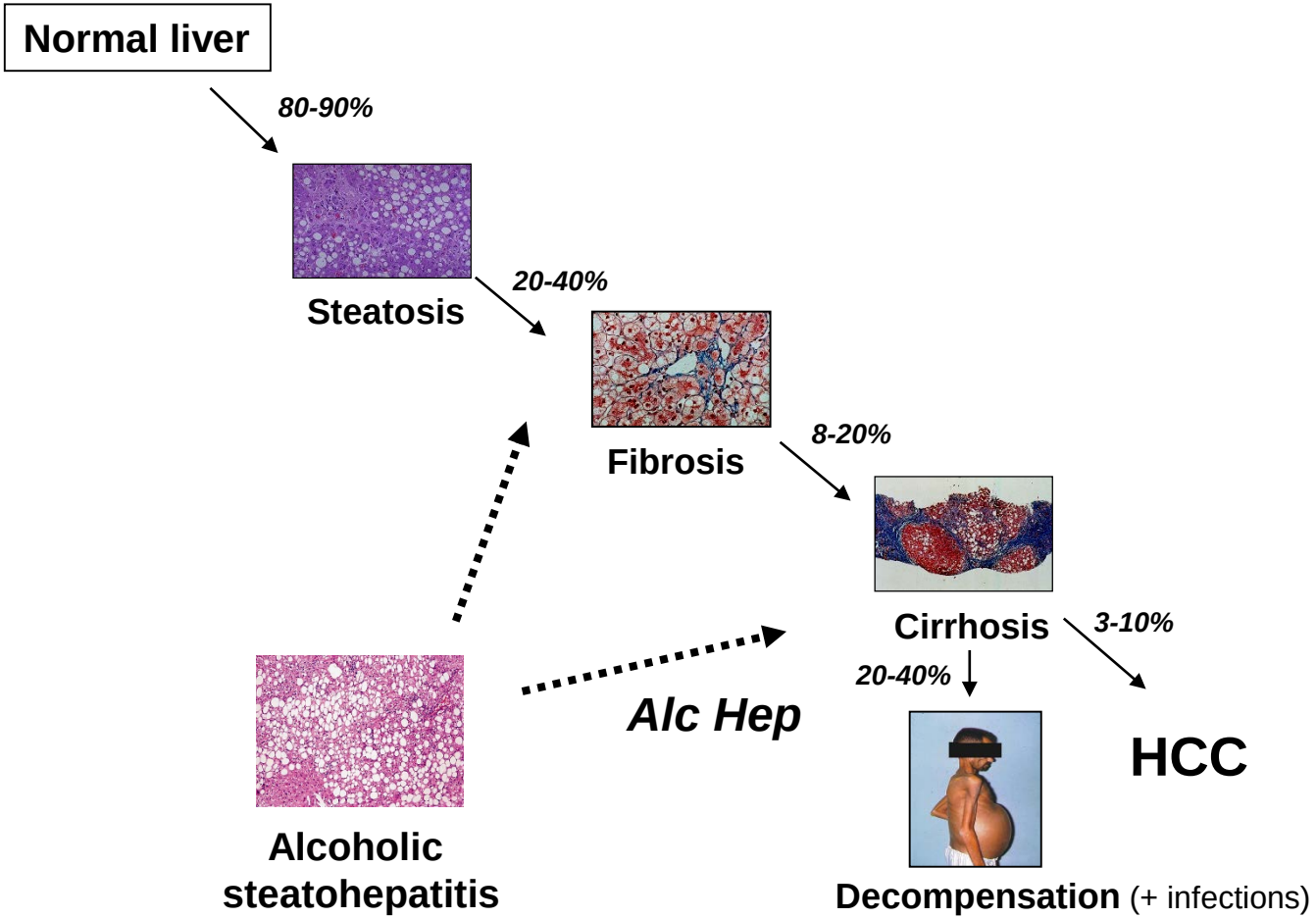
UPMC LIFE CHANGING MEDICINE

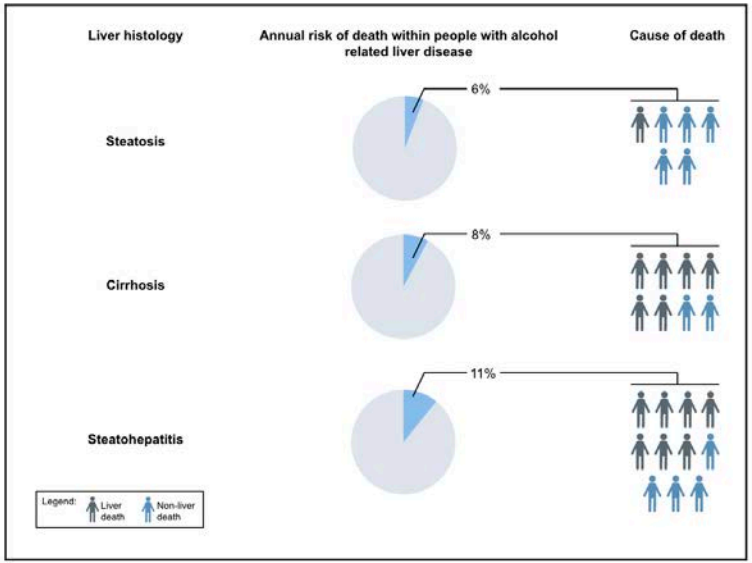
NATURAL HISTORY OF ALD



IMPACT HISTOLOGY ON MORTALITY

Natural history of histologically proven alcohol-related liver disease: A systematic review

Richard Parker[1,*], Guruprasad P. Aithal[2,3], Ulrik Becker[4,5], Dermot Gleeson[6], Steven Masson[7], Judith I. Wyatt[8], Ian A. Rowe[1,9], on behalf of the WALDO study group



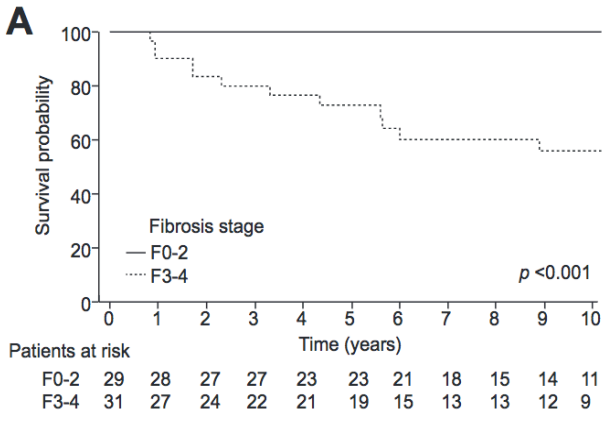
Highlights

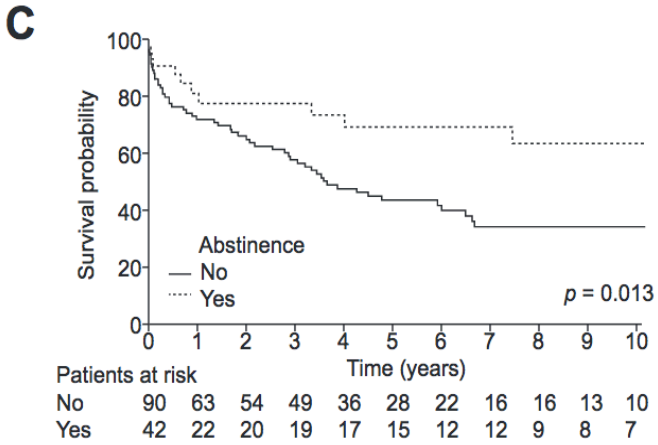
- Approximately 15% of hazardous drinkers may have normal liver histology.
- Progression to cirrhosis is most common in people with steatohepatitis (10% per year).
- Liver-related factors are the predominant cause of death in people with steatohepatitis or cirrhosis.
- Hepatic steatosis is not benign, with an annual mortality rate of ~6%/year, but deaths are mainly non-liver related.

IMPACT HISTOLOGY ON MORTALITY

Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease

Carolin Lackner[1,*,†], Walter Spindelboeck[2,†], Johannes Haybaeck[1], Philipp Douschan[2], Florian Rainer[2], Luigi Terracciano[3], Josef Haas[4], Andrea Berghold[5], Ramon Bataller[6], Rudolf E. Stauber[2]





DETECTION OF EARLY vs ADVANCED ALD WORLDWIDE: THE GLADIS STUDY

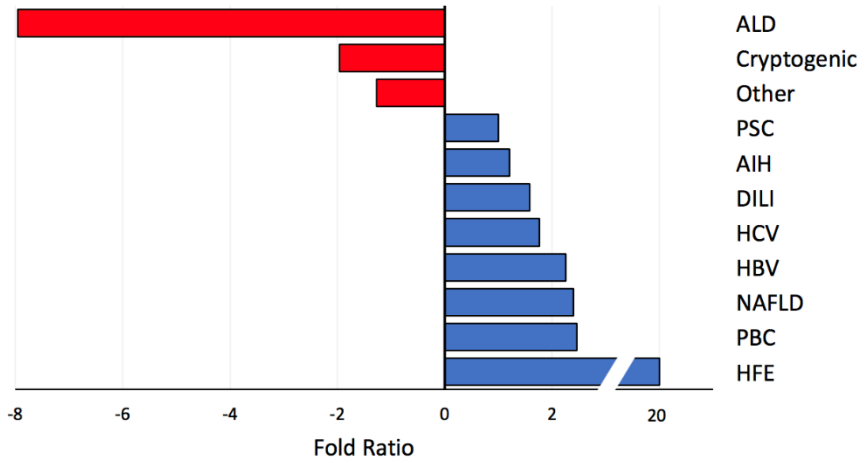
Alcohol-Related Liver Disease Is Rarely Detected at Early Stages Compared With Liver Diseases of Other Etiologies Worldwide

Neil D. Shah,[*,a] Meritxell Ventura-Cots,[‡,§,a] Juan G. Abraldes,[‖] Mohamed Alboraie,[¶,#] Ahmad Alfadhli,[¶] Josepmaria Argemi,[‡,**] Ester Badia-Aranda,[‡‡] Enrique Arús-Soler,[§§] A. Sidney Barritt IV,[*] Fernando Bessone,[‖‖] Marina Biryukova,[¶¶] Flair J. Carrilho,[##] Marlen Castellanos Fernández,[§§] Zaily Dorta Guiridi,[¶¶] Mohamed El Kassas,[***] Teo Eng-Kiong,[‡‡‡] Alberto Queiroz Farias,[##] Jacob George,[§§§] Wenfang Gui,[‖‖‖] Prem H. Thurairajah,[‡‡‡] John Chen Hsiang,[‡‡‡] Azra Husić-Selimovic,[¶¶¶] Vasily Isakov,[¶¶] Mercy Karoney,[###] Won Kim,[****] Johannes Kluwe,[‡‡‡‡] Rakesh Kochhar,[§§§§] Narendra Dhaka,[§§§§] Pedro Marques Costa,[‖‖‖‖] Mariana A. Nabeshima Pharm,[##] Suzane K. Ono,[##] Daniela Reis,[‖‖‖‖] Agustina Rodil,[##] Caridad Ruenes Domech,[§§] Federico Sáez-Royuela,[‡‡] Christoph Scheurich,[‡‡‡‡] Way Siow,[§§§] Nadja Sivac-Burina,[¶¶¶] Edna Solange Dos Santos Traquino,[§§] Fatma Some,[###] Sanjin Spreckic,[¶¶¶] Shiyun Tan,[¶¶¶¶] Julio Vorobioff,[‖‖] Andrew Wandera,[###] Pengbo Wu,[¶¶¶¶] Mohamed Yacoub,[####] Ling Yang,[‖‖‖] Yuanjie Yu,[¶¶¶¶] Nerma Zahiragic,[¶¶¶] Chaoqun Zhang,[¶¶¶¶] Helena Cortez-Pinto,[‖‖‖‖] and Ramon Bataller[*,‡]

DETECTION OF EARLY vs ADVANCED ALD WORLDWIDE: THE GLADIS STUDY

Worldwide Lack of Early Referral of Patients with Alcoholic Liver Disease: Results of the Global Alcoholic Liver Disease Survey (GLADIS)

Neil D. Shah[1], Meritxell Ventura Cots[1,2], Nerma Zahiragic[7], Mohamed Yacoub[10], Andrew Wandera[3], Julio Vorobioff[13], Edna Solange Dos Santos Traquino[11], Prem Harichander Thurairajah[8], Sanjin Spreckic[7], Enrique R Arus Soler[11], Nadja Sivac[7], Way Siow[9], Christoph Scheurich[4], Federico Sáez-Royuela[12], Agustina Rodil[13], Daniela Reis[16], Suzane Ono[12], Mariana Nabeshima[12], Mercy Karoney[3], Marlen Castellanos Fernández[11], Alberto Farias[12], Caridad Ruenes Domech[11], Pedro Marques Costa[16], Marina Biryukova[6], Ahmad Alfadhli[15], Fatma Some[3], Johannes Kluwe[4], Won Kim[5], Vasily Isakov[6], Azra Husić-Selimovic[7], John Hsiang[8], Jacob George[9], Mohamed El-Kassas[10], Zaily Dorta[11], Flair J. Carrilho[12], Fernando Bessone[13], Ester Badia Aranda[14], Mohamed Alboraie[15], Helena Cortez-Pinto[16], Ramon Bataller[1]



Shah N et al, Clin Gastroenterol Hepatol 2019

EARLY ALD IS THE MOST OVERLOOKED PHENOTYPE IN CLINICAL HEPATOLOGY

Pancreatitis

Neuropathy ?

Myocardiopathy ?

Nephropathy ?

CAMPAIGNS AIMED AT DETECTING SILENT FORMS OF ALD WITH ADANCED FIBROSIS ARE URGENTLY NEEDED AT A GLOBAL LEVEL

HOW CAN WE REVEAL ALCOHOL USE UDERREPORTING ?

- **Suspect alcohol** as a factor or co-factor of liver disease: physical exam, labs (AST, GGT), exclusion other causes.

- **Build trust** in your relationship with your patient before asking.

- **Be sensitive** to the stigma (gender, background, religion, legal).

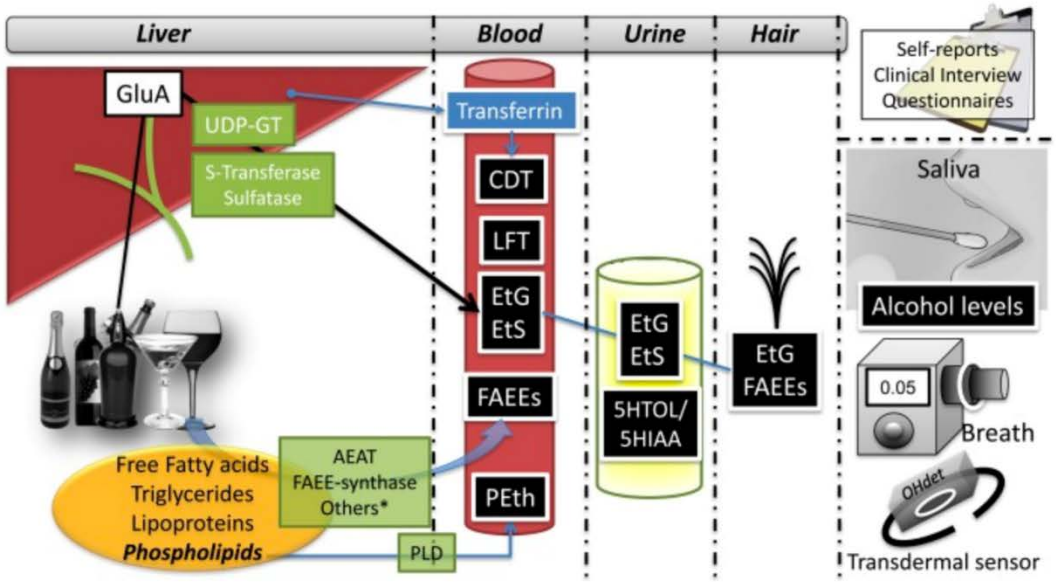
- Ask **family members**.

- **Overshooting** (“ask in a relaxed way if the last drink was this morning or last night”).

- **Alcohol or metabolites detection** in urine or blood.

- **Liver biopsy** in severe cases with uncertain alcohol assessment ?

ALCOHOL BIOMARKERS

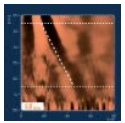


Sources and biological samples of biomarkers of alcohol consumption.

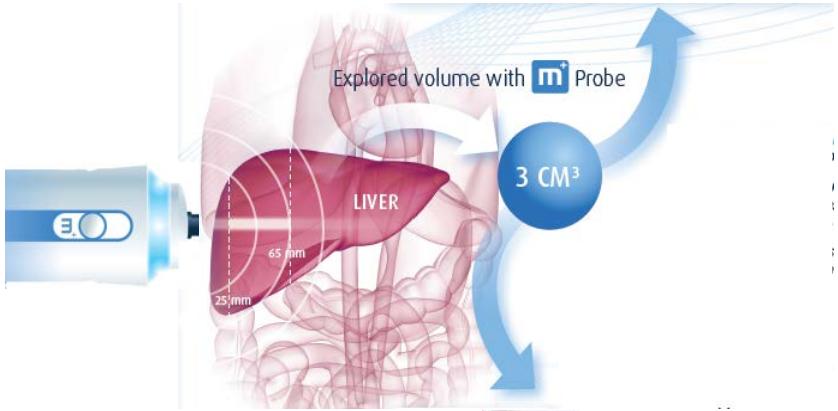
*Refers to other enzymes with FAEE-synthase activity: pancreatic lipase, lipoprotein lipase, glutathione transferase. Abbreviations: AEAT, acyl-coenzyme a-ethanol *O*-acyltransferase; CDT, carbohydrate-deficient transferrin; EtS, ethyl sulfate; GluA, glucuronic acid; LFT, liver function tests; PLD, phospholipase D; UDP-GT, uridine diphosphate.

Cabezas, Lucey & Bataller. Clin Liver Dis 2017

FIBROSCAN IN PATIENTS WITH ASYMPTOMATIC ALD



Stiffness → ~ fibrosis



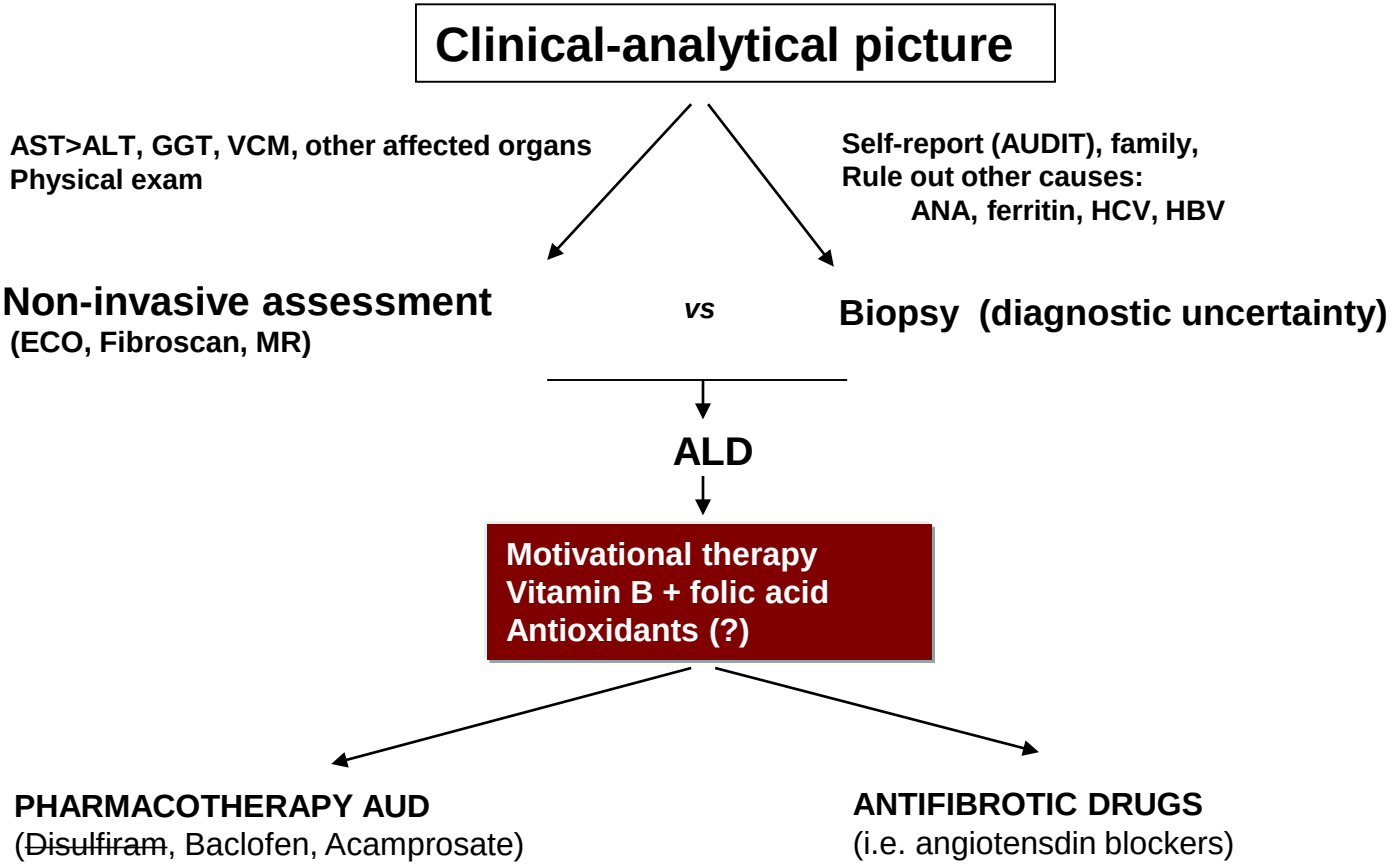
F01 vs F234: varies from 0.89 to 0.96
F0123 vs F4: varies from 0.90 to 0.94

CAP (CONTROLLED ATTENUATION PARAMETER) → ~ steatosis

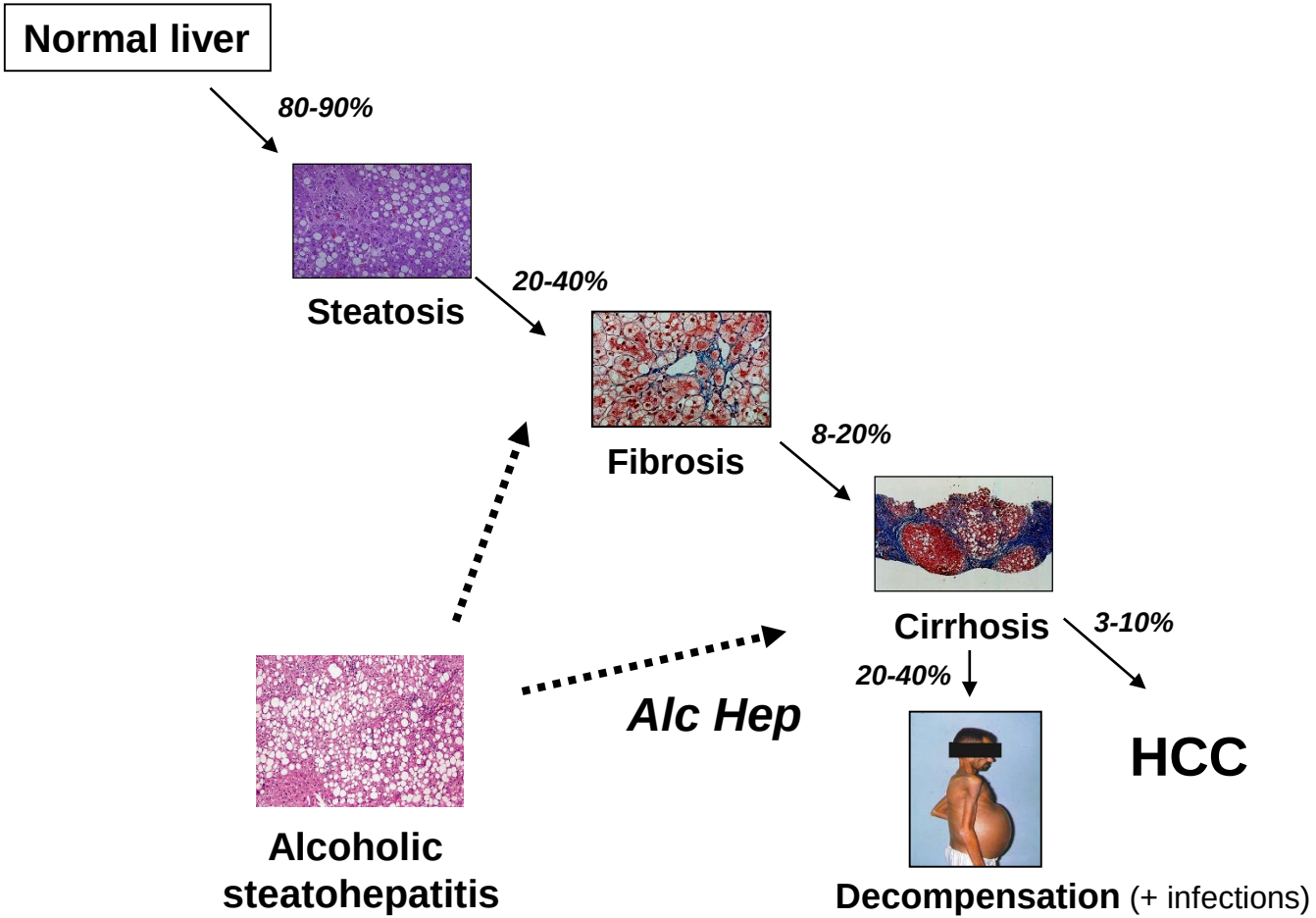
PRIMARY CARE CENTERS **ADDICTION CENTERS**

Melin et al. Alcohol Addicto 2005
Nahon et al. J Hepatol 2008
N'Guyen-Khac et al. Alimen Pharmacol Therap 2008
Mueller S. W J Gastroenterol 2010

MANAGEMENT OF PATIENTS WITH COMPENSATED-SILENT ALD



NATURAL HISTORY OF ALD



BARIATRIC SURGERY PREDISPOSES TO ALCOHOL USE DISORDER AND ALCOHOL-ASSOCIATED LIVER DISEASE.

Edilmar Alvarado-Tapias[1,2,3], Josepmaria Argemi[1,4], Kevin Kennedy [5], Carlos Fernández-Carrillo[1,6], Meritxell Ventura-Cots[1,3,7], Dalia Morales Arraez[1,8], Stephen R. Atkinson[1,9], Ana Clemente[1,10], Ramon Bataller[1].

1 Center for Liver Diseases, Division of Gastroenterology, Hepatology and Nutrition, Pittsburgh Liver Research Center, University of Pittsburgh Medical Center, Pittsburgh, PA. 2 Department of Gastroenterology, Hospital Santa Creu i Sant Pau, Instituto de Reserca Sant Pau, Universidad Autónoma de Barcelona, Barcelona, Spain. 3 Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain. 4 Liver Unit, Clinica Universidad de Navarra, University of Navarra, Pamplona, Spain. 5 Mid-America Heart Institute St. Luke's Health System, Kansas City, MO. 6 Gastroenterology, Liver Unit, Hospital Universitario Puerta de Hierro-Majadahonda, IDIPHISA, Madrid, Spain. 7 Liver Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institute of Research, Universitat Autònoma de Barcelona, Barcelona, Spain. 8 Department of Gastroenterology, Hospital Universitario de Canarias, Tenerife, Spain. 9 Division of Digestive Diseases, Department of Surgery and Cancer, Imperial College London, London, SW7 2AZ, UK. 10 Liver Unit and Digestive Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain.

INTRODUCTION

Obesity is a serious public health problem in the US.

Bariatric surgery (BS) is the most effective treatment for severe obesity. Roux-en-Y gastric bypass is one of the most common bariatric procedures, yet it is potentially associated with vitamin deficiencies, drug abuse and alcohol use disorder (AUD).

Changes in **alcohol metabolism and the addiction** transfer (cross-addiction) are potential mechanisms in this association. However, there is limited data regarding the risk of AUD and alcoholic liver disease (ALD) after BS.

AIM

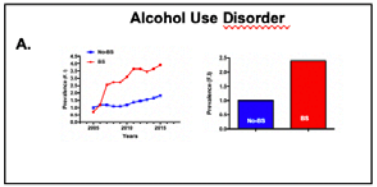
This study aimed at evaluating the association between Bariatric surgery , alcohol use disorder and alcohol liver disease.

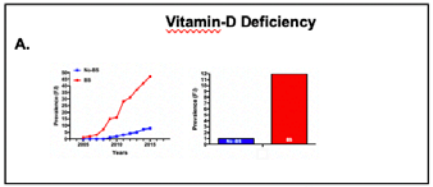
METHOD

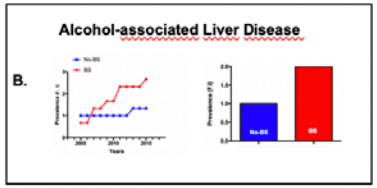
- Cross sectional study.
- We use thr National inpatient Sample (NIS)-the largest all payor national database 2005-2015, was extracted and analysed **diagnostic and comorbidity**, according to **ICD-9-CM codes**.
- **Two main groups:**
- **Study group:** Admissions with previous ¨Bariatric Surgery (**BS**)¨.
- **Control group:** Admissions control patients with other abdominal surgeries¨ No –Bariatric Surgery (**No-BS**)¨.

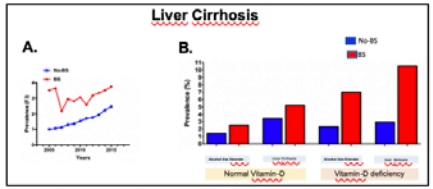
Compared outcomes between BS and No-BS using stratified logistic regression accounting for matched pairs. **Primary outcomes were risk of AUD and ALD after BS.**

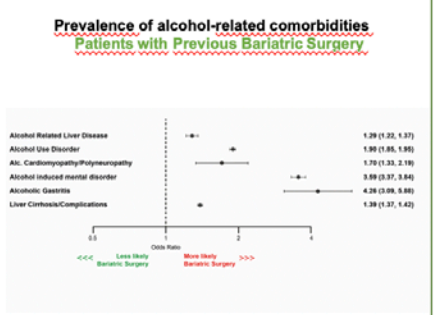
RESULTS



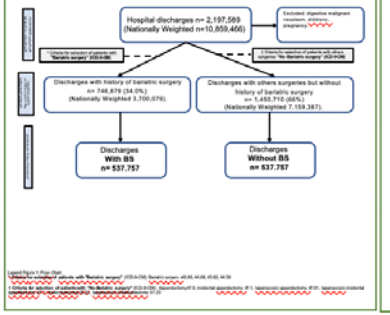








STUDY DESIGN



RESULTS

Baseline Characteristics of the Study Cohort

	No-BS n=1,450,710	BS n=746,879	P Value
Sex (Male/Female) (%)	621,668 (43%) / 814,147 (56.7%)	173,582 (23%) / 572,396 (76.7%)	<0.001
Age (years)	44.93 ± 22	49.14 ± 15	<0.001
Race, (%)			
Race Caucasian	799,054 (65.3)	476,877 (72.8)	<0.001
Race Black	106,081 (8.7)	90,696 (13.8)	
Race Hispanic	230929 (18.9)	60364 (9.2)	
Race other	87291 (7.1)	27430 (4.2)	
Primary pay, (%)			
Medicare	331,335 (22.9)	193,895 (26)	<0.001
Medicaid	232,399 (16.1)	86,233(11.6)	
Private Insurance	681,505 (47.1)	404,033 (54.2)	

CONCLUSIONS

1. History of previous BS is associated with higher prevalence of AUD and ALD.
2. Vitamin D deficiency could play a pathogenic role.
3. Development of alcohol misuse and subsequent ALD should be prevented in patients undergoing BS.
4. Prospective studies are needed to investigate the underlying pathophysiological mechanisms.

CONTACT INFORMATION

ALCOHOLIC HEPATITIS

IS THERE ANYTHING NEW IN THE DIAGNOSIS OR MANAGEMENT ?

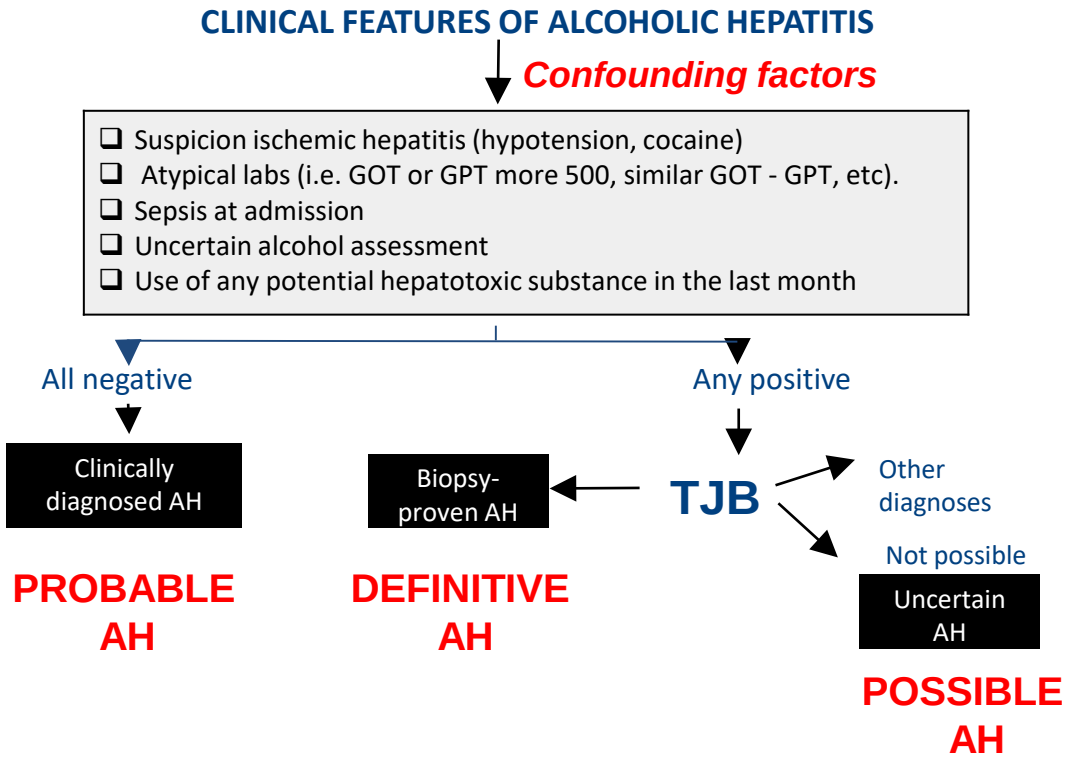
Can we establish a definitive diagnosis of alcoholic hepatitis based on clinical/analytical parameters ?

*Are there **confounding** factors ?*

*What is the **certainty** of the diagnosis without a liver biopsy ?*

DIAGNOSIS OF AH

Standard Definitions and Common Data Elements for Clinical Trials in Patients With Alcoholic Hepatitis: Recommendation From the NIAAA Alcoholic Hepatitis Consortia



Gastroenterology 2016;150:785–790

How can we assess the severity of the episode and the need for specific therapy ?

PROGNOSTIC MODELS FOR ALC HEP

Model	Bilirubin	PT/INR	Creatinine	Urea	Age	Leucocytes	
Maddrey DF*	✓	✓					32
MELD	✓	✓	✓				21
GAHS*	✓	✓		✓	✓	✓	9
ABIC*	✓	✓	✓		✓		

Severe *vs* non-severe

Modified from EASL CPG: Management of Alcoholic Liver Disease. J Hepatol 2012.

A large worldwide study shows that MELD is the best scoring system to predict mortality in alcohol-associated hepatitis

Morales Arraez D[1](daliafma@gmail.com), Ventura Cots M[1], Altamirano J[2], Abraldes JG[3], Clemente A[1], Alvarado-Tapias E[1], Argemi J[1], Arab JP[4], Atkinson SR[1,5], Brown RS Jr[6], Chavez-Araujo R[7], Duarte-Rojo A[8], Fernández-Carillo C[1], García-Tsao G[9], González JA[10], Higuera-de la Tijera MF[11], Kamath PS[12], Kim W[13], Louvet A[14], Lucey MR[15], Mathurin P[14], Rincon D[16], Restrepo-Gutiérrez JC[17], Rautou PE[18], Singal AK[19], Sarin SK[20], Shah VH[12], Torre A[21], Thursz MR[5], Verna EC[22], Vargas V[23], Zamarripa F[24], Bataller R[1]

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INTRODUCTION

- There are several scoring systems developed to predict mortality in alcohol-associated hepatitis (AH).
- Maddrey's discriminant function (mDF) and MELD were developed in USA, Glasgow Alcoholic Hepatitis Score (GHAS) in the UK and ABIC in Spain.
- While they have been validated in additional countries, a worldwide global validation considering genetic, climatic, and local factors is lacking.
- In addition, MELD-Na has not been previously validated for AH.

- **AIMS**: In this large global study, we aimed to assess the accuracy of the different scores to predict short-term mortality in AH including MELD-Na and investigated if additional factors may improve their accuracy.

PATIENTS AND METHODS

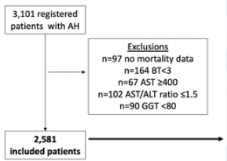
- Prospective study from 85 tertiary centers from 11 countries and 3 continents
- Patients admitted at hospital with definitive or probable AH diagnosis were included according to NIAAA criteria.
- Inclusion criteria:
  - Alcohol intake of >60 g/day in men and >40 g/day in women
  - Aspartate aminotransferase <400 U/L
  - Gamma-glutamyl transpeptidase >80 U/L
  - Altered coagulation tests (INR or prothrombin time)
  - Bilirubin > 3 mg/dl
- Exclusion criteria:
  - Other identifiable causes of liver disease
  - Vascular liver disorders
  - Hepatocellular carcinoma or other cancers
  - Human immunodeficiency virus infection
  - Other extrahepatic severe illness with poor life expectancy
- Baseline demographic and laboratory variables were obtained.
- Main outcome was any-cause mortality at 28 and 90 days.
- Statistical analysis: ROC curves (AUROC), method of DeLong, Cox regression analysis.

CONCLUSIONS

- These results suggest that mDF score should no longer be used to assess the prognosis in AH.
- MELD score showed the best performance in predicting short-term mortality.
- The independent predictors of survival do not that improve the accuracy of MELD score to predict 28 and 90 d mortality.

RESULTS

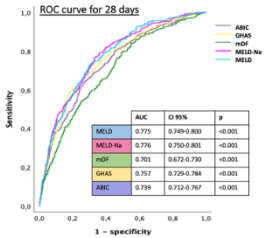
- A total of 3,101 patients with AH were initially included. After exclusions (n=520), 2,581 patients (74.4% male, median 48, IQR 40.9-55 years) were finally included.

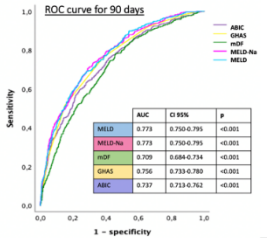


Country	n	Centers
Spain	84	Hospital Vall d'Hebron (n=44) Hospital Gregorio Marañón (n=40)
Mexico	222	Hospital Juárez (n=40) INCMNSZ (n=36) Hospital Universitario (n=10) Hospital General (n=71)
Korea	274	Boramae Medical Centre (n=206) National University Hospital (n=68)
USA	291	UAMS (n=61) UAB (n=65) Mayo Clinic (n=64) Columbia (n=8) University of North Carolina (n=26) University of Pittsburgh (n=10) University of Wisconsin (n=31) Weill Cornell Medicine (n=4) Yale University (n=22)
Colombia	40	Hospital Tobón Uribe (n=40)
France	41	Beaujon (n=41) Lille (n=25)
Brazil	90	UNICAMP (n=26) USP/RP (n=64)
India	366	ILBS (n=366)
Chile	28	Universidad Católica (n=28)
UK	1,092	60 hospitals across the UK
Canada	28	Alberta (n=28)

												Total
Deaths at 28 days (%)	14.3	37.8	10.1	24.1	17.3	13.4	22.2	23.6	14.3	13.9	7.1	20
Deaths at 90 days (%)	20.2	56.8	22.3	36.8	27.5	25.8	33.3	35	17.9	26.2	32.1	30.9
MELD	22.7 (18.3-27.4)	30.9 (24.9-37.4)	20.3 (16.7-25.7)	24.7 (21.1-31)	25.5 (19.1-31.5)	22.3 (19.5-26.5)	26.5 (21.2-35.7)	22.6 (19.3-26.1)	21.2 (17.7-26.8)	23.4 (21-26.4)	21.8 (19.9-26.5)	23.5 (20.5-27.8)
MELD-Na	21.2 (19-24.5)	32.7 (28-38.3)	23.5 (20.1-29.7)	28.4 (24.6-33.3)	27.5 (21.7-33.1)	25.3 (22.9-29)	30.7 (24.7-38.1)	-	22.6 (18.9-32.1)	26.3 (23.8-29.6)	25.8 (23.4-30.4)	26.8 (23.4-31.3)
Maddrey	56.3 (40.1-87.4)	71.6 (50.4-103.1)	38 (21-61.3)	52.5 (37.5-72.2)	51.6 (25.3-76.6)	47.3 (34.6-67.8)	53.9 (45.8-90.8)	66.1 (46.8-97.4)	40.9 (22.3-51.8)	55.4 (43.1-73.7)	-	55.6 (41.4-78.9)
Glasgow	9 (8-10)	10 (9-11)	8 (7-9)	9 (8-10)	9 (8-11))	-	9 (8-10)	-	8 (7-9)	8 (7-9)	8 (7-9.7)	9 (7-10)
ABIC	7.6 (6.7-8.8)	8.5 (7.4-9.9)	7.5 (6.7-8.8)	7.9 (6.8-9.2)	8.8 (7.3-10)	8.2 (7.4-9.1)	8.3 (7-11))	7.5 (6.6-8.4)	8.2 (6.7-9.3)	8 (7.1-9)	8.1 (7.5-8.7)	7.9 (6.9-9)

- The AUROC for the accuracy to predict mortality at 28 days ranged from 0.776 for MELD-Na and 0.775 for MELD to 0.701 for mDF, whereas for 90 days-mortality prediction ranged from 0.773 for MELD-Na and MELD to 0.709 for mDF.





- The performance of GHAS and ABIC were inferior to MELD but better than Maddrey's DF. mDF had the worst AUROC to predict death, with significant differences between all scores and mDF.

	AUC for 28-day mortality	Comparison with mDF	AUC for 90-day mortality	Comparison with mDF
mDF	0.701 (0.672-0.730) p<0.001	-	0.709 (0.684-0.734) p<0.001	-
MELD	0.775 (0.749-0.800) p<0.001	<0.001	0.773 (0.750-0.795) p<0.001	<0.001
MELD-Na	0.776 (0.750-0.801) p<0.001	<0.001	0.773 (0.750-0.795) p<0.001	<0.001
ABIC	0.739 (0.712-0.767) p<0.001	0.006	0.737 (0.713-0.762) p<0.001	0.004
GHAS	0.757 (0.729-0.784) p<0.001	<0.001	0.756 (0.733-0.780) p<0.001	<0.001

- The AUC for 28 and 90 days of MELD associated to age compared to MELD alone was 0.761 vs. 0.750, p<0.001, and 0.760 vs. 0.749, p<0.001, respectively.

Age-MELD score = -6.031+0.033*lnAGE+0.141*lnMELD

- 55 years or over was associated with an increased risk of death (AUC 0.567, p<0.001; sensitivity 34.5%, specificity 77%).

- Regarding a global score containing all independent predictors of mortality did not increase the accuracy of MELD in predicting short-term mortality (AUC for 28 days 0.795 vs. 0.779, p=0.026, and AUC for 90 days 0.779 vs. 0.775, p=0.570).

- In the multivariate analysis, independent predictors of short-term mortality were: bilirubin (p<0.001), age (p<0.001), leucocytes (p<0.001), INR (p<0.001), creatinine (p<0.001), sodium (p<0.001), and AST (p=0.005 for 28 days and p=0.024 for 90 days)

Global-AH =
[0.445+0.042*ln(bilirubin)+0.041*ln(age)+0.039*ln(leukocytes)+0.460*ln(INR)+0.002*ln(AST)+0.452*ln(Cr)+(-0.041)*ln(Na)

Gastroenterology 2014;146:1231–1239

CLINICAL—LIVER

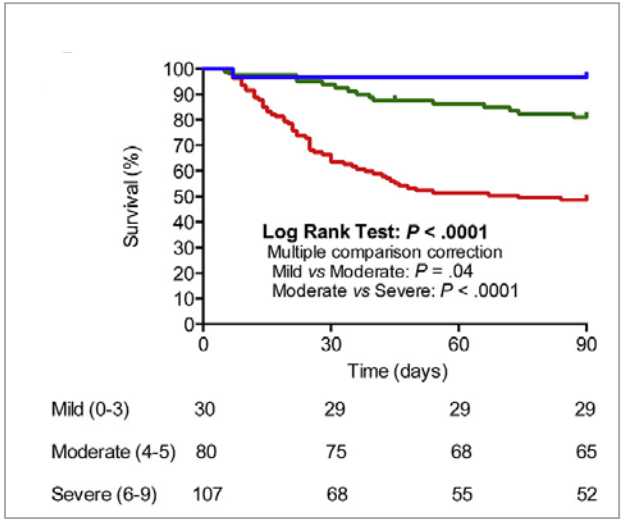
A Histologic Scoring System for Prognosis of Patients With Alcoholic Hepatitis

José Altamirano,[1] Rosa Miquel,[2] Aezam Katoonizadeh,[3] Juan G. Abraldes,[4,5] Andrés Duarte–Rojo,[6,7] Alexandre Louvet,[8] Salvador Augustin,[9] Rajeshwar P. Mookerjee,[10] Javier Michelena,[1] Thomas C. Smyrk,[11] David Buob,[12] Emmanuelle Leteurtre,[12] Diego Rincón,[13] Pablo Ruiz,[1] Juan Carlos García–Pagán,[1,5] Carmen Guerrero–Marquez,[14] Patricia D. Jones,[15] A. Sidney Barritt IV,[15] Vicente Arroyo,[1] Miquel Bruguera,[1] Rafael Bañares,[13] Pere Ginès,[1] Juan Caballería,[1] Tania Roskams,[3] Frederik Nevens,[16] Rajiv Jalan,[10] Philippe Mathurin,[8] Vijay H. Shah,[6] and Ramón Bataller[1,15]

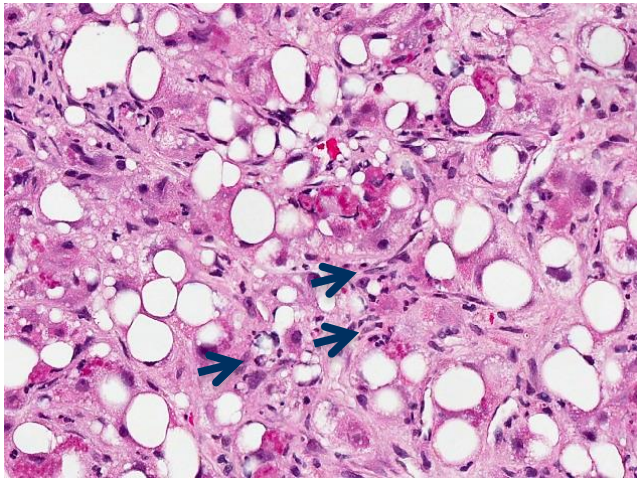
Table 3. AHHS for Prognostic Stratification of AH

	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

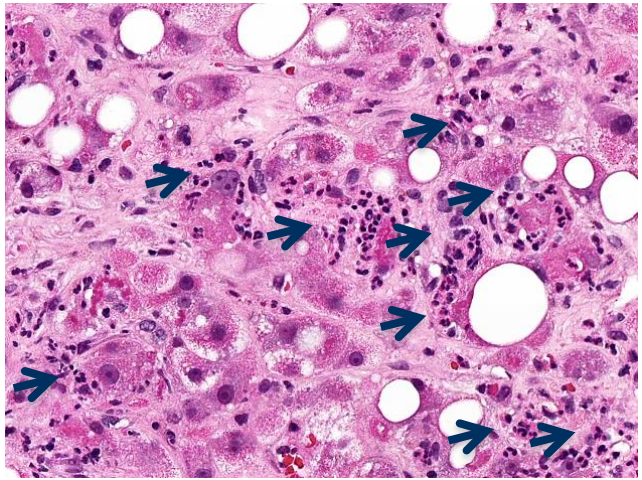
NOTE. The AHHS categories are as follows: mild, 0–3; intermediate, 4–5; severe, 6–9. Histologic features included in the AHHS were the product of the multivariate logistic regression analysis (Table 2). Weighting of each histologic feature was based on the odds ratio of the updated model (training plus test set samples). See Supplementary Methods for information on model building.



None/mild *vs* severe PMN infiltration



Patient #1



Patient #2

4-times more chances to survive

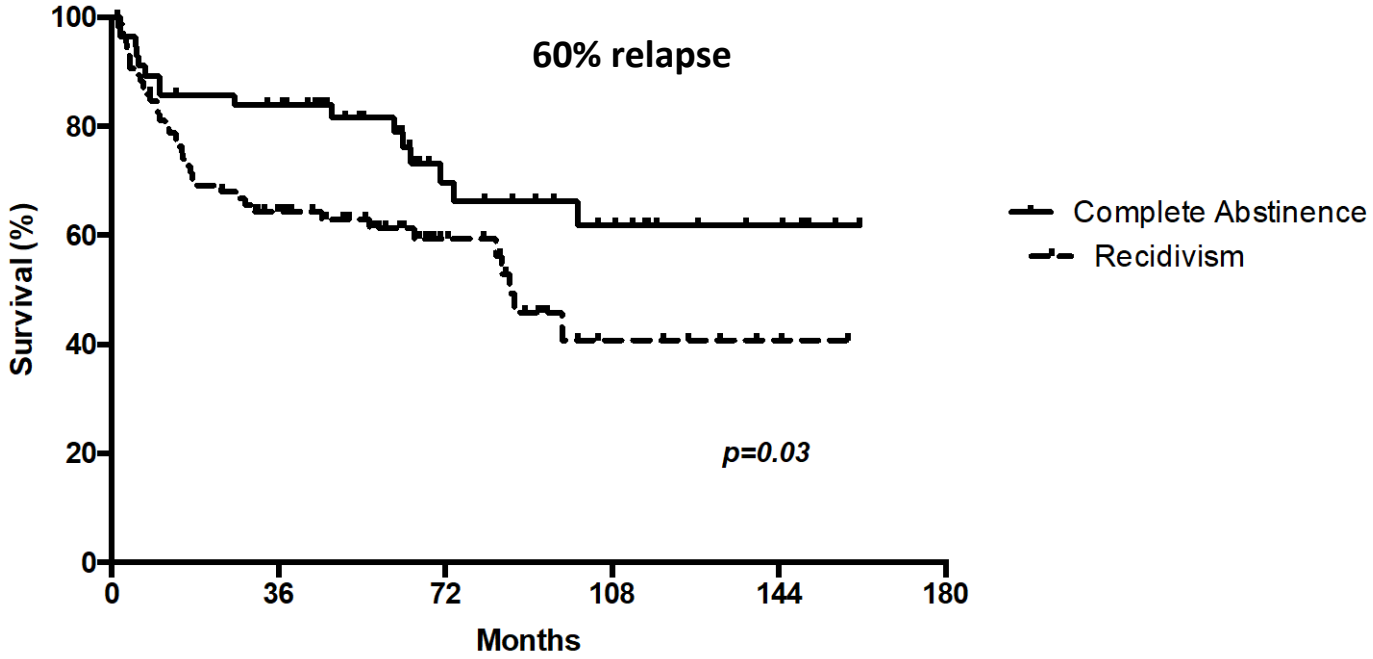
General measures

- Patients start w/**supportive** measures
- Enteral **nutrition** (2,000 kcal/day)
- **Infection screening**
  - Urine culture negative
  - Blood culture negative
  - Chest X ray no signs of infection
  - Ascitic fluid not infected.
- **Prophylaxis** bacterial infections
- A short-intervention for the alcohol misuse was started by **an addiction therapist**

Does alcohol relapse influence long-term survival ?

How I can help the patient ?

IMPACT ALCOHOL RELAPSE ON SURVIVAL



Altamirano et al, Hepatology 2017

TREATING AUD IN A PATIENT-CENTERED MANNER

GENETIC-ENVIRONMENTAL FACTORS

- Family history
- Genetic risk
- Other addictions

SOCIAOECONOMIC FACTORS

- Isolation
- Stigma
- Transportation
- Insurance

COMMON ASSOCIATED CONDITIONS

- PTSD
- Sexual abuse
- Depression
- Anxiety
- Sleep
- Pain

MULTIDISCIPLINARY ALD CLINIC

- *Specialized nurse*
- *Addiction therapist*
- *Social worker*
- *Financial counselor*
- *Hepatologist*

AASLD November 13-16, 2020
The Liver Meeting®
Digital Experience

Early alcohol relapse after an episode of alcohol-induced hepatitis (AH): prevalence, impact on liver function, genetic and non-genetic factors and identification of distinct risk profiles.

Ana Clemente-Sánchez[1,2], Stephen R. Atkinson[1,3], Luke D. Tyson[3], Meritxell Ventura-Cots[1,2], Josepmaría Argemí[1], Nikhil Vergis[3], Sylvia Manimaran[4], Marsha Y Morgan[4], Andrew McQuillin[5], Dalia Morales-Arraez[1], Edilmar Alvarado-Tapias[1,2], Carlos Fernández-Carrillo[1], Aline Oliveira-Mello[1], Juan G Abraldes[6], Francisco Bosques[7], Robert S Brown Jr[8], Juan Caballeria[9,10], Guadalupe Garcia-Tsao[11], Joan Genescà[9,12], Michael Lucey[13], Alexandre Louvet[14], Phillipe Mathurin[14], Bernd Schnabl[15], Debbie L Shawcross[16], Victor Vargas[9,12], Elizabeth Verna[17], Mark R. Thursz[3], Ramón Bataller[1].

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BACKGROUND

- Alcoholic hepatitis (AH) is the most severe manifestation of alcoholic-related liver disease and carries a high-mortality rate.
- Alcohol relapse negatively influences long-term survival in AH.
- The incidence, predictors and impact of early relapse are poorly defined.

AIMS

- To determine the **prevalence of** early alcohol relapse defined as resumption of alcohol consumption within 3 months of presentation with AH.
- To explore the **impact** of early relapse on **liver function** based on the level of alcohol consumption.
- To identify genetic and non-genetic **predictors** in order to develop a tool to estimate relapse risk.

METHODS

- **Demographic**, **biochemical** and **genetic** data with early relapse status information were obtained from 478 patients of STOPAH trial.
- **Alcohol relapse** was **defined** as a return to alcohol consumption irrespective of the degree self-reported. The severity of relapse was categorized as:
  i) abstinent, ii) reduced intake or iii) similar intake as at presentation.
- Ten single nucleotide polymorphisms (**SNPs**) recently associated with Problematic Alcohol Use (PAU; Zhou H et al Nat Neurosci. 2020) and a polygenic risk score from 2,000 SNPs were also evaluated.
- **Logistic regression** (LR) was used to test associations with relapse and **Latent Class Regression** (LCR) to identify latent profiles with different relapse risk.
- Results were **validated** in a cohort of 194 patients from InTeam Consortium.

RESULTS

- A total of 157/478 patients **(33%)** in the STOPAH cohort and 43/194 patients **(22%)** in the InTeam cohort relapsed within 90 days of admission.
- Relapse prevented the **improvement in liver function** at 90 days compared to abstinence in a dose-dependent fashion (Fig. 1).
- Variables associated with **early relapse** in STOPAH cohort are show in Table 1. Variables associated with early relapse in InTeam cohort were MELD [OR 0.89 (0.82 - 0.96) p=0.004)] and social support [OR 3.68 (1.65 – 8.41) p=0.001)].
- Common variables with statistical significance in the LR models as well as those considered clinically relevant based upon prior studies were selected for LCR analysis (Fig. 2).

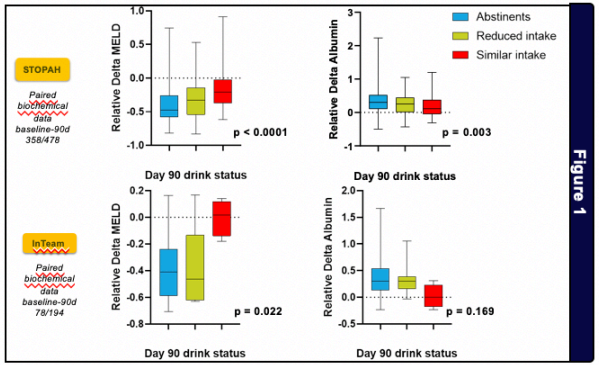

Figure 1

STOPAH

Variable	Multivariate OR (CI 95%)	*p*
Age	0.9667 (0.9375 - 0.9961)	**0.0281**
MELD	0.9143 (0.8518 - 0.9781)	**0.0108**
Smoking		
Ref. category Never		
• Former	0.4919 (0.2409 – 0.979)	**0.0465**
• Current	0.8941 (0.5078 – 1.5758)	0.6976
Employment		
Ref. category Employed (Full or part-time)		
• Retired	1.6181 (0.5937 - 4.3248)	0.3394
• Unemployed	1.2444 (0.6507 - 2.4176)	0.5124
• Carer	0.9442 (0.1227 - 4.9724)	0.9493
• Long-term sick	2.0413 (0.9787 - 4.3124)	0.0585
Relationship		
Ref. category Married/Co-habiting/Partner		
• Single/Widowed/Divorced	1.8711 (1.0777 - 3.3164)	**0.0284**

Table 1

▶ After correction for multiple testing no genetic variant or the PRS was associated with relapse risk in multivariate LR analysis.

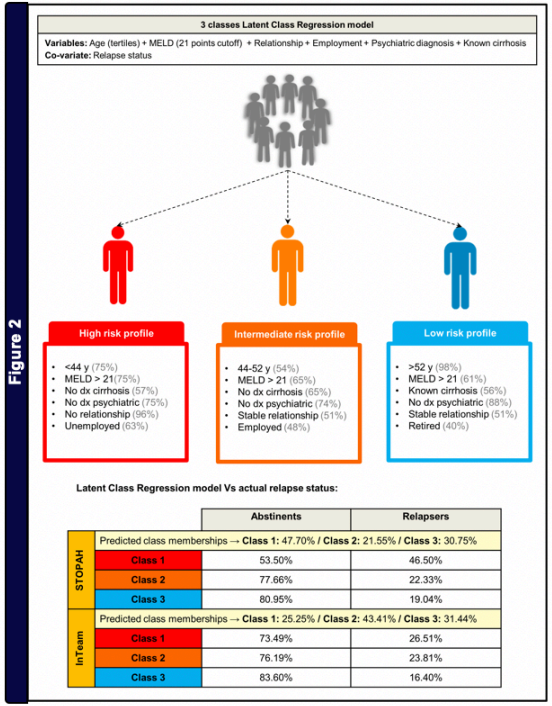

Figure 2

Latent Class Regression model Vs actual relapse status:

		Abstinents	Relapsers
STOPAH	Predicted class memberships → **Class 1:** 47.70% / **Class 2:** 21.55% / **Class 3:** 30.75%		
	Class 1	53.50%	46.50%
	Class 2	77.66%	22.33%
	Class 3	80.95%	19.04%
InTeam	Predicted class memberships → **Class 1:** 25.25% / **Class 2:** 43.41% / **Class 3:** 31.44%		
	Class 1	73.49%	26.51%
	Class 2	76.19%	23.81%
	Class 3	83.60%	16.40%

Figure 1. Relationship between the degree of alcohol relapse and changes in liver function within 90 days of AH episode.

Table 1. Multivariate logistic regression analysis in the STOPAH cohort for early alcohol relapse prediction.

Figure 2. Latent Class Regression analysis and latent profiles according to early alcohol relapse risk. Validation of the model in the InTeam cohort.

CONCLUSIONS

- Early relapse after an AH episode is a **frequent event** with a significant dose-dependent impact on **liver function**.
- **Non-genetic factors** predict early relapse whilst targeted loci associated with PAU seems not to significantly alter the risk in this cohort.
- We identified distinct profiles with differing relapse risk that may allow personalization of treatment strategies.

CONTACT INFORMATION

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6 PRACTICAL ADVISE TO MANAGE PATIENS WITH ALD

1. Start talking about alcohol in every single visit even if the patient is abstinent.

2. Be motivational and not confrontational.

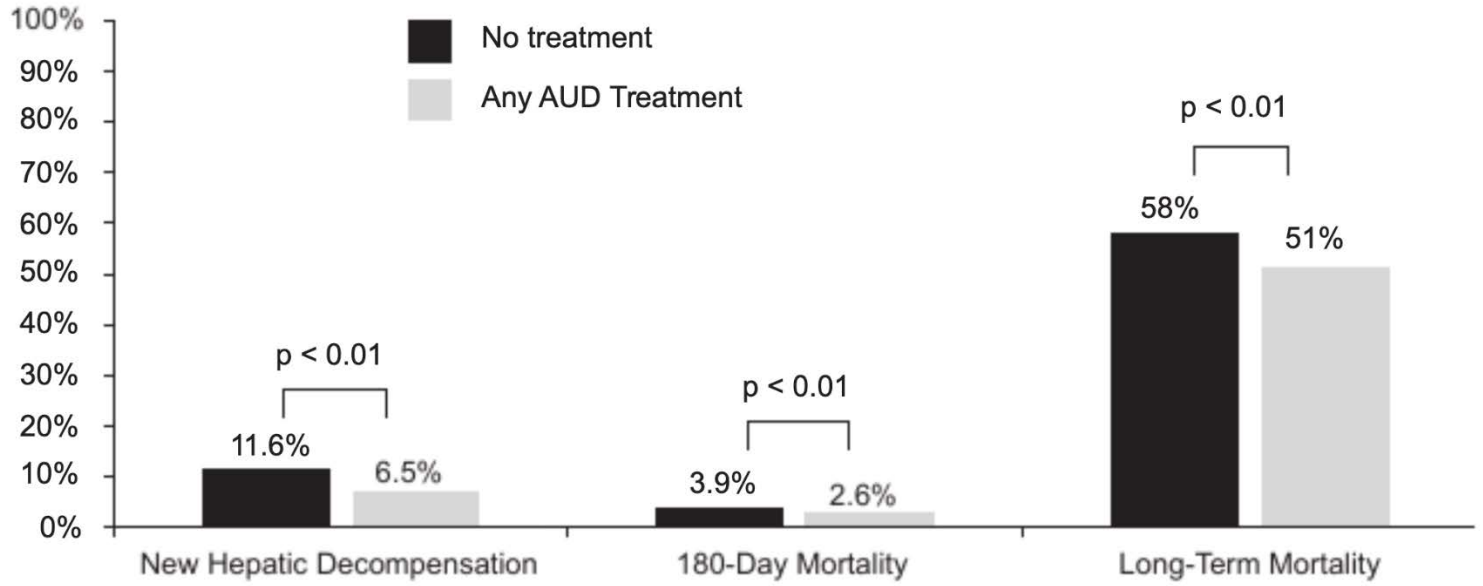
3. First counseling session in the first visit / hospitalization by an addiction specialist (or by the liver GI specialist).

4. Remember that some patients need in-house detox !!

5. Early visit after patient's discharge (free slots in a specialized clinic).

6. Fight for them ! They sense if you care. If you succeed, it is very rewarding.

IMPACT OF TREATMENT OF AUD IN ALCOHOLIC CIRRHOSIS



Rogal S et al, Hepatology 2020

WITHDRAWAL SYNDROME IN PATIENTS WITH AlcHep

1. Timing: 12h – few days after alcohol cessation
2. Symptoms: agitation, confusion, coma, sweating, hypertension, animal hallucinations (ants)
3. Differential diagnosis
    - Encephalopathy: flapping, high ammonia levels
    - Chronic cognitive impairment (previous history, atrophy CT scan)
    - Delirium not related to alcohol in hospitalized patient (ICU, hypoxia, sepsis)
    - Stroke: neurological signs, CT/MRI
    - Status epilepticus: EEG, previous episodes, can be a manifestation WDS.
    - Wernicke-Korsakoff: deficit vit B1, ophthalmoplegia, fabulation, malnourished patient, iv glucose
    - Meningitis: fever, signs physical exam, LP results
    - Encephalitis: clinical symptoms viral serology, MRI results, LP results
4. Prophylaxis: chlordiazepoxide, flunitrazepam-clonidine, chlormethiazole, baclofen.
5. Therapy: CIWA-based diazepam: risk coma, aspirative pneumonia.

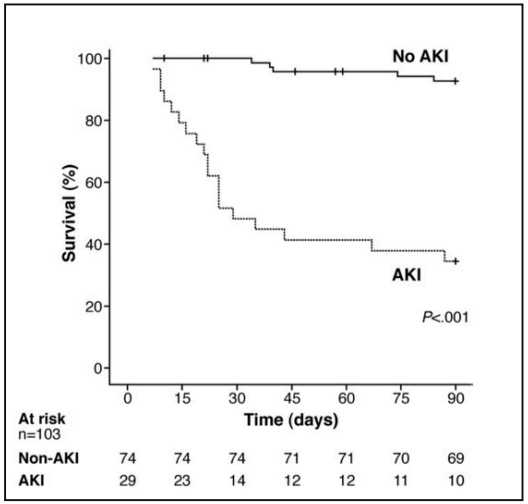
CASE PRESENTATION

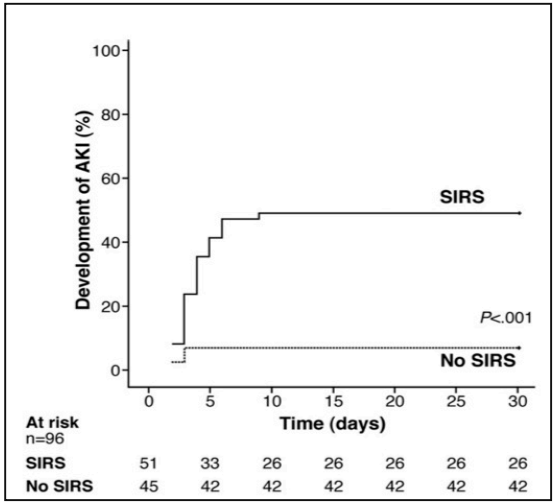
- At day 3, **serum creatinine** increased from 0.8 mg/dl to 2.0 mg/dl

AKIN CRITERIA of AKI:

Increase in serum creatinine of ≥ 0.3 mg/dl

Increase in serum creatinine of ≥50%





Altamirano et al, Clin Gastroenterol Hepatol 2012

What are the specific therapeutic options for this patient ?

Pentoxifylline *or* Prednisolone ??

CORTICOSTEROID THERAPY IN SEVERE ALCOHOLIC HEPATITIS*

A Double-Blind Drug Trial

HENRIK P. PORTER, M.D., FRANCIS R. SIMON, M.D., CHARLES E. POPE, II, M.D., WADE VOLWILER, M.D., AND L. FREDERICK FENSTER, M.D.

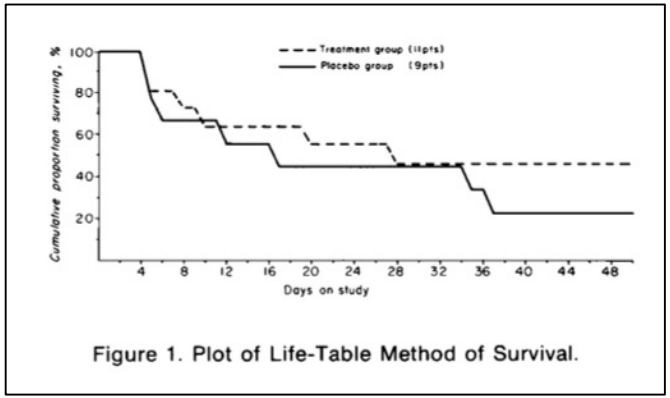
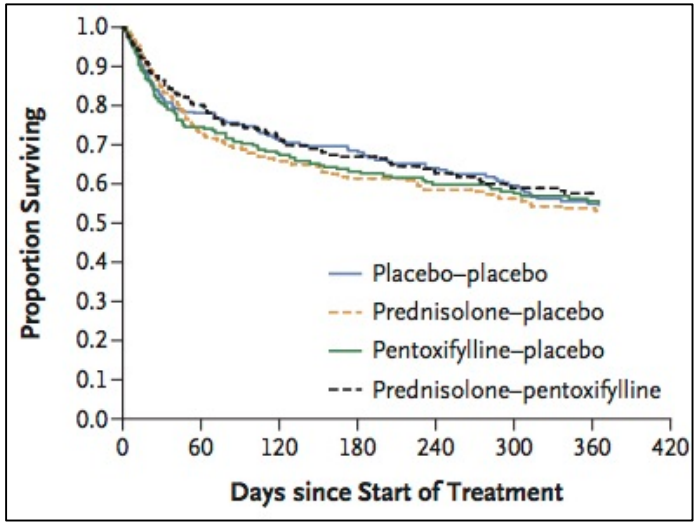


Figure 1. Plot of Life-Table Method of Survival.

1971

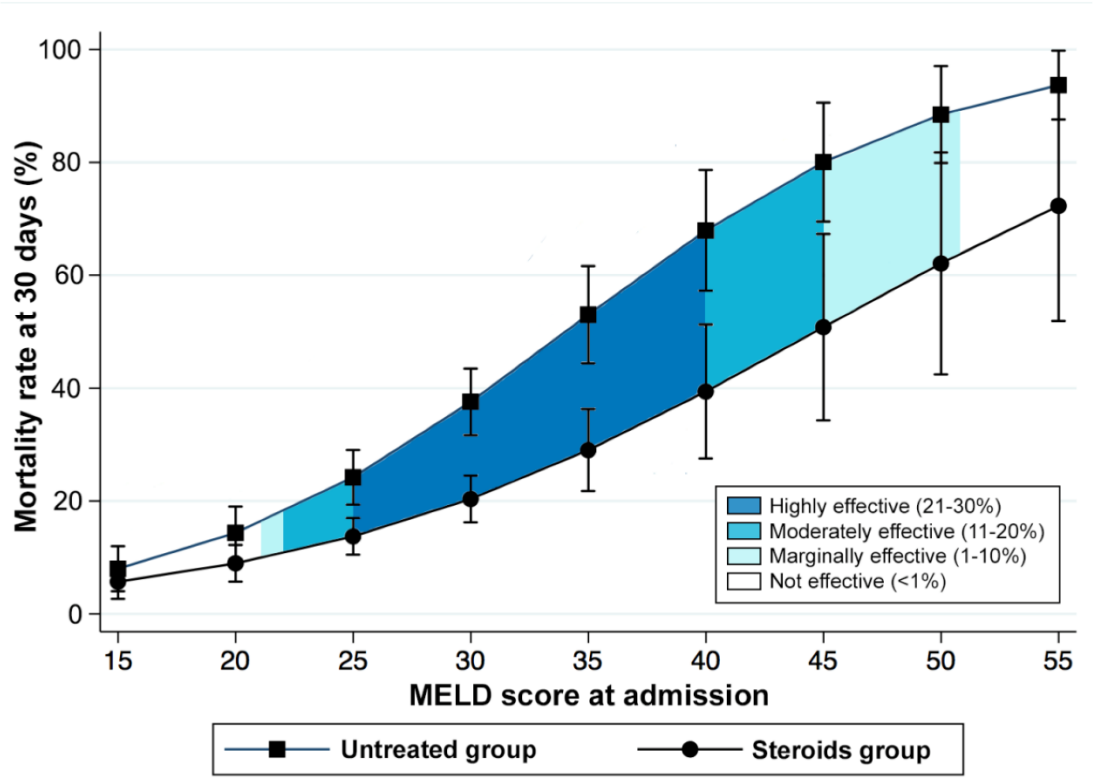
Prednisolone or Pentoxifylline for Alcoholic Hepatitis

Mark R. Thursz, M.D., Paul Richardson, M.D., Michael Allison, Ph.D., Andrew Austin, M.D., Megan Bowers, M.Sc., Christopher P. Day, M.D., Ph.D., Nichola Downs, P.G. Cert., Dermot Gleeson, M.D., Alastair MacGilchrist, M.D., Allister Grant, Ph.D., Steven Hood, M.D., Steven Masson, M.A., Anne McCune, M.D., Jane Mellor, M.Sc., John O'Grady, M.D., David Patch, M.D., Ian Ratcliffe, M.Sc., Paul Roderick, Ph.D., Louise Stanton, M.Sc., Nikhil Vergis, M.B., B.S., Mark Wright, Ph.D., Stephen Ryder, D.M., and Ewan H. Forrest, M.D., for the STOPAH Trial*



2015

THERAPEUTIC WINDOW FOR THE BENEFIT OF STEROIDS



Arab JP et al, AASLD 2020

Is there any effective therapy for patients non-responding to prednisolone ?

ORIGINAL ARTICLE

Early Liver Transplantation for Severe Alcoholic Hepatitis

Philippe Mathurin, M.D., Ph.D., Christophe Moreno, M.D., Ph.D., Didier Samuel, M.D., Ph.D., Jérôme Dumortier, M.D., Ph.D., Julia Salleron, M.S., François Durand, M.D., Ph.D., Hélène Castel, M.D., Alain Duhamel, M.D., Ph.D., Georges-Philippe Pageaux, M.D., Ph.D., Vincent Leroy, M.D., Ph.D., Sébastien Dharancy, M.D., Ph.D., Alexandre Louvet, M.D., Ph.D., Emmanuel Boleslawski, M.D., Ph.D., Valerio Lucidi, M.D., Thierry Gustot, M.D., Ph.D., Claire Francoz, M.D., Christian Letoublon, M.D., Denis Castaing, M.D., Jacques Belghiti, M.D., Vincent Donckier, M.D., Ph.D., François-René Pruvot, M.D., and Jean-Charles Duclos-Vallée, M.D., Ph.D.

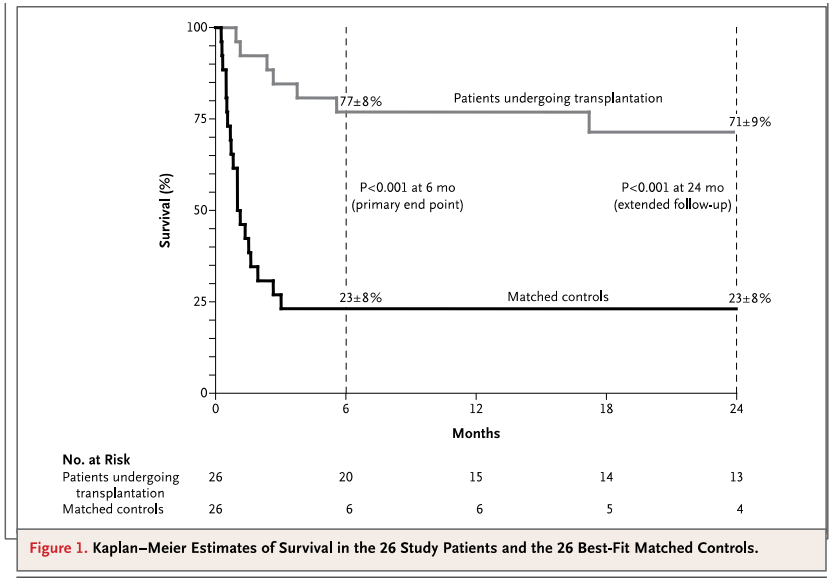


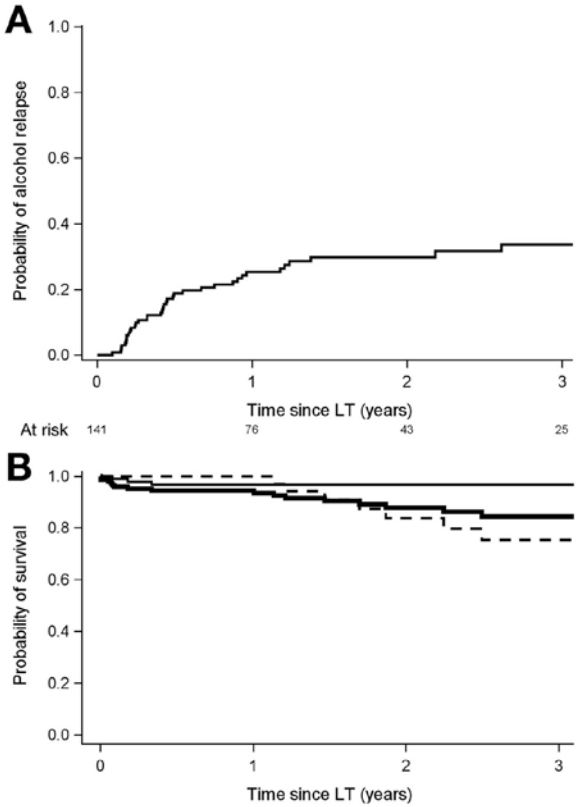
Figure 1. Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

- Offered to **highly selected** patient with corticosteroid-resistant Alc Hep (< 2% admitted patients).

- Very **low relapse rate**: 3 out of 26 patients.

US STUDY: ACCELERATE

- **Retrospective study of 12 centers in 8 UNOS Regions**
- 147 LT for severe AH
- Median MELD 39
- **3-year survival:**
  - 100% in non-relapsers
  - 75% in relapsers (*p=0.03*)
  - 84% overall survival



Gastroenterol 2018; 155:422-430

MANAGEMENT OF ALCOHOLIC HEPATITIS

CLINICAL PICTURE

- Patient with heavy **alcohol intake** (*> 60 g/day >6 months).* In some patients last drink up to 8 weeks before admission. Underreporting is common: suspect if stigmata of alcoholism, compatible labs, positive alcohol test, other alcohol-induced organs damage (polyneuropathy, chronic pancreatitis). [4]
- **Clinical presentation**: recent-onset jaundice, malaise, ascites, edema, itching, fever, SOB due to massive ascites, confusion/lethargy/agitation (DDx: PSE, WDS, alcohol induced cognitive dysfunction, Wernicke-Korsakoff, seizures).
- **Physical exam findings**: signs of alcohol abuse (facial erythema, rhinophyma, Dupuytren, muscle wasting), stigmata cirrhosis, ascites, tender hepatomegaly, splenomegaly, pedal edema, asterixis, altered mental status, signs of cerebellar dysfunction/peripheral neuropathy.
- **LABS**: abrupt rise in TBil >3 mg/dl (usually > 5 mg/dl), Elevation AST (AST>ALT usually >2, both < 500 U/L), GGT >100 U/mL, Alk Phos mildly elevated, Albumin <3.0 g/L, INR >1.5, Platelet count <150,000, Hb <12 g/L, elevated MCV.

GENERAL MEASURES

- **Assessment and infection work-up**: mental status, presence of signs PSE or WDS, ascites (diagnostic tap in all cases; FFP if INR>2.5), presence of infections (pneumonia, cellulitis, SBP, UTI, meningitis). EKG, pan-culture, chest X-Ray, urinary sediment in all patients, presence of SIRS (2 elevated out of: T, HR, RR and leukocyte count), urinary output. CT scan if first episode.
- Prevent/treat **OH withdrawal**: *moderate*, Baclofen 30 mg/day, *severe*, benzodiazepines, chlordiazepoxide preferred (caution: they can precipitate PSE, aspiration and favor further addiction); *if intubation needed*, Propofol preferred.
- Parenteral Vit K weekly (5-10 mg), Vit B (1, 6 and 12) and folic acid supplementation.
- Ensure adequate **caloric and fluid intake**: daily protein intake of 1.5 g/kg bw. Consider NGT if malnutrition and preserved mental status and peristalsis. TPN only indicated in severe cases [4]
- If fever >38C or clinical/microbiological signs of **infection**: BSA according to UPMC guidelines. If SIRS criteria (eg. leukocytosis) without clear infection and fever: BSA not clearly indicated but high risk of renal failure and multiorgan failure. [2]
- If ascites or GI hemorrhage: **primary prophylaxis** with oral ciprofloxacin (500 mg/d) and or ceftriaxone (2 g/day) as indicated.
- Early detection of **AKI**: albumin (20-40 g/day for 3 days), consider octeotride /midodrine or even NE if progressive HRS-1.
- Motivational intervention: consult **Addiction Medicine** and schedule visit with Behavioral Specialist (Kristen Radage. Consider Baclofen (10-20 mg/tid) or Acamprosate (when liver function improves (TBil <10 mg/dL). [4]

SCREENING CAUSES OF JAUNDICE

- Rule out biliary obstruction, metastases or HCC (CT scan and if indicated, MRI or MRCP).
- Rule out drug-induced liver injury (DILI): http://livertox.nih.gov
- Rule our acute viral hepatitis (A, B and C) if first episode and/or clinical suspicion.
- Rule out severe autoimmune hepatitis if first episode and/or clinical suspicion (ANA, ASMA, IgG).

DO WE NEED TO DO A TJB FOR DIAGNOSIS ? [5]

- Suspicion ischemic hepatitis: hypotension/massive bleeding or recent cocaine.
- Sepsis at admission (clinical diagnosis or positive culture plus SIRS).
- Suspicion of malignant liver disease based on clinical and/or imaging criteria.
- Atypical labs (eg. AST or ALT >500 U/L, Alk Phos >400 U/L, etc).
- Uncertain alcohol assessment including under-reporting.
- Use of any potential hepatotoxic substance in the last 3 months.
- Possible indication of a salvage liver transplantation.

All negative → **Clinically diagnosed PROBABLE Alc Hep**

Any positive → TJB recommended

TJB recommended: YES → **Biopsy-proven DEFINITE Alc Hep**; NO → **Clinical confounders POSSIBLE Alc Hep**

MELD >21

Prednisolone 40 mg/day
(if not active bleeding nor infection)

http://www.lillemodel.com/score.asp, *7 days*

4 weeks Prednisolone
(consider 2 week taper 20 mg and 10 mg)

<0.45

≥0.45

- Stop Prednisolone [4]
- Consider **early LT** if meets criteria (first AH episode, no previous decompensations, favorable socio-psychological profile). [2]

Follow-up

- Early **follow-up** visit in UPMC Alcohol-related Liver Disease Clinic (scheduler: Angelina Fair, lokara@upmc.edu).
- Prevent/treat **early relapse**: Refer outpatient CLD Behavioral specialist (Kristen Radage, radagekm@upmc.edu), Baclofen 10-20 mg/tid if craving, consider Acamprosate if improved liver function (Bil <10 mg/dL). Random alcohol tests recommended (urine alcohol metabolites and/or PEth). Consider in-hopital detox in McKeesport or Marcy if risk WDS. [4]
- Management **underlying liver disease**: HCC and EV screening, treat fluid retention diuretics and LVP as needed, PT and nutrition if deconditioning.
- If persistent **liver failure and/decompensation** despite documented abstinence/counseling after 4 months: consider TIPS (if Bil <3 mg/dL and no PSE) or LT rereferral. [3]