2019 Annual Update in
Medical Hepatology

An Integral Approach to Treat Alcohol-Induced Liver Disease

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PITTSBURGH LIVER RESEARCH CENTER
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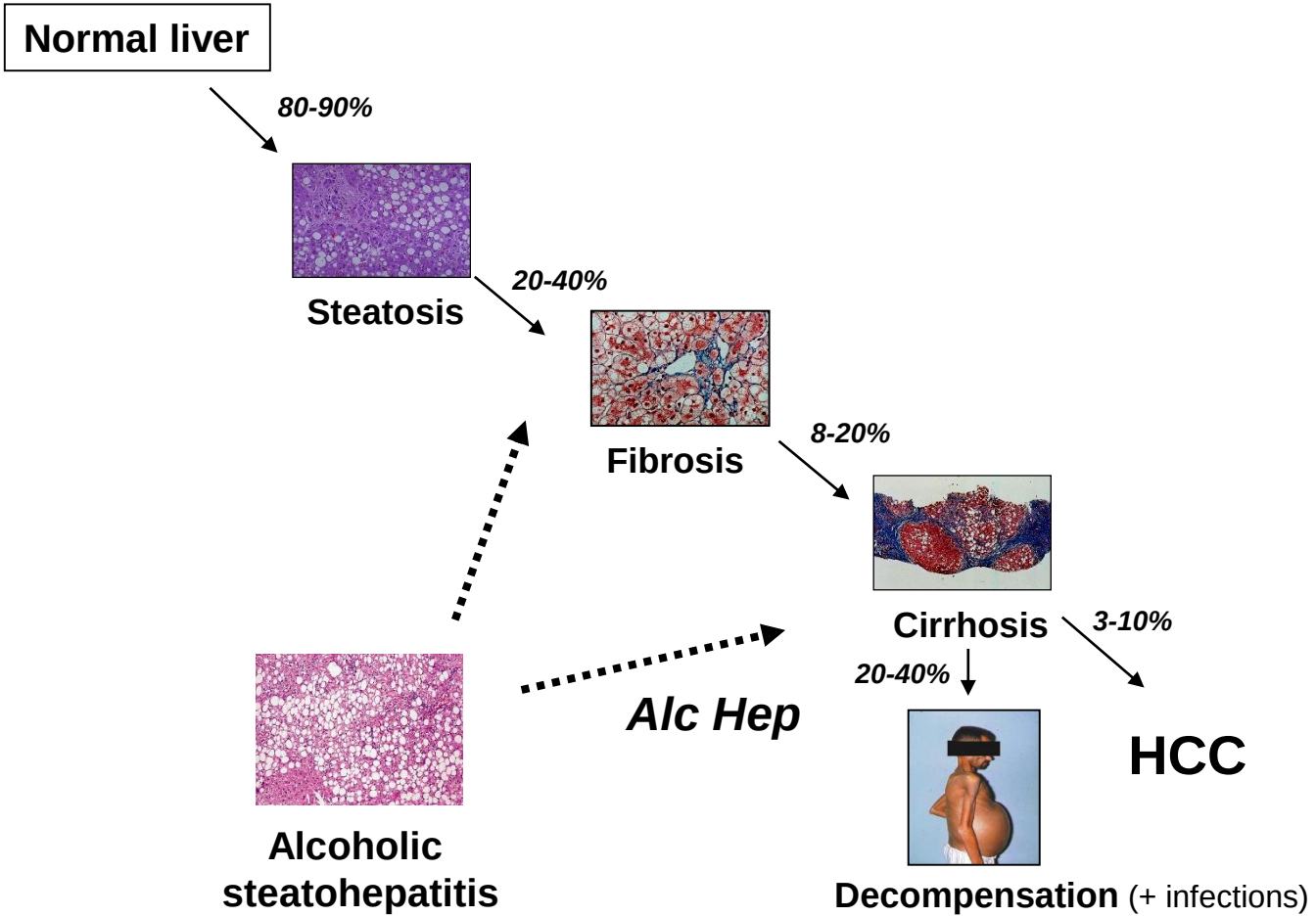
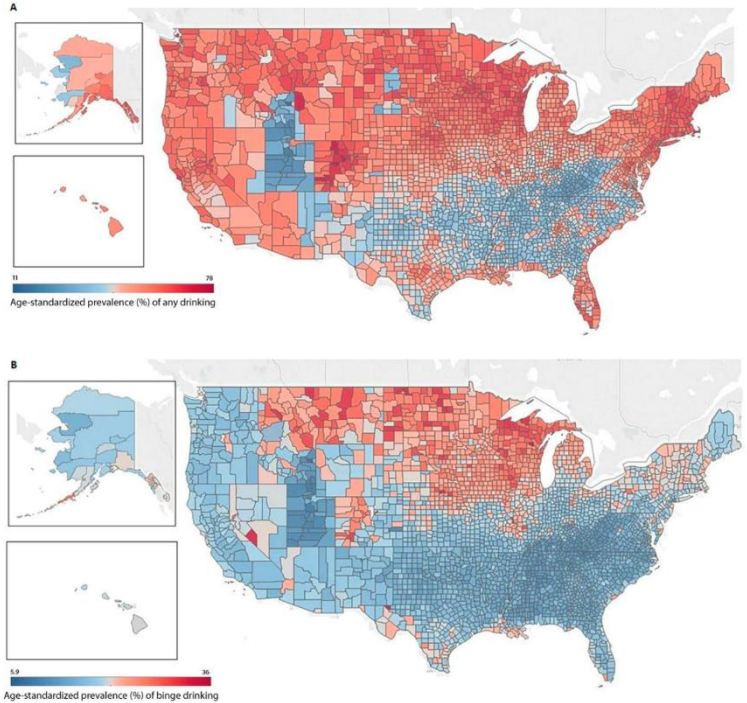
UPMC LIFE CHANGING MEDICINE

NATURAL HISTORY OF ALD



COLD WEATHER AND SUNLIGHT HOURS AND ALCOHOL ABUSE



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Living in a cold, dark climate linked to heavy drinking

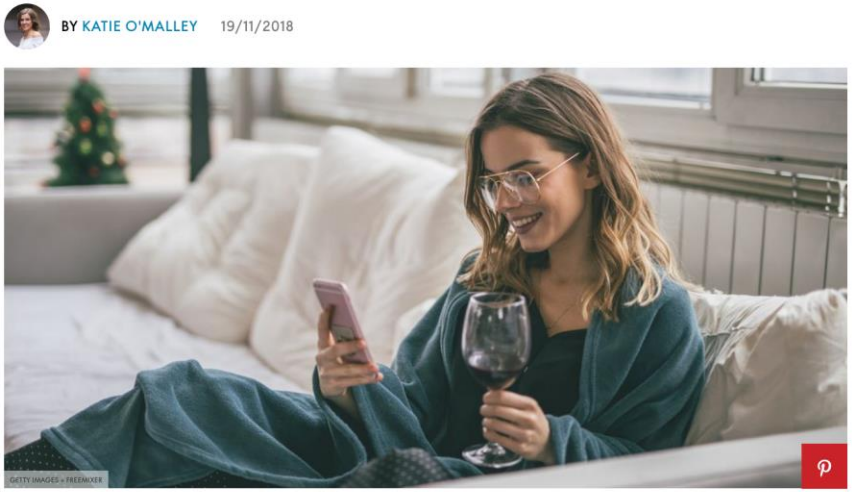
28 November 2018 Share

There are calls for restrictions on alcohol advertising in the winter months

VENTURA-COTS M ET AL, HEPATOLOGY 2018

The Scientific Reason We Want To Drink More Alcohol When It Gets Colder And Darker

A new study from the US has found a direct link between decreasing temperatures and hours of sunlight with alcohol consumption.



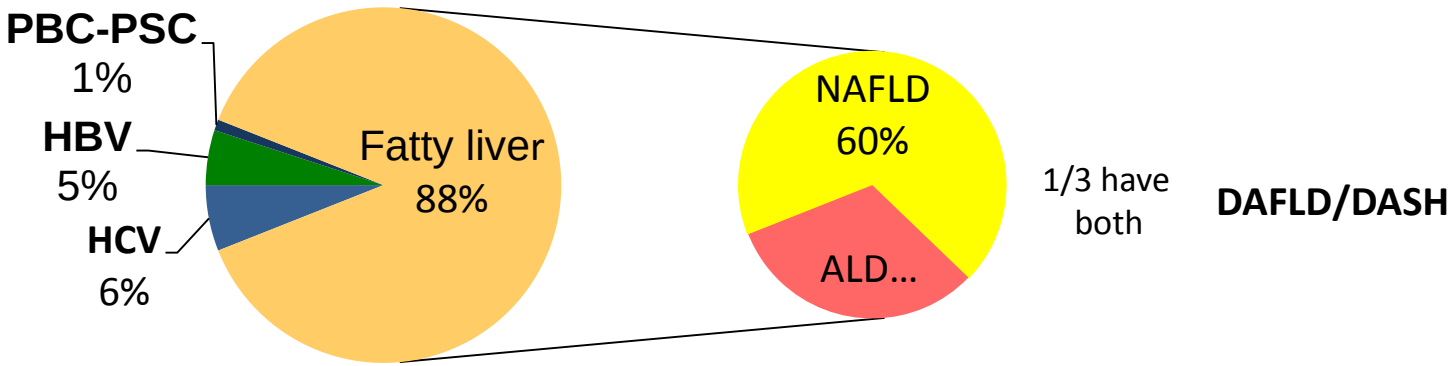
BY KATIE O'MALLEY 19/11/2018

A bottle of Merlot shared over a takeaway with a friend. A round of pale ales in the pub on a Saturday night. Several rum and cokes at a work Christmas party.

CAUSES OF MODERATE LIVER DISEASE

Prevalence of liver fibrosis in 1,358 subjects in France: 7.5%

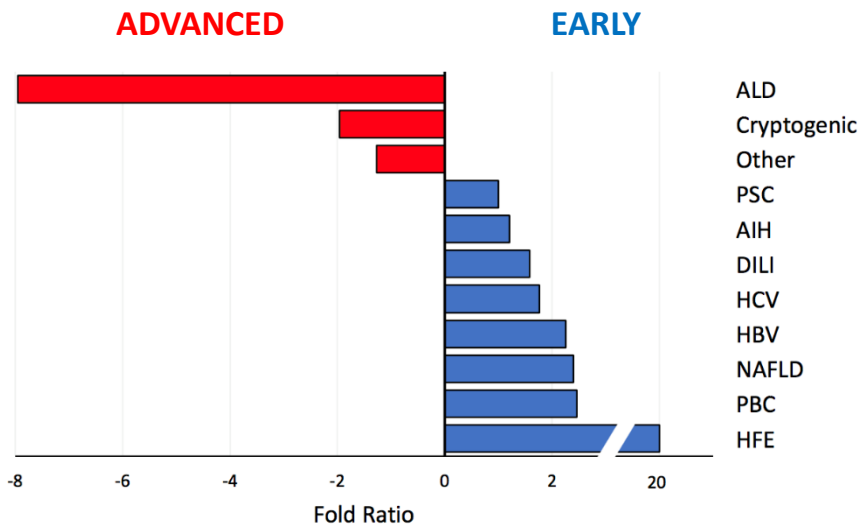
Underlying cause of liver fibrosis:



Roulot et al, Gut 2010

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]



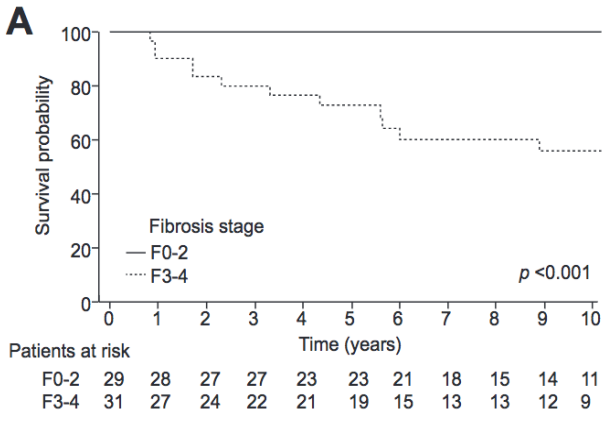
Shah N et al, Clin Gasteroenterol Hepatol 2019

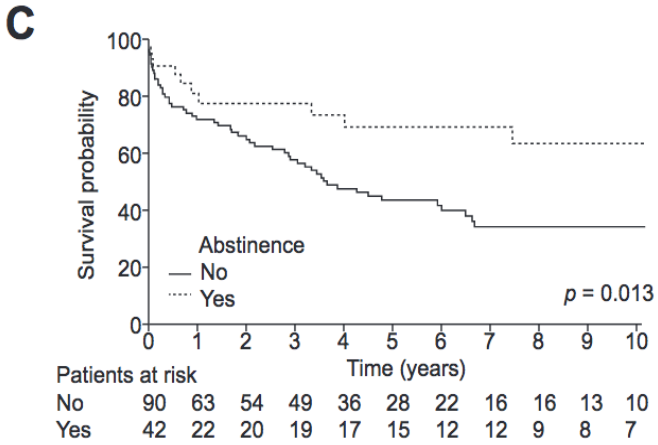
EARLY ALD IS THE MOST OVERLOOKED POHENOTYPOE IN CLINICAL HEPATOLOGY

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

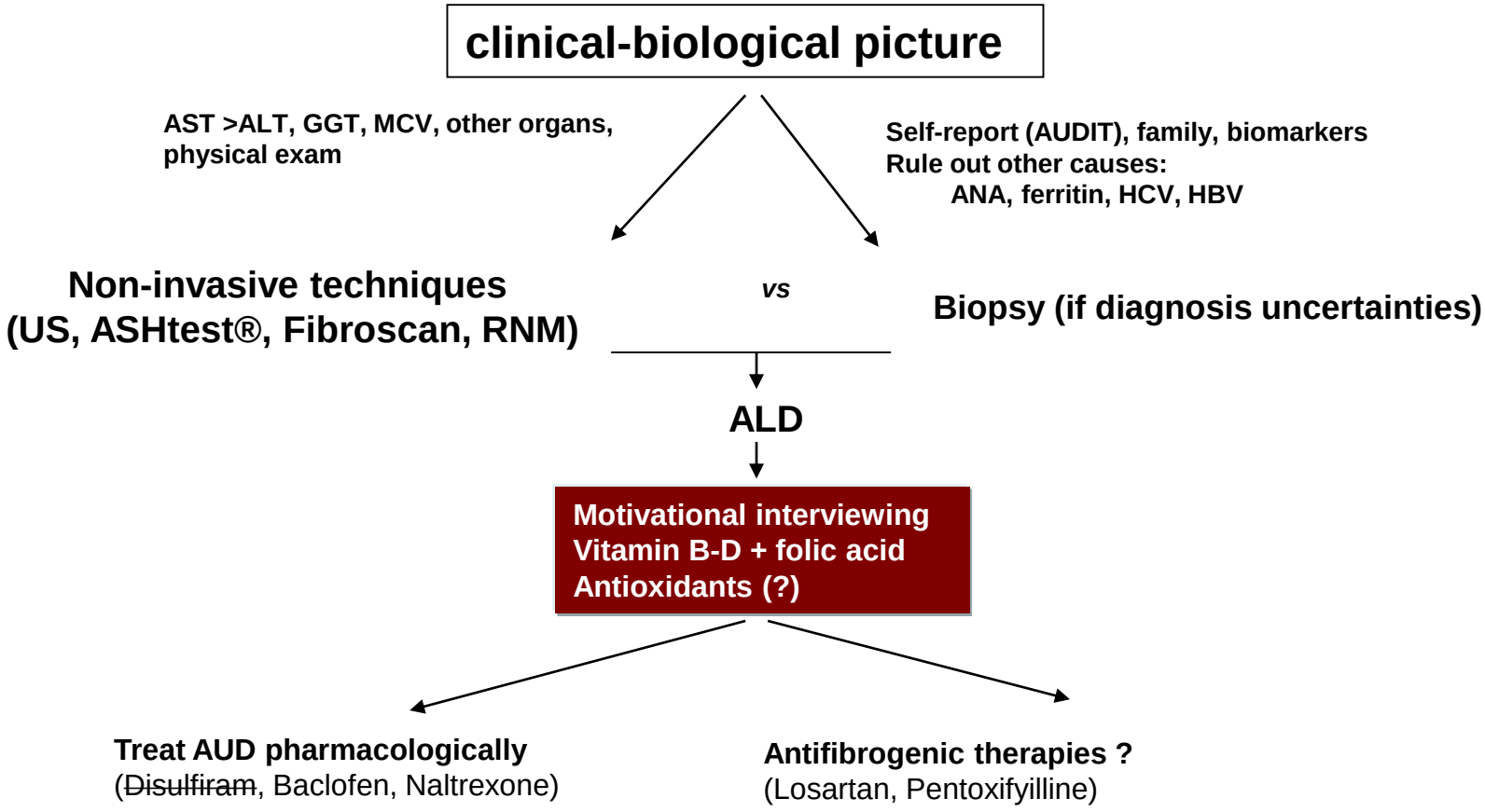
Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease

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]

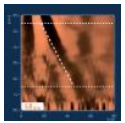




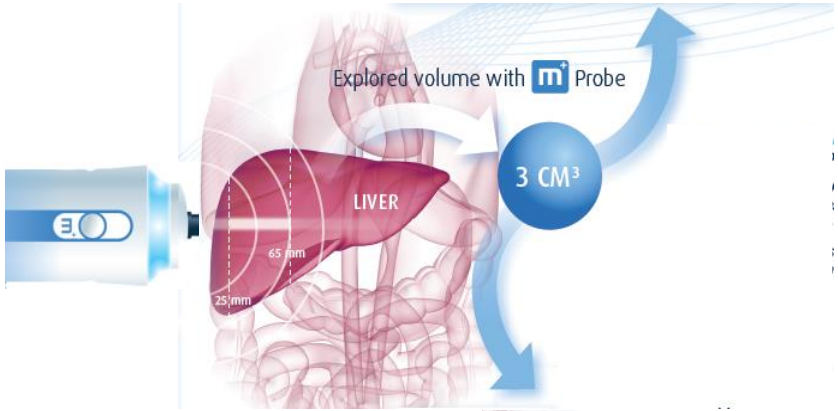
MANAGEMENT OF MODERATE-SILENT ALD



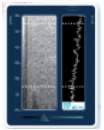
FIBROSCAN IN PATIENTS WITH ASYMPTOMATIC ALD



Stiffness → ~ fibrosis



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

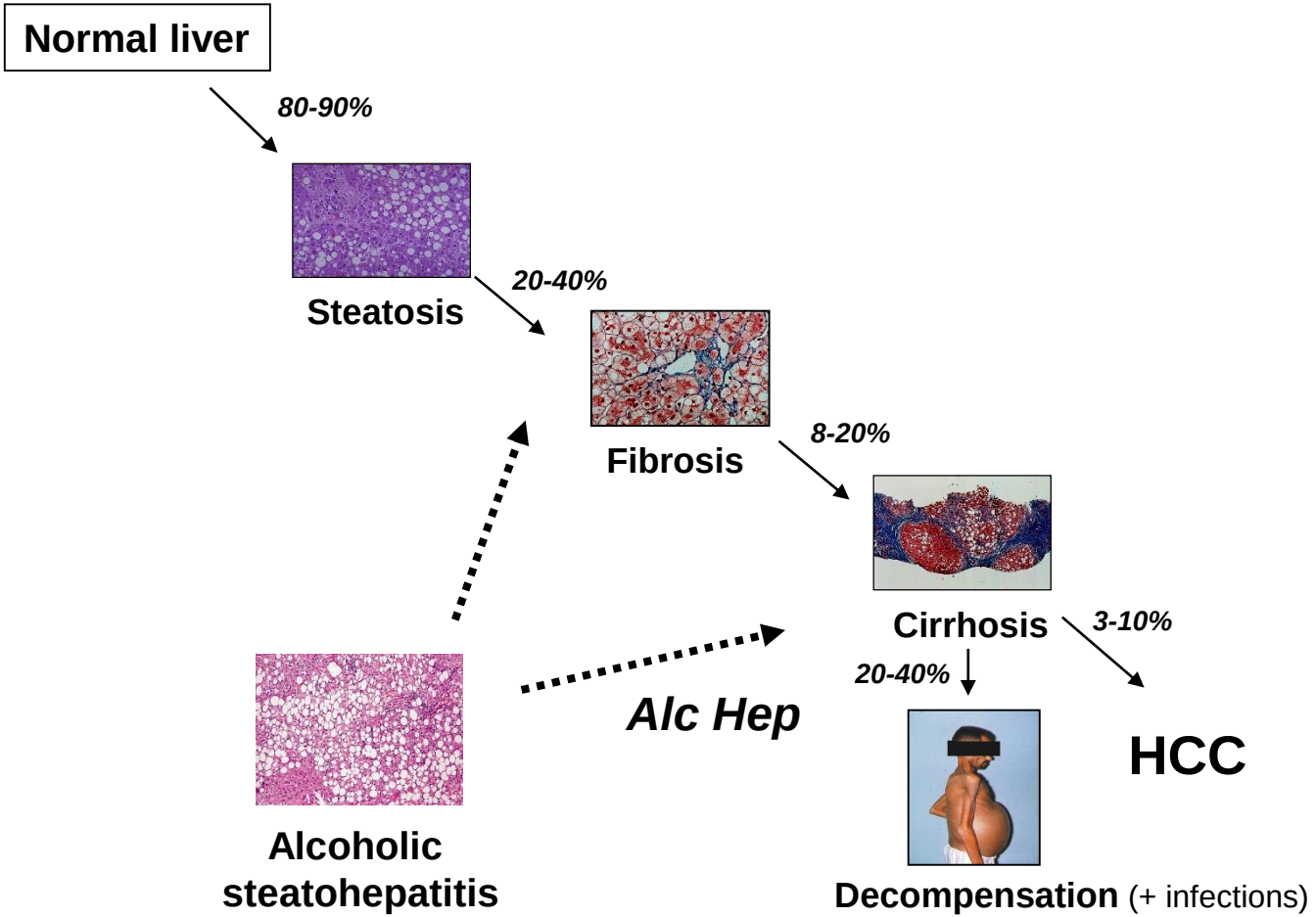


CAP CONTROLLED ATTENUATION PARAMETER → ~ steatosis

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

NATURAL HISTORY OF ALD



ALCOHOLIC HEPATITIS

IS THERE ANYTHING NEW IN THE DIAGNOSIS OR MANAGEMENT ?

CASE PRESENTATION

- **Vital signs**: BP 90/60 mmHg, HR 105, RR 22, T 37.8˚C

- **Biochemical data at admission:**

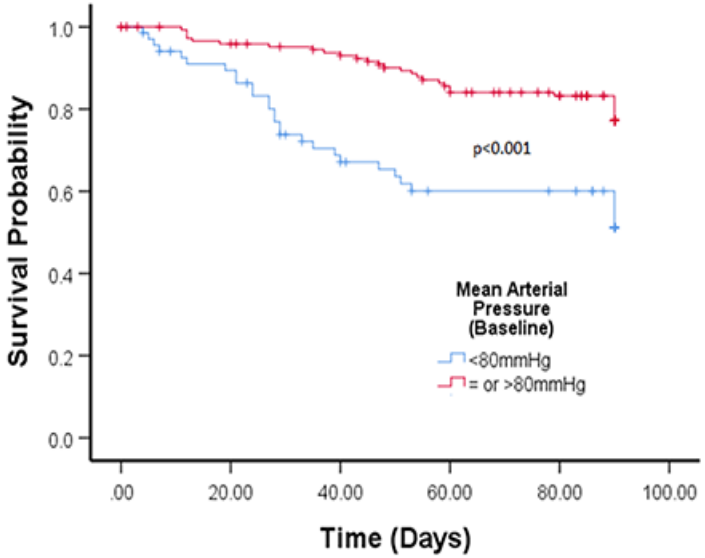
WBC (10^9/l)	**13.2**	**Creatinine (mg/dl)**	**0.8**
Hemoglobin (gr/dl)	**11.7**	**Albumin (gr/dl)**	**2.7**
Platelets (10^9/l)	**100**	**PT /control PT (seg)**	**45/15**
Bilirubin (mg/dl)	**24**	**INR**	**3.7**
AST (UI/l)	**159**	**Na (mEq/l)**	**134**
ALT (UI/l)	**74**	**CRP (mg/L)**	**46**
GGT	**653**	**HBsAg, Anti-HCV Abs, HIV**	**negative**

- **Abdominal US**: steatosis, signs of cirrhosis, no HCC, no PVT, ascites

ARTERIAL PRESSURE INFLUENCES SURVIVAL IN AH

Mean arterial pressure at admission predicts mortality in patients with alcoholic hepatitis independently of MELD.

Meritxell Ventura-Cots[1], Carlos Fernández-Carrillo[1], JosepMaria Argemi[1], Juan G Abraldes[2], Francisco Bosques[3], Robert S Brown Jr[4],Guadalupe Garcia-Taso[5], Juan Genesca[6], Samuel Ho[7], Phillipe Mathurin[8],
Alexander Louvet[8], Michael Lucey[9], Debbie Shawcross[10], Victor Vargas [6], Elisabeth Verna[11], Ramon Bataller[1].



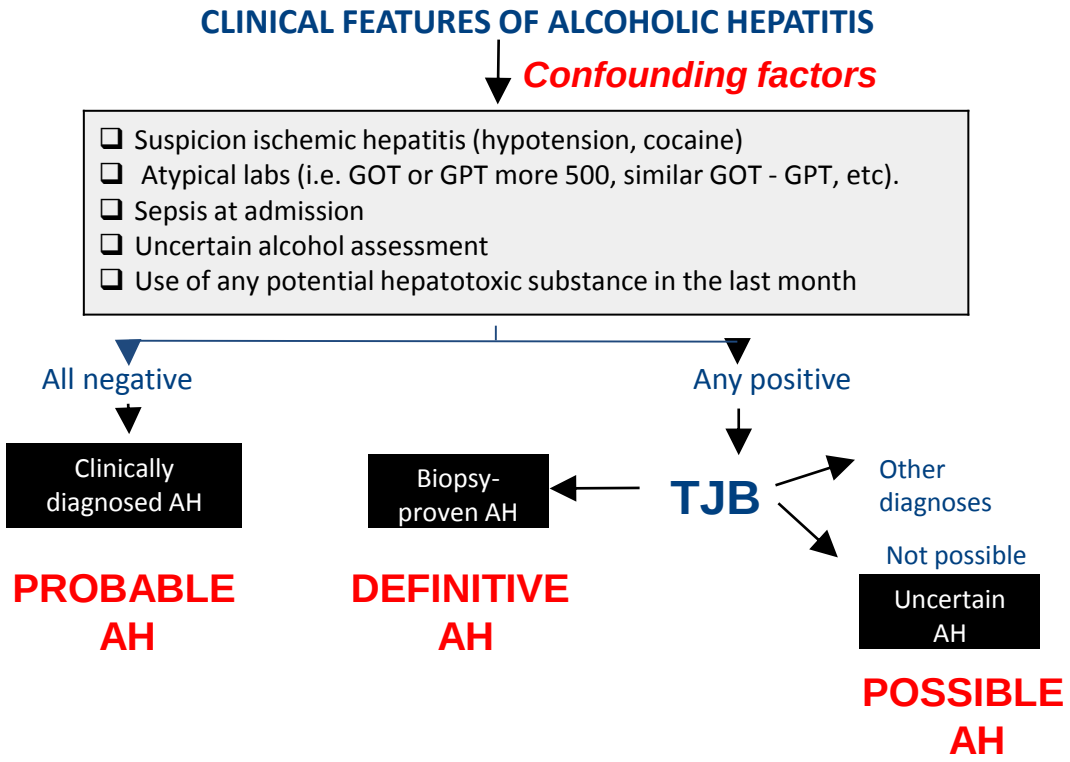
Can we establish a definitive diagnosis of alcoholic hepatitis based on clinical/analytical parameters ?

*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*	✓	✓	✓		✓		6.7

Severe *vs* non-severe

CASE PRESENTATION

- Patient underwent TJB (INR 3.0) at day 2
  - Diagnosis of ASH was <u>confirmed</u>
    - *<u>Histological features</u>*
      - Fibrosis Stage : F4
      - Moderate PMN infiltration
      - Megamitochondria neg

- Hepatocanalicular/Ductular Bilirubinostasis

AHHS: 7

- Scoring Systems
  - **Maddrey's DF: 62**
  - **MELD: 33**
  - **GAHS: 9**
  - **ABIC: 10.2**

Severe Episode of Alcoholic Hepatitis

- Prednisolone 40 md/day for 1 week (Lille: no responder). Developed nosocomial infection, MOF and death. He was considered a suboptimal candidate for early liver transplantation.

EARLY LT FOR SEVERE AH

Early Liver Transplantation in Acute Alcoholic Hepatitis

Christine E. Haugen, MD, PhD[1] Andrew M. Cameron, MD, PhD[1]

Table 1 Recent studies of early liver transplantation for severe acute alcoholic hepatitis

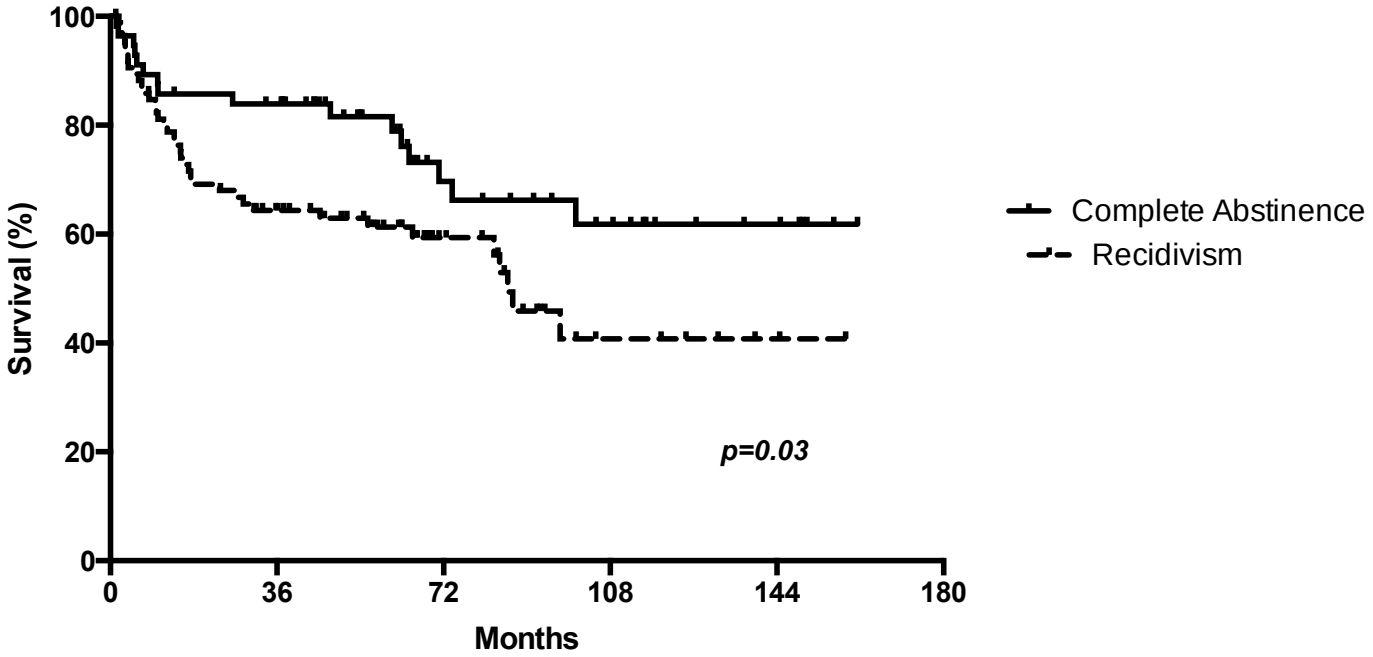
Study	Mathurin	Im	Lee	ACCELERATE-AH
Transplant recipients, *N*	26	9	17	147
Center(s)	France, Belgium	Mount Sinai	Johns Hopkins	United States
Study period	2005–2010	2012–2015	2012–2015	2006–2017
Comparison group	Severe AAH, medical treatment	Severe AAH, medical treatment	Alcoholic cirrhosis, LT with ≥6 mo abstinence	–
Age, years[a]	47	41	43	43
Abstinence prior to LT, days[a]	< 90	30	40	55
6-mo survival, %	77	89	100	94[b]
Any alcohol use post-LT, %	12	22	24	29
Harmful alcohol use post-LT, %	8	11	24	11

Does alcohol relapse influence long-term survival ?

How I can help the patient ?

Figure 1

- MI during hospitalization
- Early follow-up outpatient clinic
- Multidisciplinary team in the clinic
- All team members should be trained



Altamirano et al, Hepatology 2017

TREATING AUD IN A PATIENT-CENTERED MANNER

GENETIC-ENVIRONMENTAL FACTORS

- Family history
- Genetic risk
- Other addictions

SOCIAOECONOMIC FACTORS

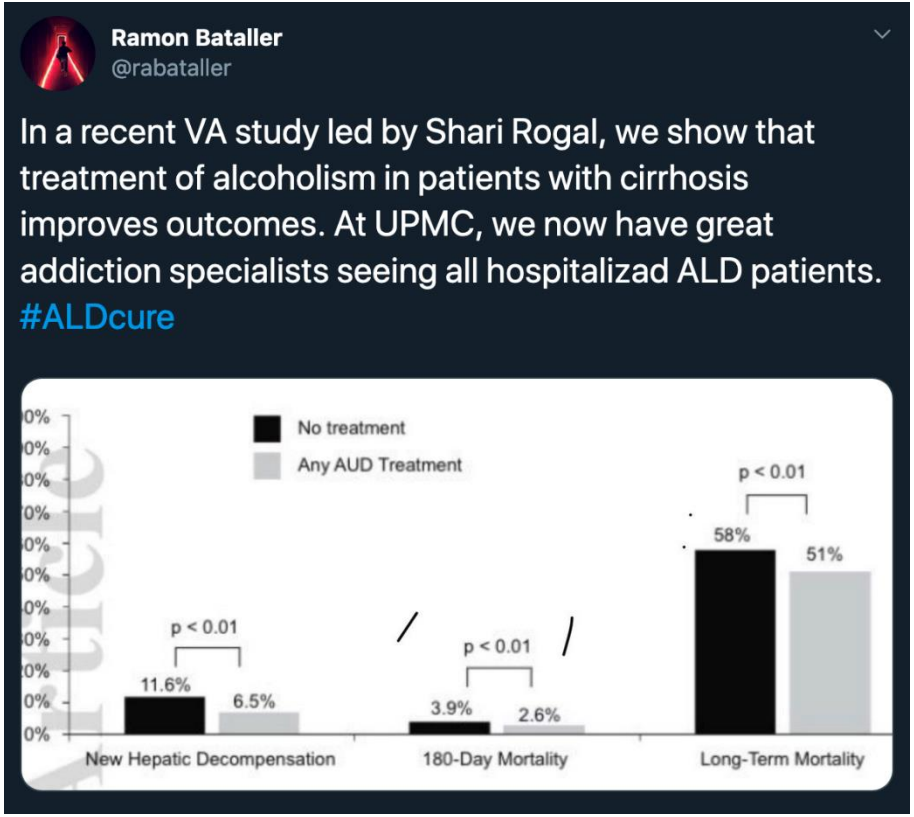
- Isolation
- Stigma
- Transportation
- Insurance

COMMON ASSOCIATED CONDITIONS

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

MULTIDISCIPLINARY ALD CLINIC

- *Specialized APP & nurse*
- *Addiction therapist*
- *Social worker*
- *Hepatologist*



Rogal S et al, Hepatology 2020 (in press)

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Alcohol-related Liver Disease

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

The *Candida albicans* exotoxin Candidalysin promotes alcohol-associated liver disease

Aim:

To evaluate the contribution of *Candida albicans* and its exotoxin Candidalysin on ALD

Methods:

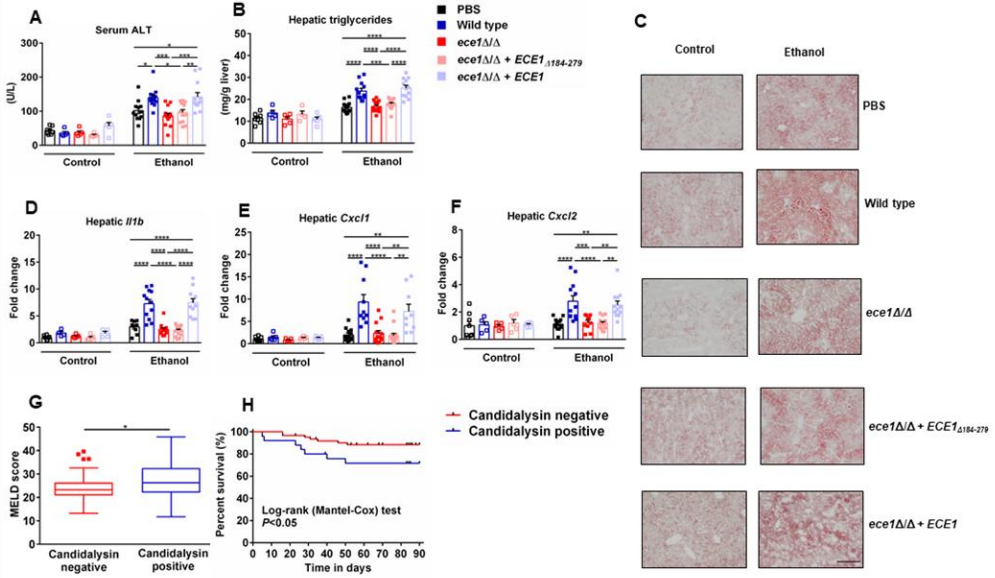
C. albicans and *ECE1* were analyzed in fecal samples from 11 non-alcoholic controls, 42 patients with alcohol use disorder (AUD) and 91 alcoholic hepatitis (AH), and mice colonized with different and genetically manipulated *C. albicans* strains were subjected to the chronic-plus-binge ethanol diet model.

Conclusions:

Candidalysin contributes to progression of ethanol-induced liver disease in preclinical models, and is associated with worse clinical outcomes in patients with alcoholic hepatitis.

Chu HK, et al., Abstract 29

Figure



Mice colonized with Candidalysin positive *C. albicans* displayed more severe ethanol-associated liver injury(A), steatosis(B and C) and inflammation(D-F).
Candidalysin was significantly associated with MELD score(G), and an increased 90 day mortality in alcoholic hepatitis patients(H).

Keratin 18 is a biomarker for the diagnosis and prognosis in acute alcoholic hepatitis

Hypothesis:

K18M65:ALT ratio may assist in distinguishing acute alcoholic hepatitis (AAH) from non-alcoholic steatohepatitis patients (NASH); K18 concentrations are potentially robust biomarkers for predicting mortality in severe AAH.

Methods:

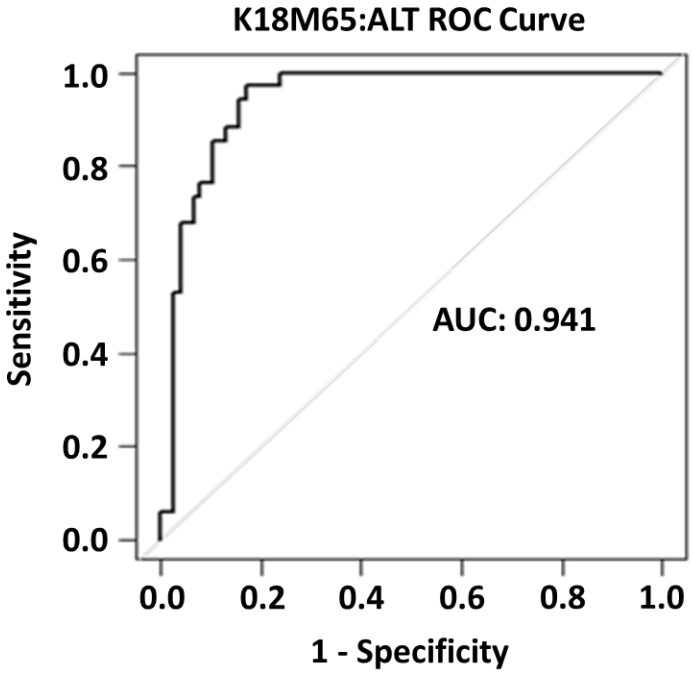
173 participants; 84 AAH patients were classified as severe (n=57, MELD ≥20), or moderate (n=27, 12≤ MELD <19); 38 Alcohol Use Disorder (AUD) patients had mild (n=28, ALT >40) or no liver injury (n=10, ALT ≤40); 34 were NASH patients; and 17 were healthy controls in this single time-point 90-day mortality assessment study.

Main Findings:

ROC curve for K18M65:ALT distinguishes AAH significantly from NASH.

Conclusions:

Keratin 18 appears to reflect the degree of hepatocyte death and liver disease severity better than AST, ALT, or other traditional biomarkers in AAH.



Vatsalya V, et al., Abstract 270