ROMA

ISTITUTO SUPERIORE DI SANITÀ
AULA ROSSI
Viale Giano della Bella, 34

10 DICEMBRE 2019

LA REALTÀ ITALIANA DELLA CIRROSI EPATICA TRA TERAPIE E IMPATTO SOCIO ECONOMICO

2019 MOTORE SANITÀ
Gestire il Cambiamento

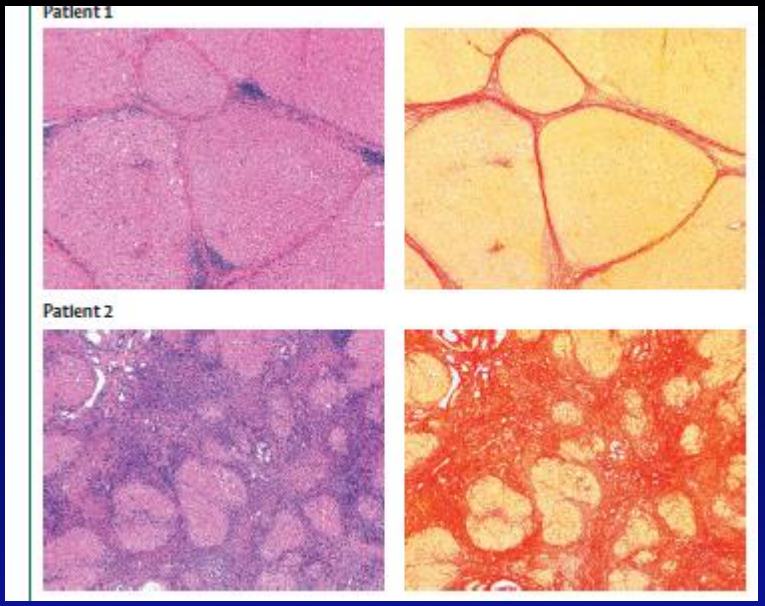
Gianni Testino

SC Patologia delle Dipendenze ed Epatologia

Centro Alcologico Regionale Ligure

ASL3 Liguria c/o Osp. Policlinico San Martino, Genova

Società Italiana di Alcologia



Cirrosi epatica

Prevalenza/incidenza: 21.000 decessi/anno per cirrosi o HCC in Italia; la mortalità incide in maniera preponderante tra i 25 e 60 anni.

Sopravvivenza a tre anni nei cirrotici stratificati secondo la classe di Child-Pugh: nei pazienti in Child A sopravvivenza a tre anni pari a 85%; al 54% in classe B; al 42% in classe C.

Lo sviluppo di HCC è la principale causa di morbilità e morte nei cirrotici postvirali. Dal 20 al 40% dei cirrotici non trattati farmacologicamente sanguina da varici entro i primi due anni di osservazione.

Livello di assistenza: Ricovero in emergenza/urgenza: encefalopatia; sanguinamento da varici. Ricovero ordinario per cirrosi scompensata, o per complicanze del versamento ascitico. Il cirrotico compensato o con ascite viene seguito ambulatorialmente con periodiche ammissioni al day hospital

Follow-up periodico clinico-ecografico ambulatoriale per diagnosi precoce di HCC

Buscarini et al, White paper of Italian Gastroenterology; Dig Liver Dis 2014

Figura 1

Le 10 principali cause di morte in Italia [redacted] (per 10^5 ab)

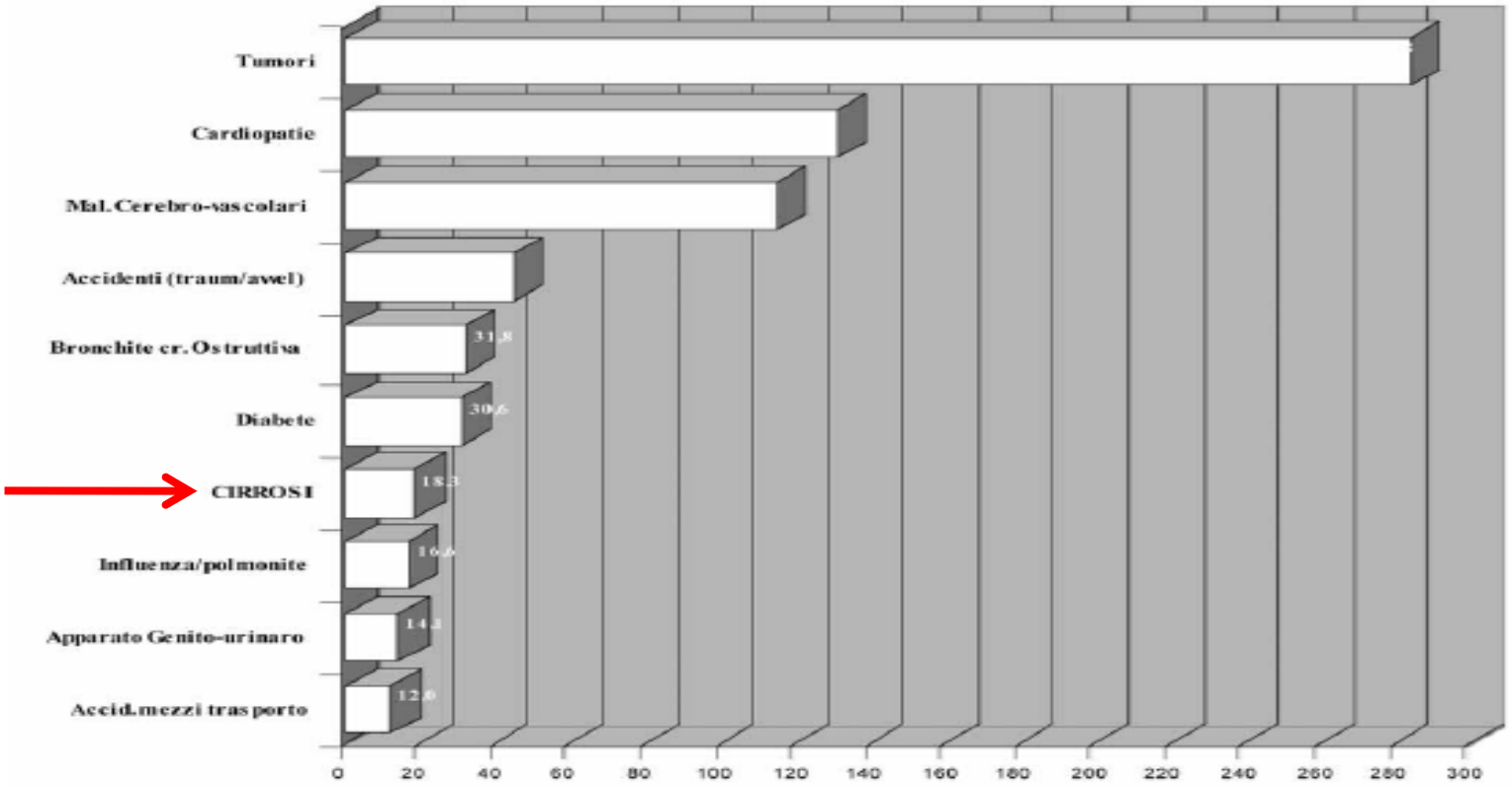
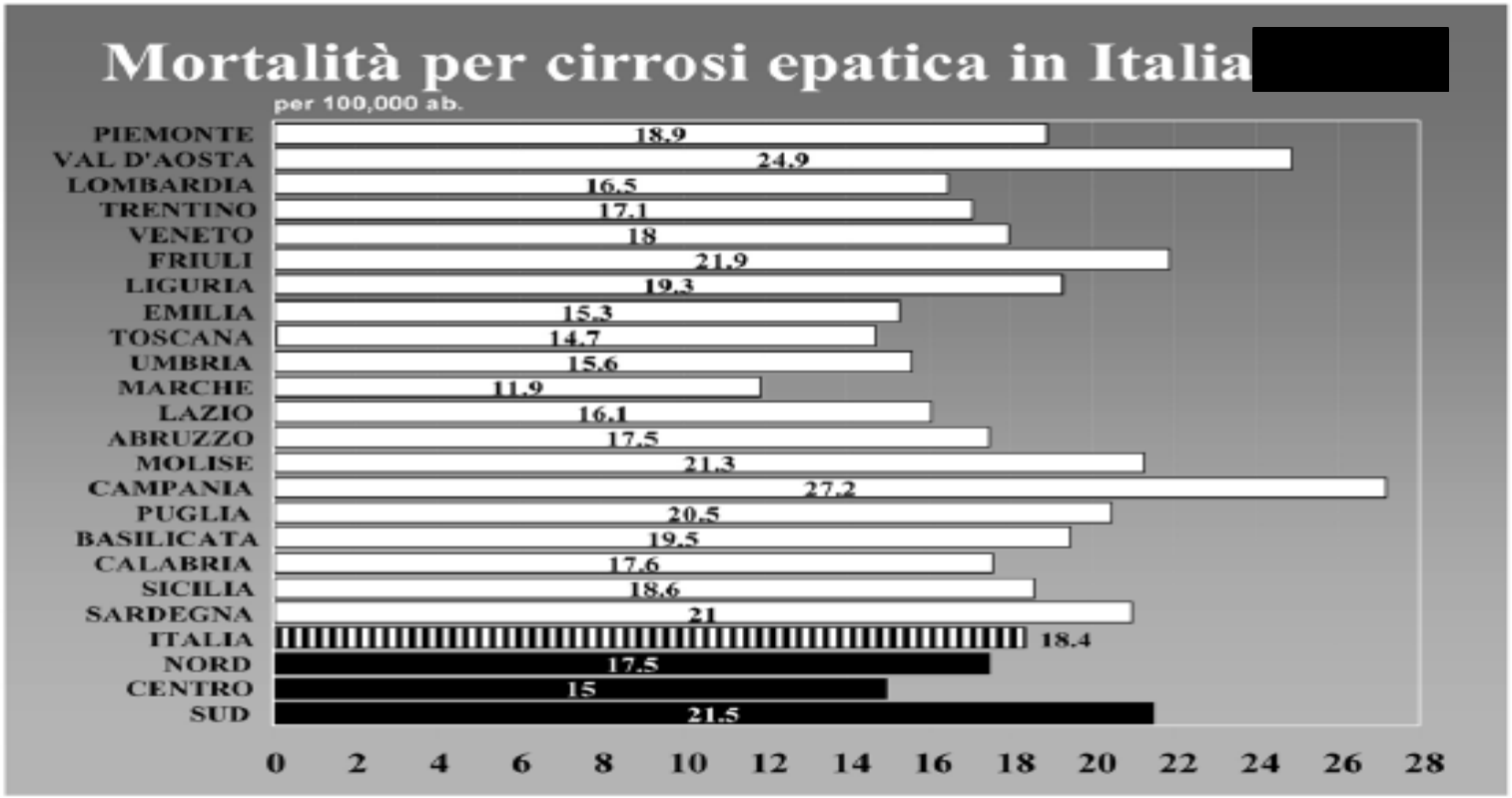
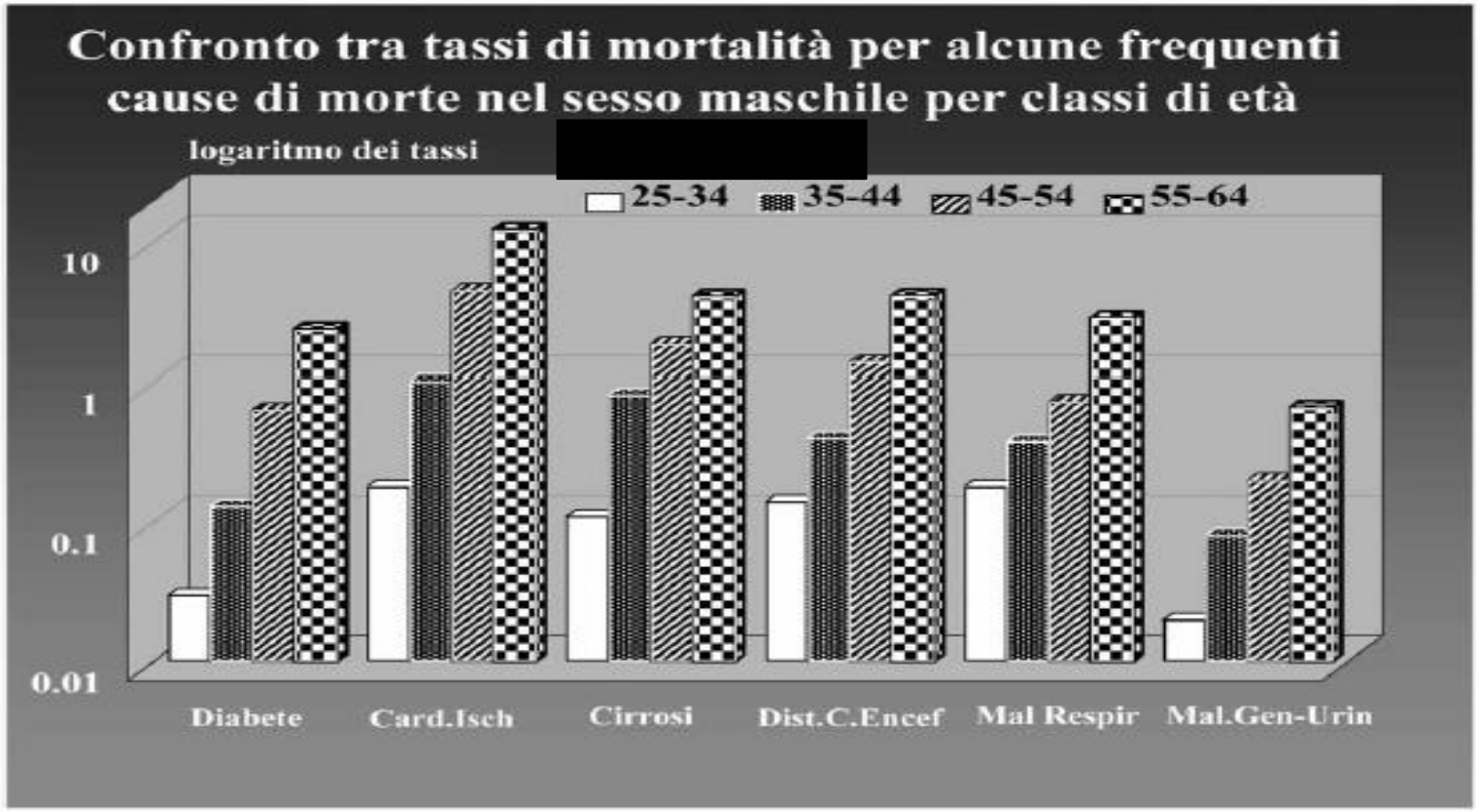


Figura 3



Associazione Italiana Studio Fegato, 2007

Figura 6



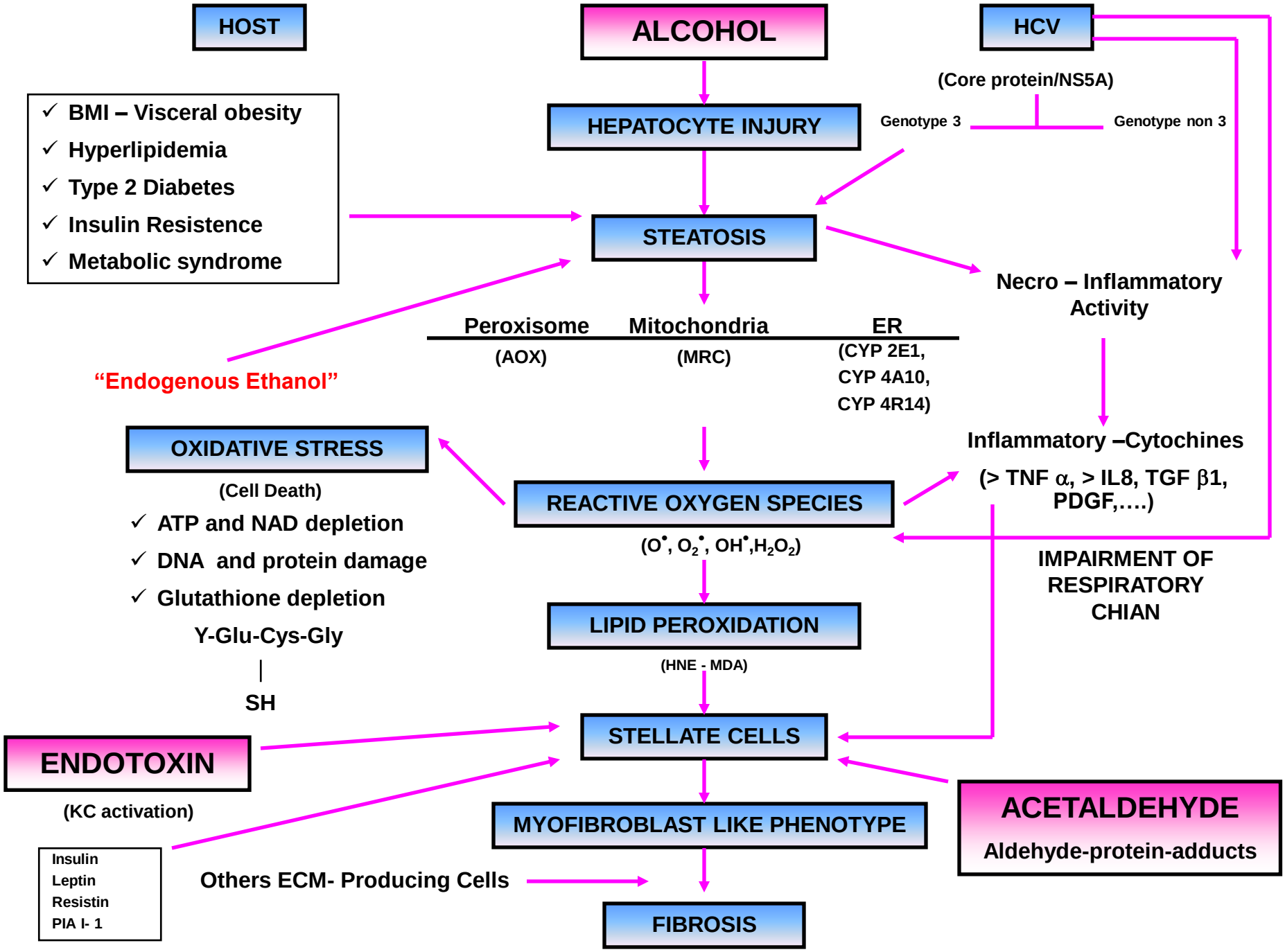
Associazione Italiana Studio Fegato, 2007

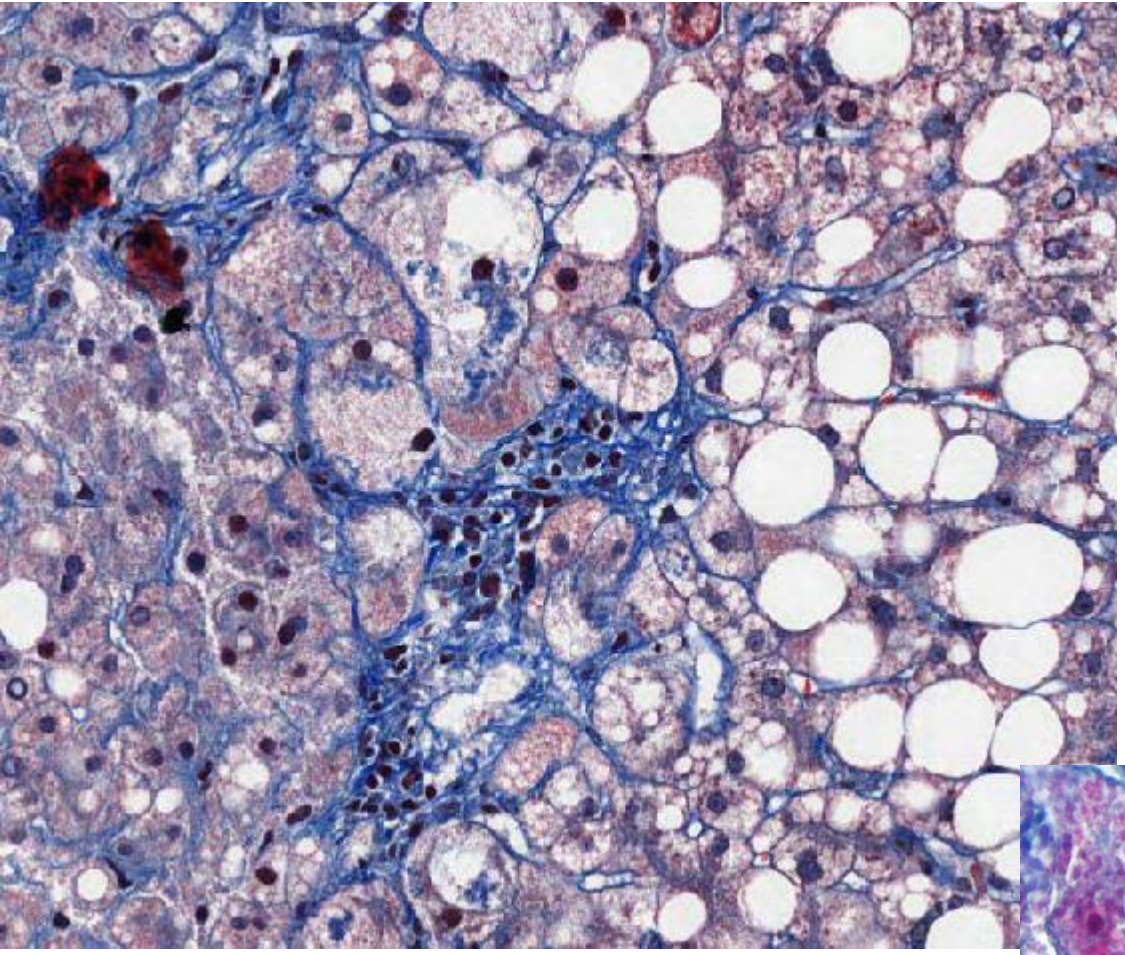
Table 1. Characteristics of the patients admitted for cirrhosis complications (mean Child–Pugh score 8.5 ± 1.7), heart failure (HF), and chronic obstructive pulmonary disease (COPD), randomly selected for costs analysis (n = 100 each)

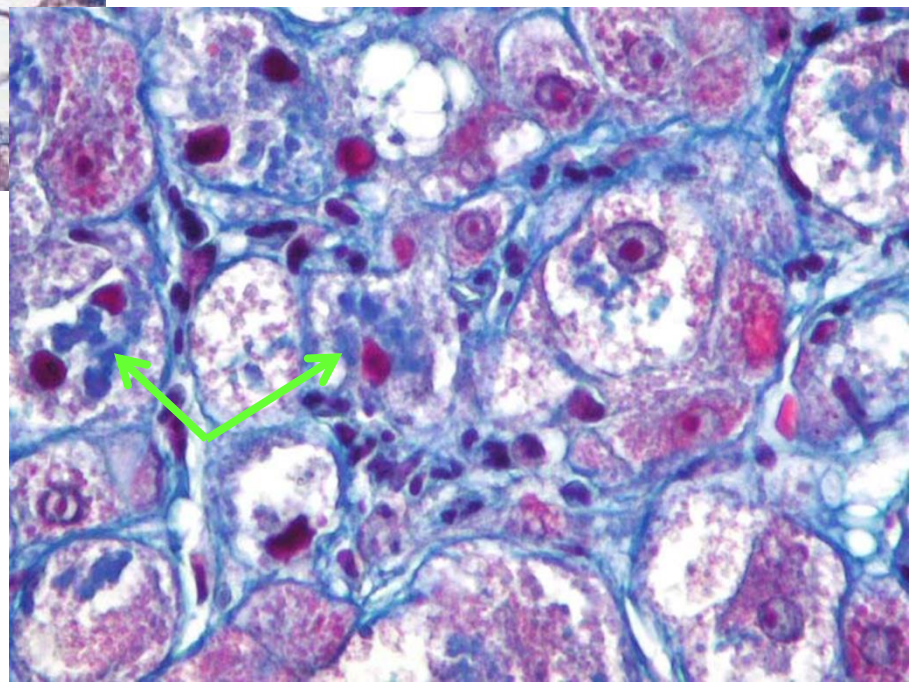
Chronic disease	Cirrhosis (A)	HF (B)	COPD (C)	p value
Age, years	69.5±10.5	82.8±8.1	79.3±9.7	<0.01 A vs. B and C
Hospitalization days				
Mean ± SD	12.1±10.1	7.9±3.8	8.7±4.5	<0.01 A vs. B
Interquartile range	5–15	5–9	6–11	<0.05 A vs. C
Mortality, %	10	8	5	ns A vs. B and C
Total cost, €	3,884±3,230	2,510±1,199	2,713±1,298	<0.01 A vs. B; <0.05 A vs. C
Daily cost, €	338±86	321±28	319±43	ns A vs. B and C

ns, not significant.

Di Pascoli M et al, Dig Dis 2016


HOST
ALCOHOL
HCV
(Core protein/NS5A)
Genotype 3
Genotype non 3
✓ BMI – Visceral obesity
✓ Hyperlipidemia
✓ Type 2 Diabetes
✓ Insulin Resistence
✓ Metabolic syndrome
HEPATOCYTE INJURY
STEATOSIS
Necro – Inflammatory Activity
Peroxisome
(AOX)
Mitochondria
(MRC)
ER
(CYP 2E1, CYP 4A10, CYP 4R14)
"Endogenous Ethanol"
OXIDATIVE STRESS
(Cell Death)
✓ ATP and NAD depletion
✓ DNA and protein damage
✓ Glutathione depletion
Y-Glu-Cys-Gly
SH
Inflammatory –Cytochines
(> TNF α, > IL8, TGF β1, PDGF,….)
REACTIVE OXYGEN SPECIES
($O^{\bullet}$, $O_2^{\bullet}$, $OH^{\bullet}$,H_2O_2)
IMPAIRMENT OF RESPIRATORY CHIAN
LIPID PEROXIDATION
(HNE - MDA)
ENDOTOXIN
(KC activation)
STELLATE CELLS
ACETALDEHYDE
Aldehyde-protein-adducts
MYOFIBROBLAST LIKE PHENOTYPE
Insulin
Leptin
Resistin
PIA I- 1
Others ECM- Producing Cells
FIBROSIS





Fibrosi sinusoidale e pericellulare in steatoepatite tipo ASH.

Freccia indica i corpi di Mallory

F. Grillo, Anatomia Patologica, Università di Genova

Shah et al, Clin Gastroenterol Hepatol, 2019

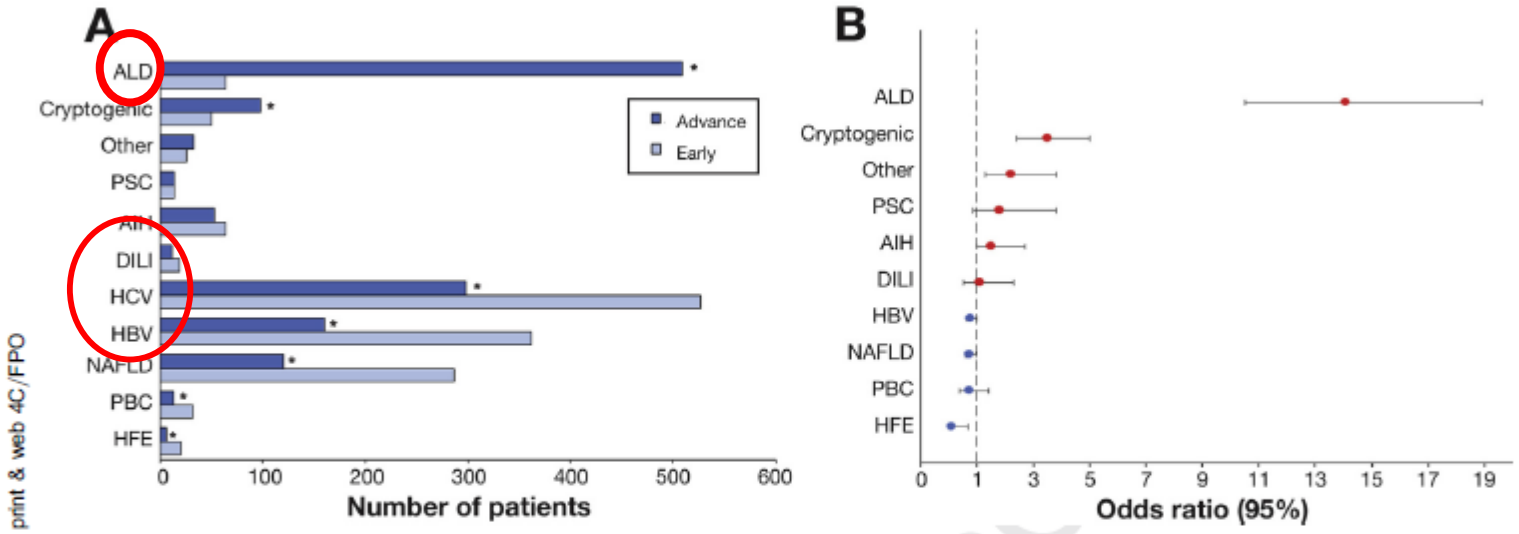


Figure 2. Medical visits at specialized centers of patients with a single etiology. (*A*) Number of patients with medical visits at advanced vs early liver stages. *$P < .05$. (*B*) Odds ratio of being seen at an advanced stage. AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; HFE, hemochromatosis; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

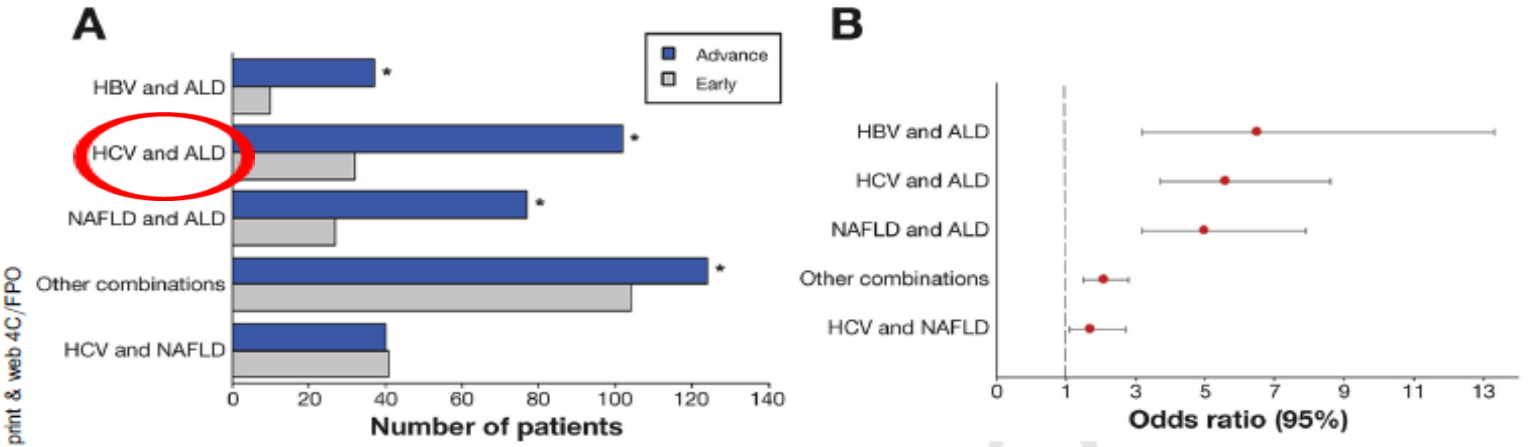
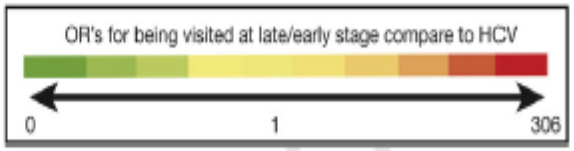


Figure 3. Medical visits at specialized centers by patients with double etiologies. (*A*) Number of patients with medical visits at advanced vs early liver stages. *$P < .05$. (*B*) Odds ratio of being seen at advanced stage vs early liver disease stages. ALD, alcohol-related liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease.

	HBV	NAFLD	DILI	AIH	Other	Double etiologies without ALD	Cryptogenic	Double etiologies involving ALD	ALD
Africa	0.7	0.4	2.7	1.4	2.5	4.1	0.6	1.3	1.9
Asia	0.9	0.4	1.4	1.9	3.5	2.6	9.2	4.5	10.3
America	0.6	2	0.7	1.2	6.2	1.3	NA	2.5	23.8
Europe	0.6	0.6	1.1	2.2	3.7	2.2	13	10.3	51.7
Oceania	1.5	3	NA	4	1	NA	NA	30	306



print & web 4C/FPO

Figure 4. Heatmap expression of the likelihood of having a medical visit at advanced vs early stages compared with HCV by continent. Red color shows those etiologies with the highest likelihood of being seen at advanced vs early stages of liver disease compared with HCV and green color shows the contrary. Because of their low global frequency, Wilson disease, hemochromatosis, schistosomiasis, and triple or quadruple etiologies were grouped with the category of *other*. AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; DILI, drug-induced liver injury; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

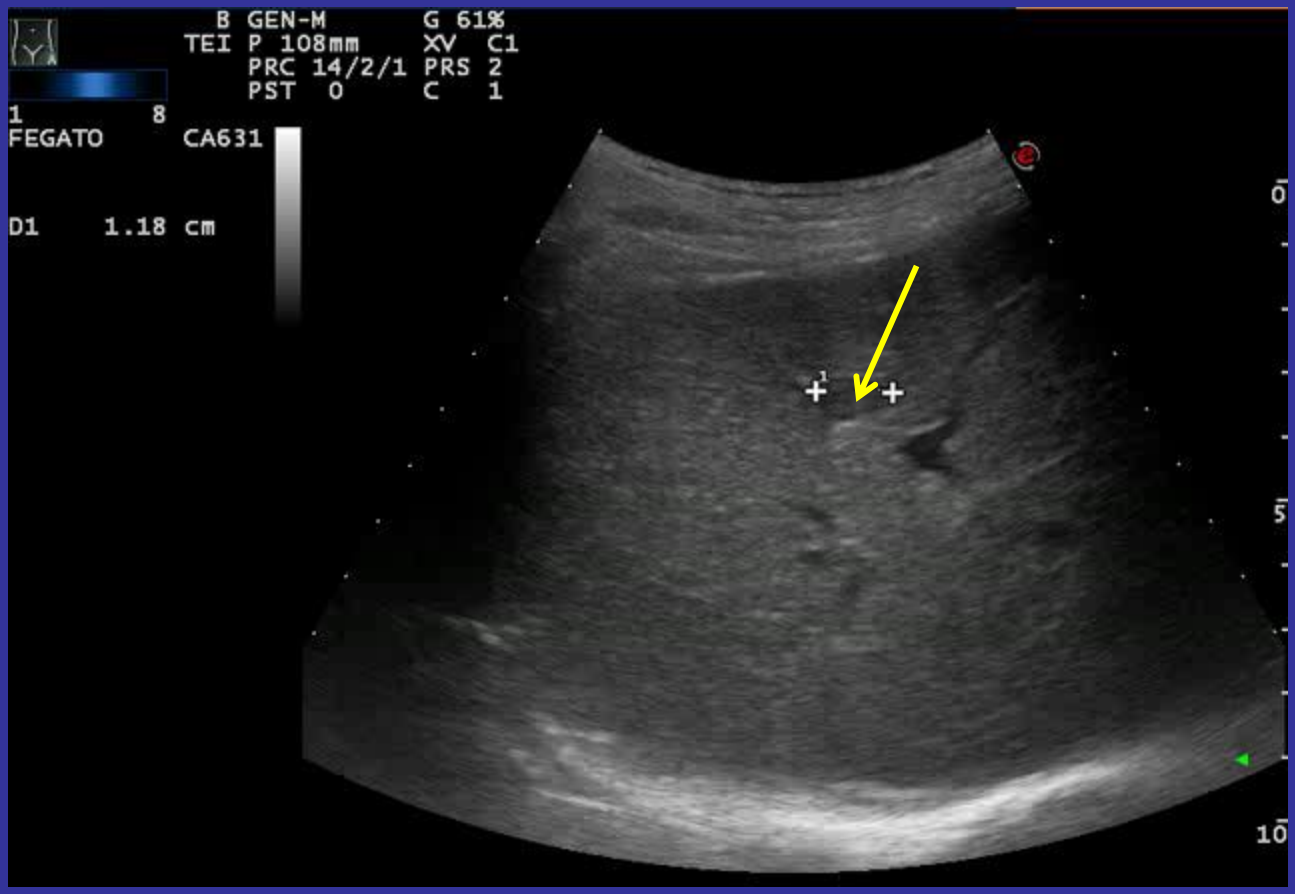
Shah et al, Clin Gastroenterol Hepatol, 2019

DELAYED DIAGNOSIS OF HCC WITH ALCOHOLIC LIVER DISEASE

Table 3. Tumor stage at diagnosis of HCC with respect to chronic liver disease etiology (p = 0.186)

	Alcoholic liver disease		Viral hepatitis	
BCLC class	n	%	n	%
A	44	14.6	20	22.0
B	92	30.5	32	35.2
C	132	43.7%	31	34.1
D	34	11.3	8	8.8

Schutte et al, Liver Cancer 2012



SC Patologia delle Dipendenze ed Epatologia

Centro Alcologico Regionale Ligure, ASL3 c/o Ospedale Policlinico San Martino, Genova

Application of hepatocellular carcinoma surveillance in a European setting. What can we learn from clinical practice ?

In a European setting, only 22% of HCCs were diagnosed by surveillance, and in more than one-third of cases, surveillance was indicated but missed. NAFLD and alcoholic liver disease were associated with deficient surveillance.

Survival was significantly better in patients who underwent surveillance compared with those in whom surveillance was missed although indicated.

Edenvik P et al, Liver Int 2015

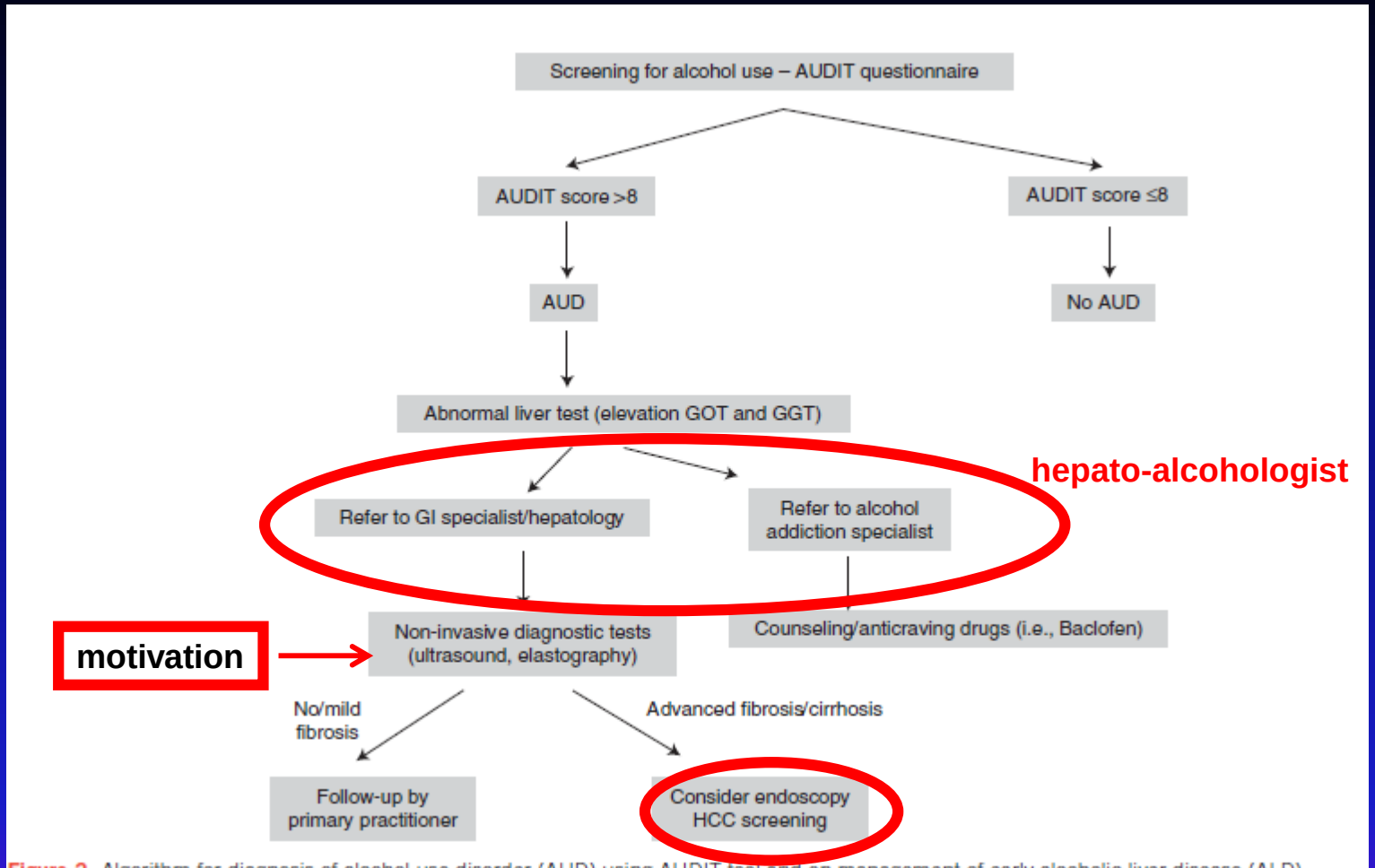
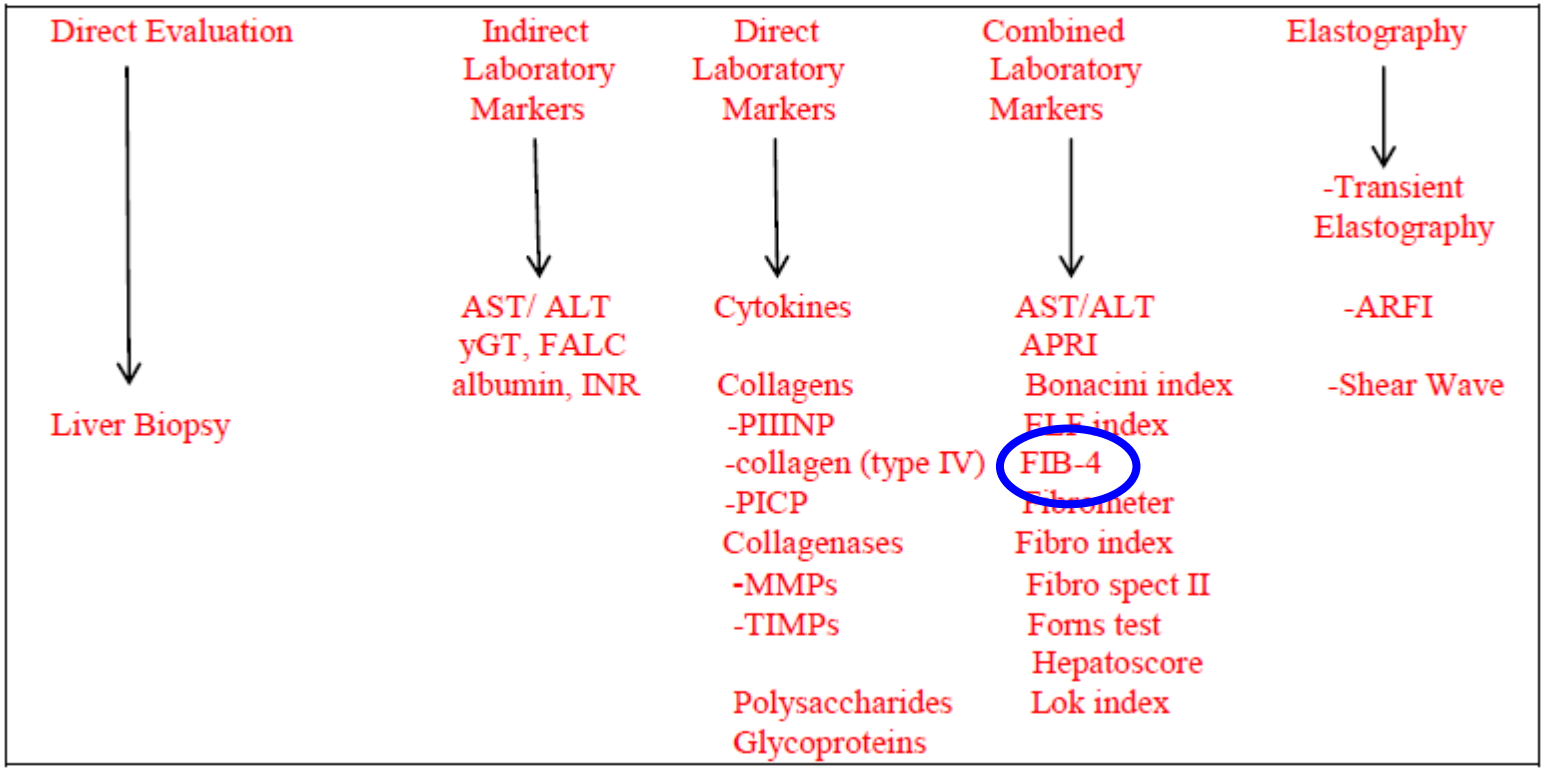


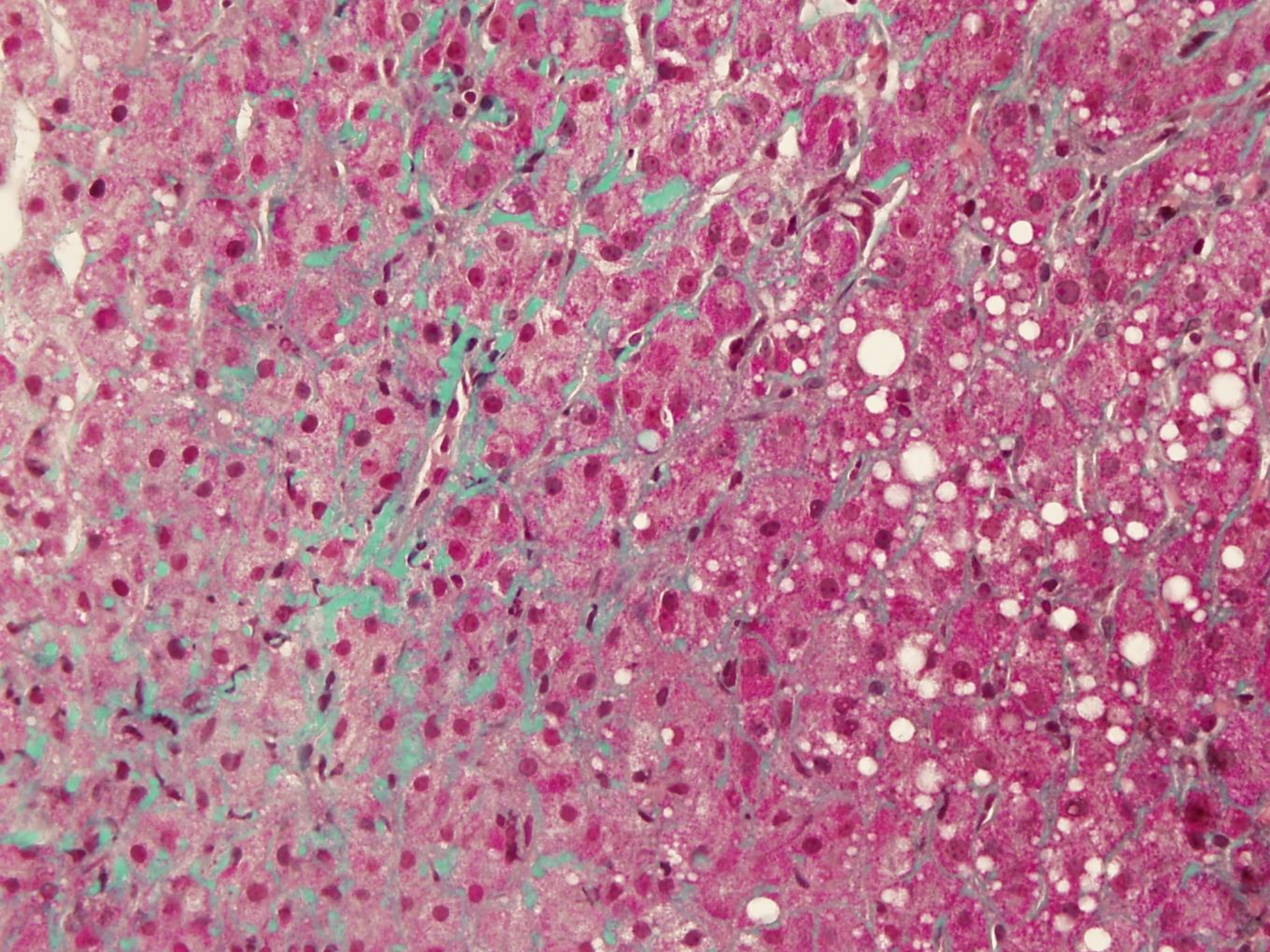
Figure 2. Algorithm for diagnosis of alcohol use disorder (AUD) using AUDIT tool and on management of early alcoholic liver disease (ALD).

Modified, from Singal et al; ACG Clinical Guideline: Alcoholic Liver disease 2018

Figure 1 – Evaluation of liver fibrosis (ARFI: acustic radiation force impulse elastography)



Testino and Pellicano 2018, in press



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OSPEDALE SAN MARTINO MI 1.4 04-11-2015
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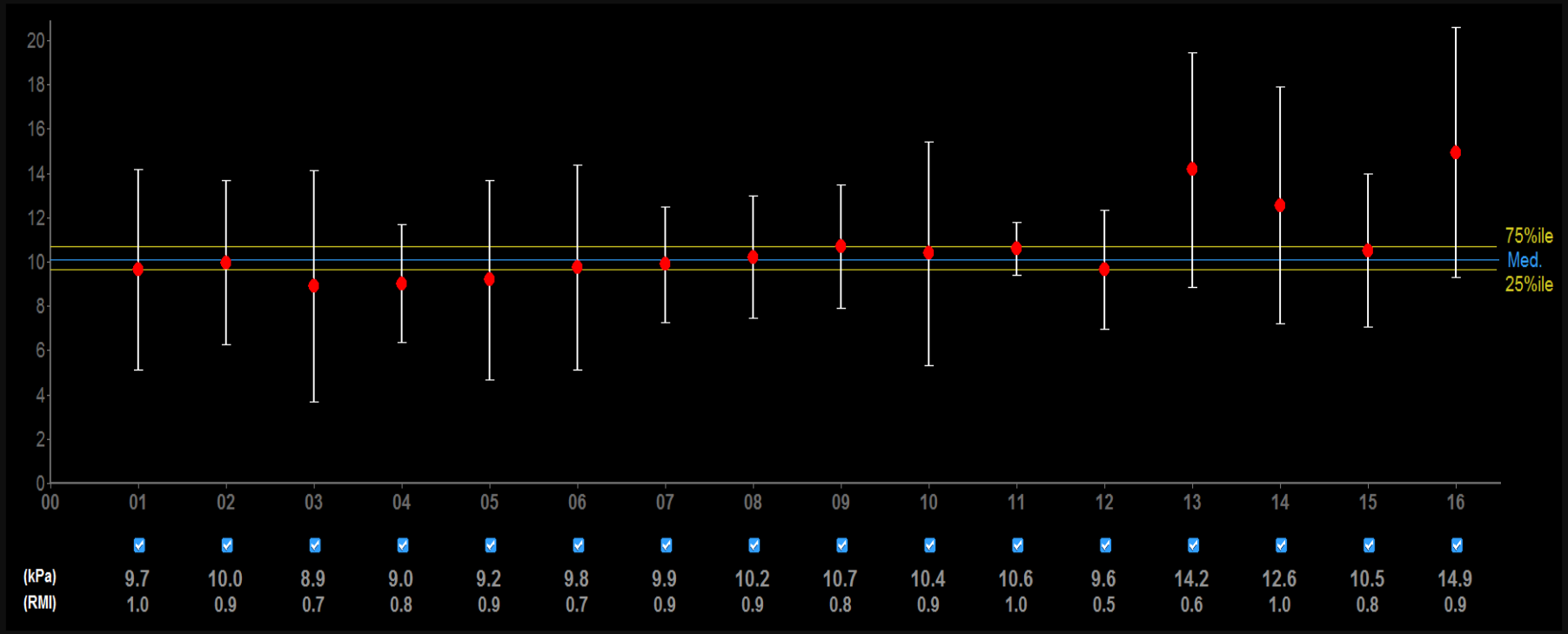
S-Shearwave Profile



	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16
(kPa)		9.7	10.0	8.9	9.0	9.2	9.8	9.9	10.2	10.7	10.4	10.6	9.6	14.2	12.6	10.5	14.9
(RMI)		1.0	0.9	0.7	0.8	0.9	0.7	0.9	0.9	0.8	0.9	1.0	0.5	0.6	1.0	0.8	0.9

Median	IQR/Med.
10.1kPa	10.4%

Total : 16 / 16 Result

OK Close

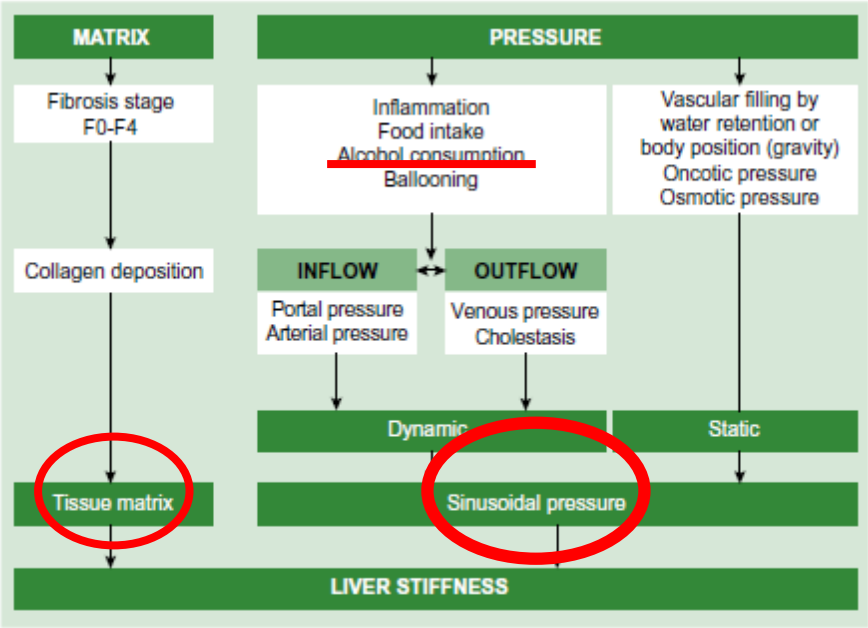
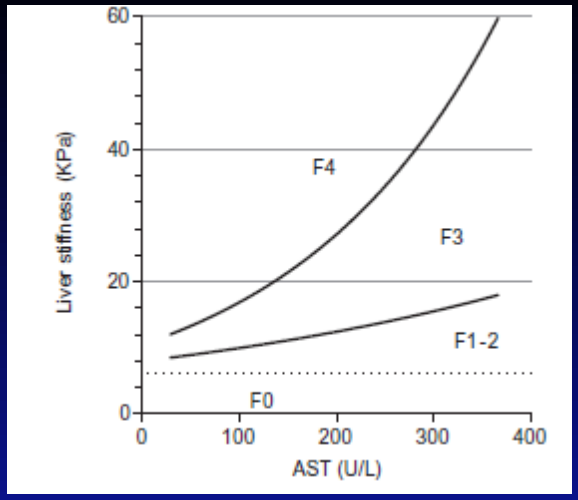


Fig. 1. Factors influencing liver stiffness measurement.



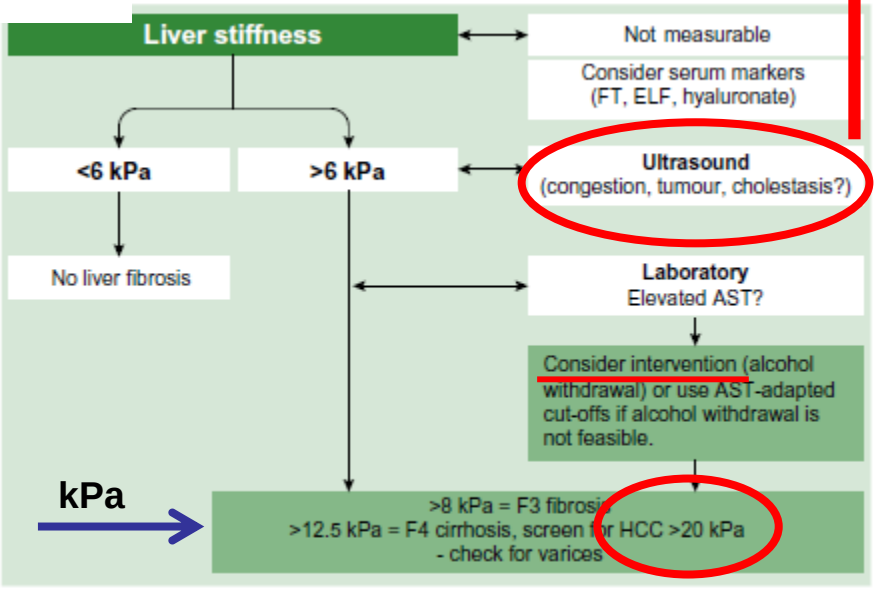


Fig. 2. Practical algorithm in patient with excessive alcohol consumption. AST, aspartate aminotransferase; HCC, hepatocellular carcinoma.

Moreno et al; J Hepatol 2019, 70:273

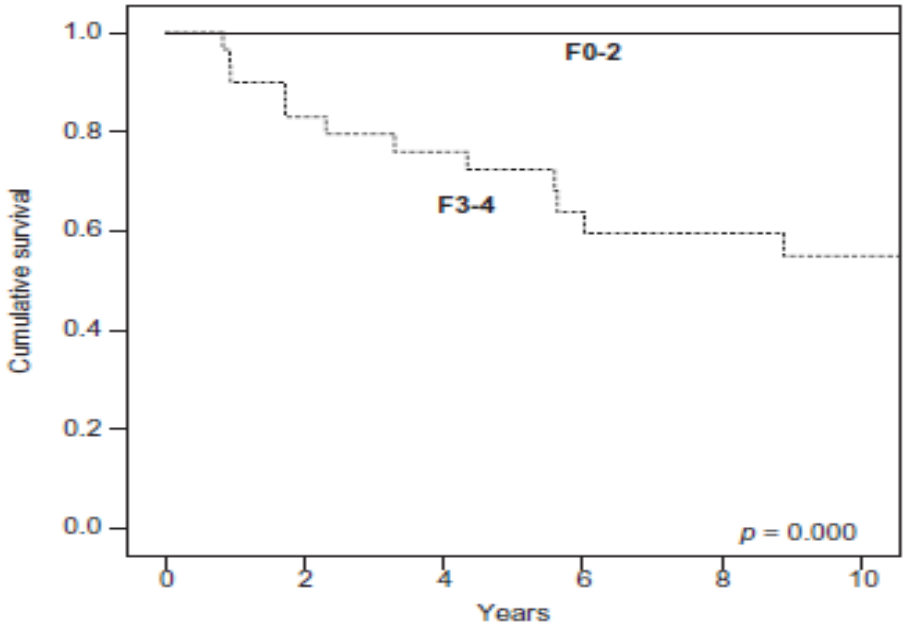
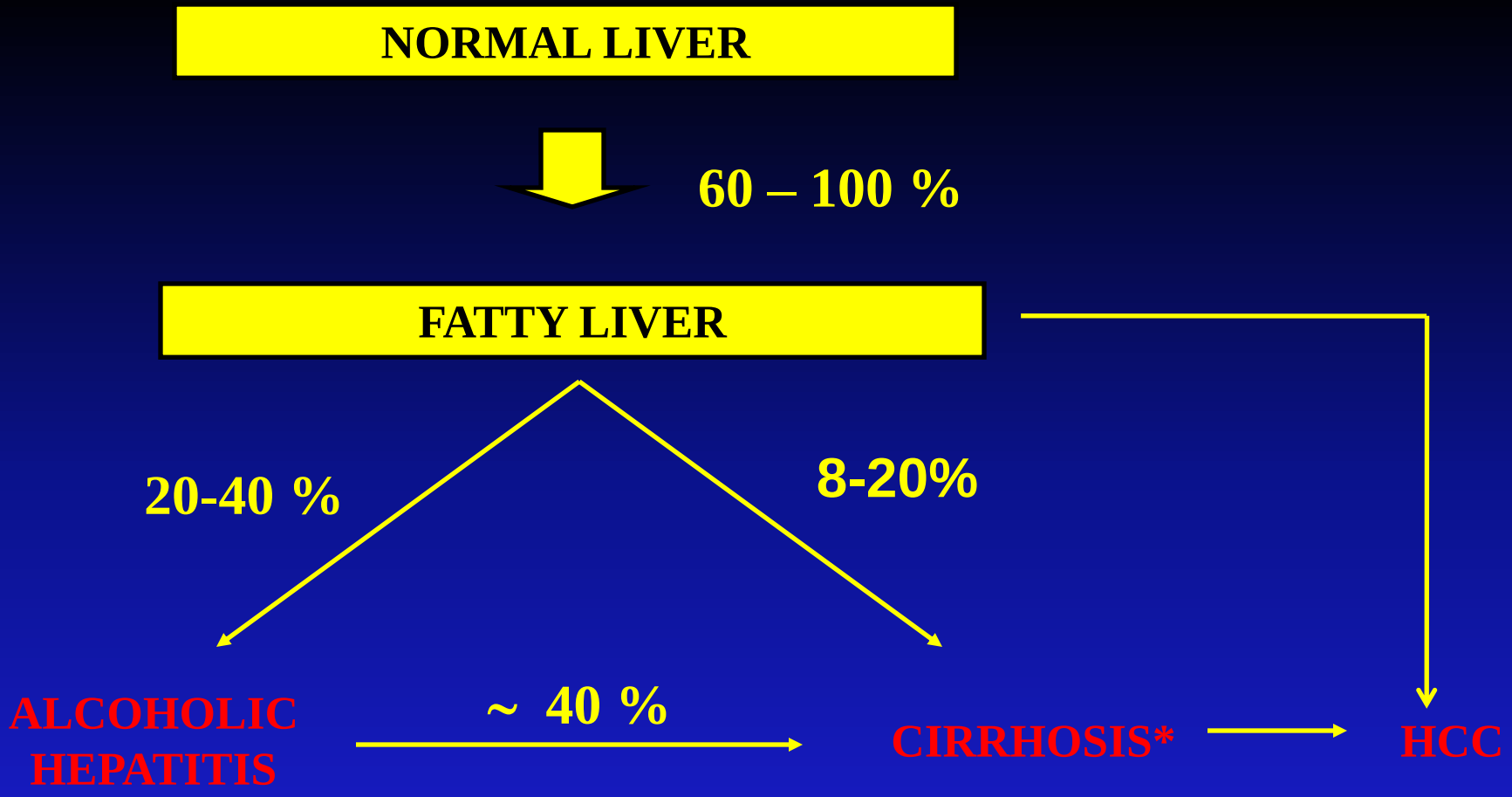


Fig. 1. Kaplan-Meier plots of survival probability of patients with early/compensated alcohol-related liver disease with respect to fibrosis stage. Survival of patients staged F3–4 is significantly worse than for patients with stage F0–2 ($p < 0.001$ by log-rank test) (reproduced with permission from[9]).

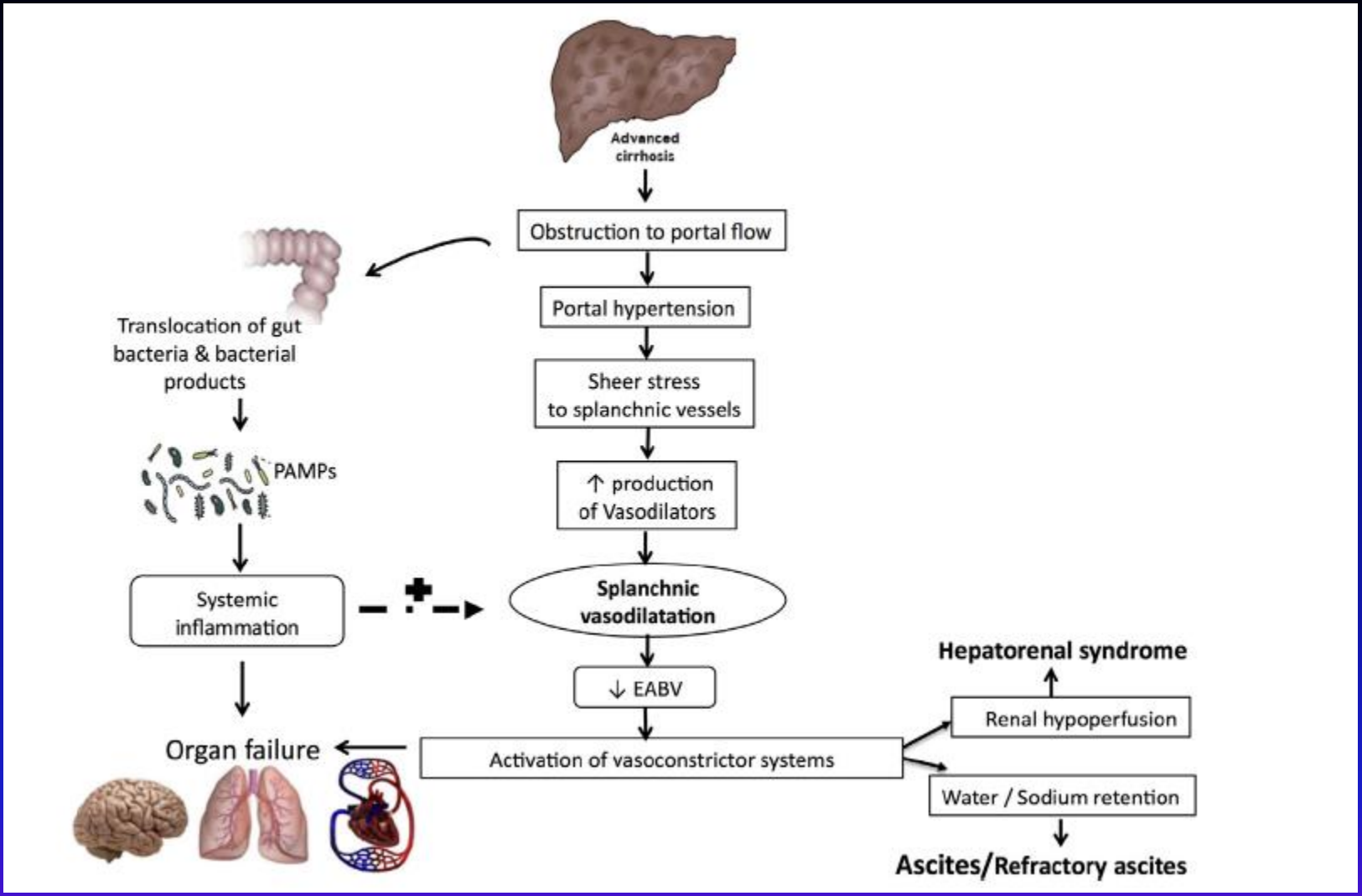
Loomba et al, Gastroenterology 2015; 149: 278-81



* 5 years survival

Compensated: Abstainer ≈ 90%,
Continue to drink < 70%

Scompensated: Abstainer ≈ 50%,
Continue to drink < 30%



PAMPs: pathogen associated molecular pattern

EABV: effective arterial blood volume

Adebayo D et al, Clin Liver Dis 2019

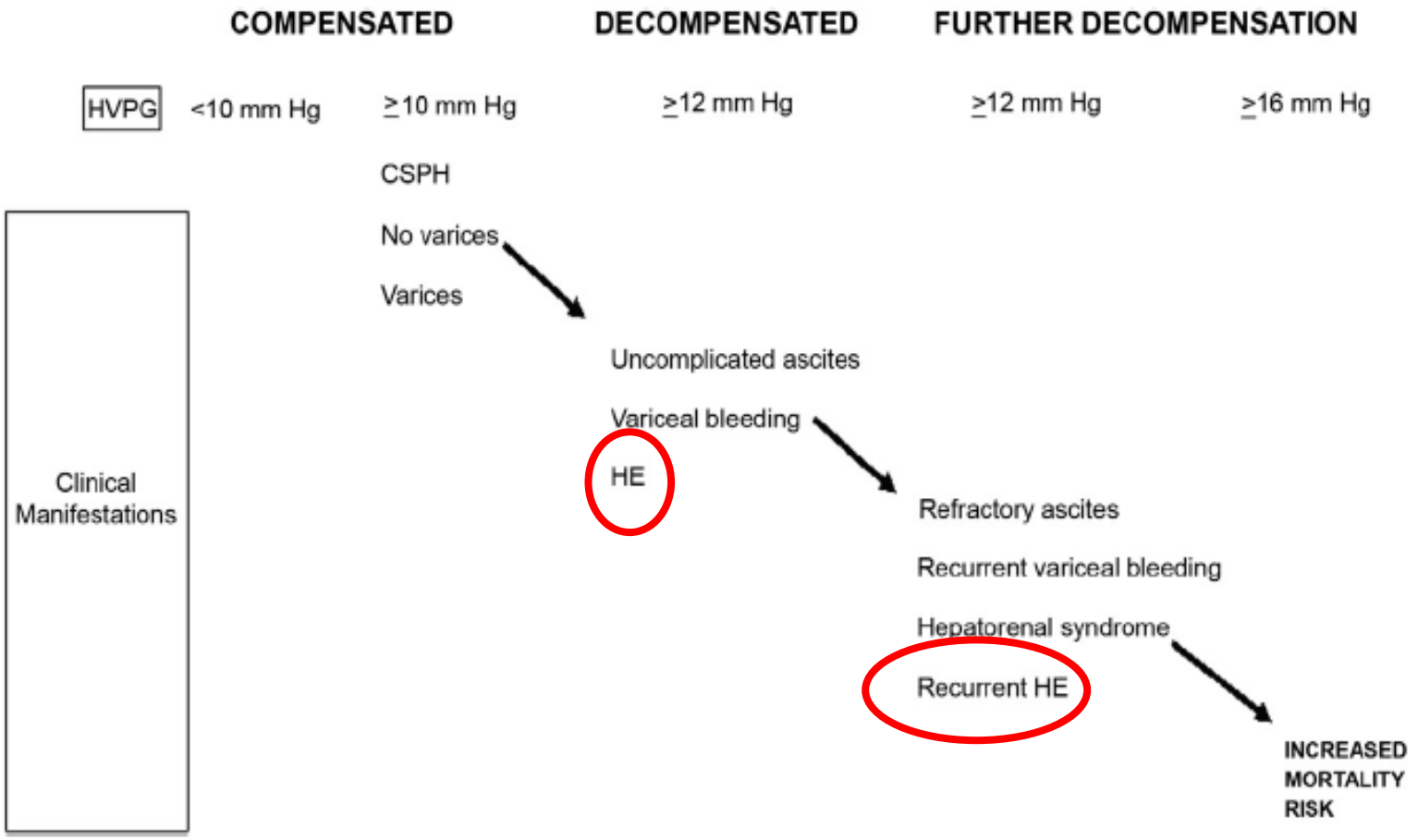


Fig. 1. Natural history of the progression of portal hypertension. HE, hepatic encephalopathy.

HVPG: hepatic venous pressure gradient

Adebayo D et al, Clin Liver Dis 2019

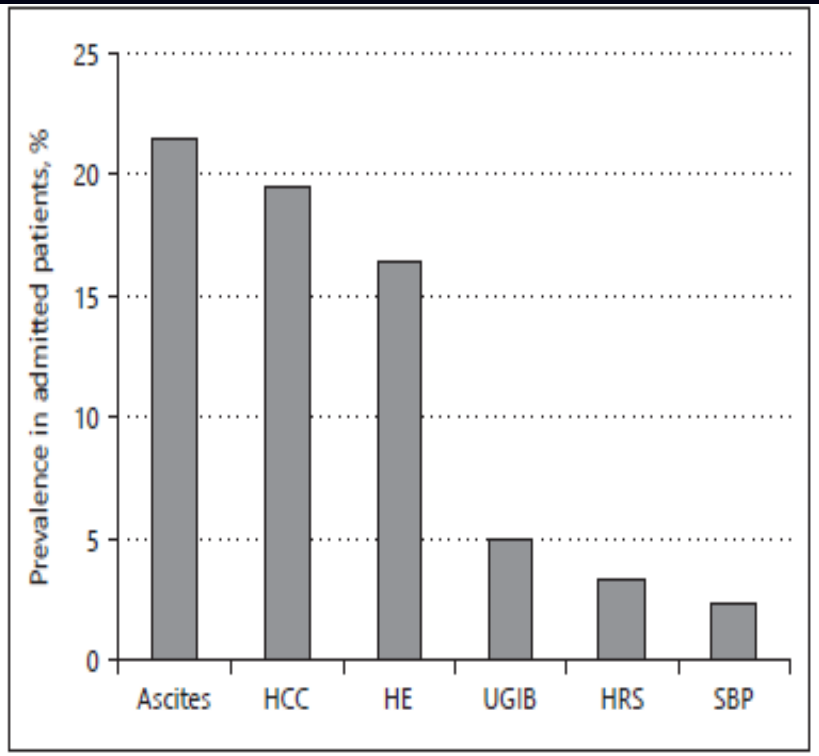


Fig. 2. Prevalence of complications among hospitalized patients with cirrhosis. HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; UGIB, upper gastrointestinal bleeding; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.

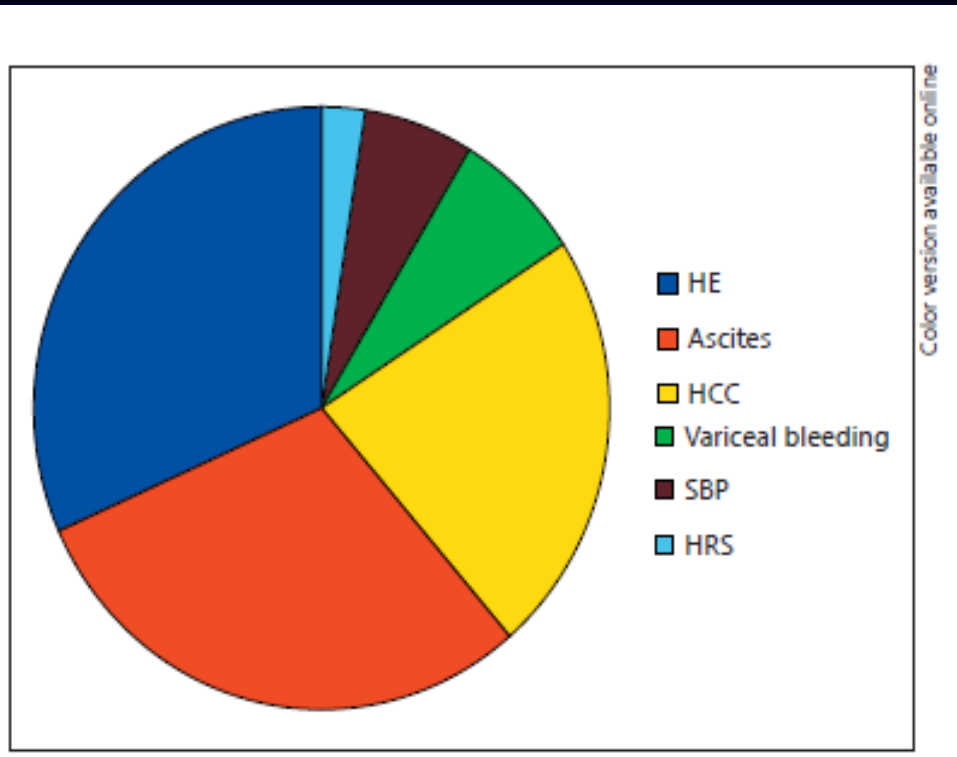


Fig. 3. Distribution of the complications of cirrhosis as first diagnosis among hospitalized patients. HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome.

Di Pascoli M et al, Dig Dis 2016

Classification of HE

WHC including MHE	ISHEN	Description	Suggested operative criteria	Comment
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	**Covert**	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change.	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis. Local standards and expertise required
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioural decay with respect to his/her standard on clinical examination, or to the caregivers	Clinical findings usually not reproducible
Grade II	**Overt**	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season or year) ± the other mentioned symptoms	Clinical findings variable but reproducible to some extent
Grade III		Somnolence to semi-stupor Responsive to stimuli Confused Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to pain stimuli	Comatose state usually reproducible

Montagnese S, Ponziani FR et al, AISF guidelines - DLD 2018

Digestive and Liver Disease 51 (2019) 1423–1429

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Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, pancreas and biliary tract

Predictive models of mortality and hospital readmission of patients with decompensated liver cirrhosis

Rui Gaspar*,[1], Susana Rodrigues[1], Marco Silva, Pedro Costa-Moreira, Rui Morais, Patricia Andrade, Helder Cardoso, Andreia Albuquerque, Rodrigo Liberal, Guilherme Macedo

Gastroenterology Department, Centro Hospitalar São João, Faculty of Medicine of the University of Porto, Porto, Portugal

427 admission

64.4% alcoholic liver disease (ALD)

13.6% ALD/HCV/HBV

58.5% readmission (median time 58 days)

31.2% (30-day)

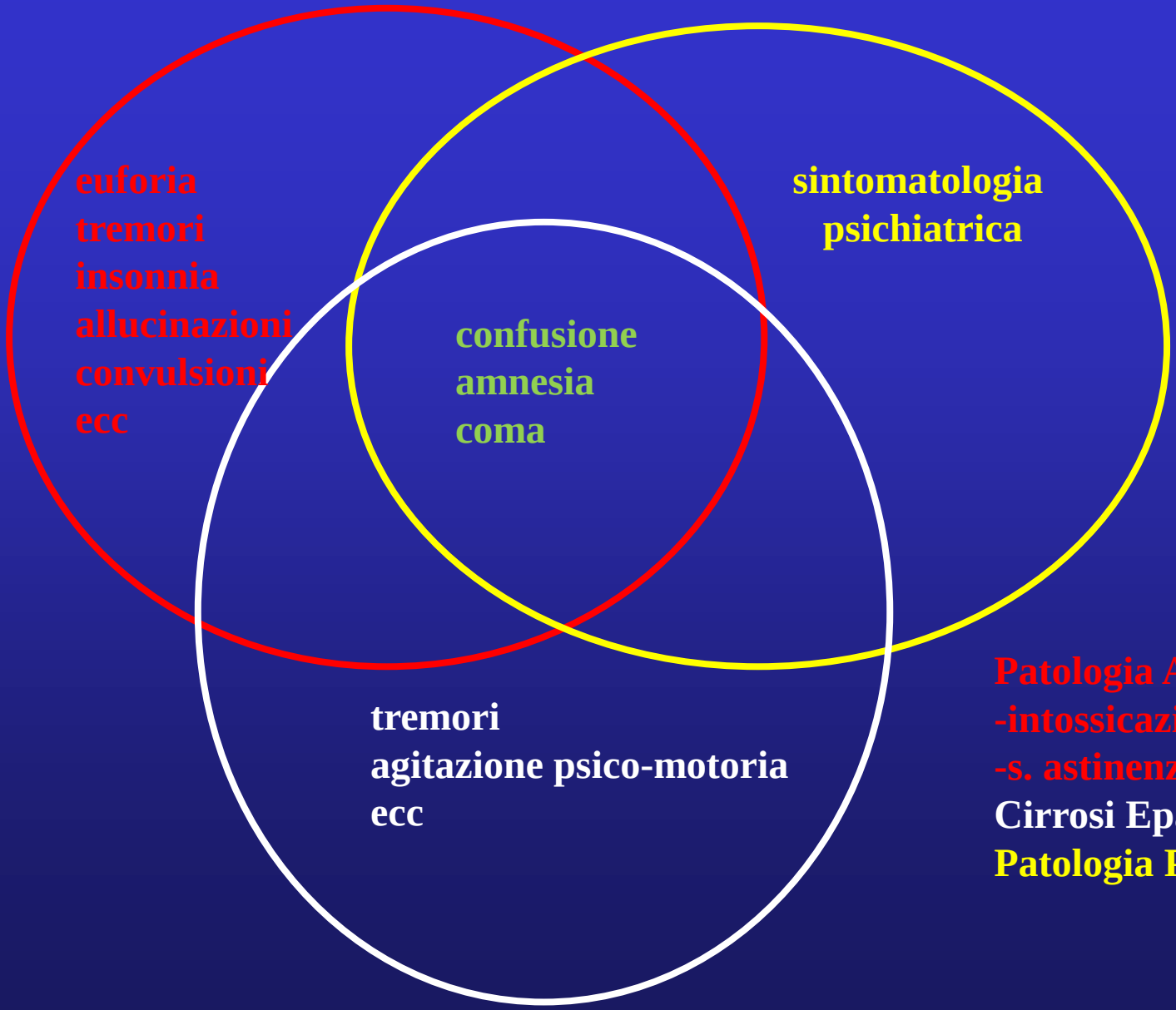
Hepatic Encephalopathy : 41%

Active drinkers 43.8%

Table 2a
Predictors of readmission – multivariate analysis.

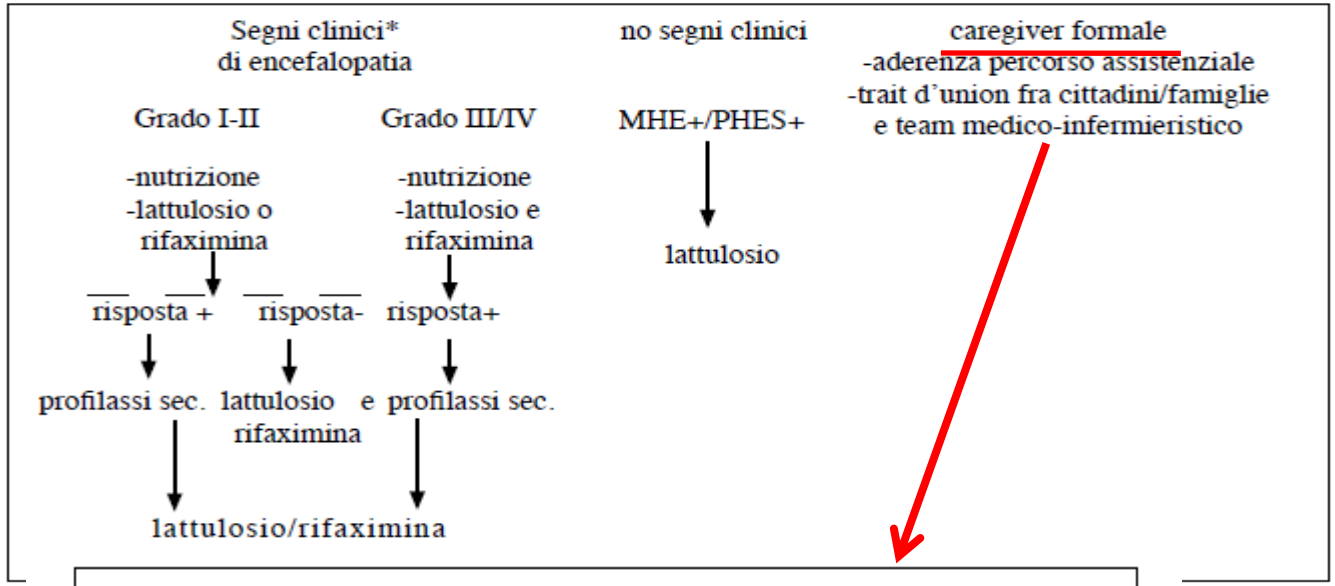
Variable	Odds Ratio [95% CI]	p-value
Creatinine	1,363 [1,094–1,698]	0,006
Albumin	0,944 [0,898–0,992])	0,023
Esophageal variceal bleeding	0,282 [0,160–0,496]	< 0,001
Previous esophageal variceal banding	5,312 [2,888–9,769]	< 0,001
Lactulose use	2,911 [1,712–4,981]	< 0,001
Rifaximin use	5,795 [2,143–15,667]	0,001
PPI use	1,810 [1,073–3,052]	0,026

ENCEFALOPATIA EPATICA IN PAZIENTE CON DISTURBO DA USO DI ALCOL



Patologia Alcol Correlata
-intossicazione
-s. astinenza
Cirrosi Epatica
Patologia Psichiatrica

P Balbinot, Genova 4 Aprile 2019



- Aderenza terapeutica (coordinamento con il team medico-infermieristico)
- Aderenza nutrizionale (coordinamento con il team medico-infermieristico)
- Aderenza utilizzo lassativi (microclisteri / clisteri)
- Controllo evacuazioni
- Osservazione delle variazioni comportamentali
- Gestione sobrietà
- Rapporto con l'auto-mutuo-aiuto di riferimento
- Gestione linea di confine fra "domicilio" e servizio di epatologia
- Gestione gruppi di auto-mutuo-aiuto per caregiver informali (familiari e badanti)

Tabella IV. Ruolo del caregiver formale come espressione di Medicina di Condivisione fra cittadino con EE, famiglie, comunità e servizio di epatologia.

Balbinot P, Testino G, Leone S, Caputo F; Digestive and Liver Disease; Letter to the Editor, in press

I BISOGNI DEL FAMIGLIARE (CAREGIVER INFORMALE)

Spesso il CI può sentirsi inadeguato e sopraffatto da una situazione complicata;

Talvolta sente la mancanza di un adeguato supporto da parte degli altri membri familiari;

può percepire l'assistito come manipolazione, ingratitudine e irragionevolezza;

da ciò ne può derivare «burnout» psico-fisico

↓

Il caregiver formale dovrà decifrare per tempo i primi sintomi di questa condizione per intervenire tempestivamente evitando danni all'integrità psico-fisica del CI e possibili ripercussioni negative sul paziente (incuria, violenza verbale, ecc)

↓

relazione d'aiuto
invio supporto psicologico

Cirrosi Epatica: Eziologia

- Epatiti virali croniche (HBV, HCV)
- Esotossica:
  - *Steatoepatite alcoolica*
  - *Farmaci*
- Epatiti autoimmuni
- Cirrosi biliare primitiva → Colangite Biliare Primitiva (CBP)
- Colangite sclerosante
- Dismetabolismo:
  - *Glicidico-lipidico*
  - *Marziale (emocromatosi primitiva e secondaria)*
  - *Cupreico (morbo di Wilson)*
  - *Deficit di α_1-antitripsina*
- Miscellanea:
  - *Parassitosi (Schistosomiasi)*
  - *Sarcoidosi*

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Review

Hepatitis C virus therapy: No one will be left behind

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Sofosbuvir
Velpatasvir
Glecaprevir
Pibrentasvir
Daclatasvir
Grazoprevir

ABSTRACT

The advent of oral direct-acting antiviral agents (DAAs) has dramatically improved the hepatitis C treatment landscape in the last 4 years, providing cure rates over 95% with shorter duration of treatment and a very good safety profile. This gave access to treatment to almost all Hepatitis C virus (HCV)-infected patients. The launch of two pangenotypic fixed-dose combinations (FDCs) in 2017 was a step forward in hepatitis C treatment, by slightly increasing efficacy and more importantly allowing the treatment of patients without HCV genotyping, and in some cases without fibrosis assessment. New triple regimens have solved the issue of retreatment of the few patients who present failure to DAAs therapy. In the present review we describe the current HCV landscape that allows almost all HCV-infected patients to be cured.

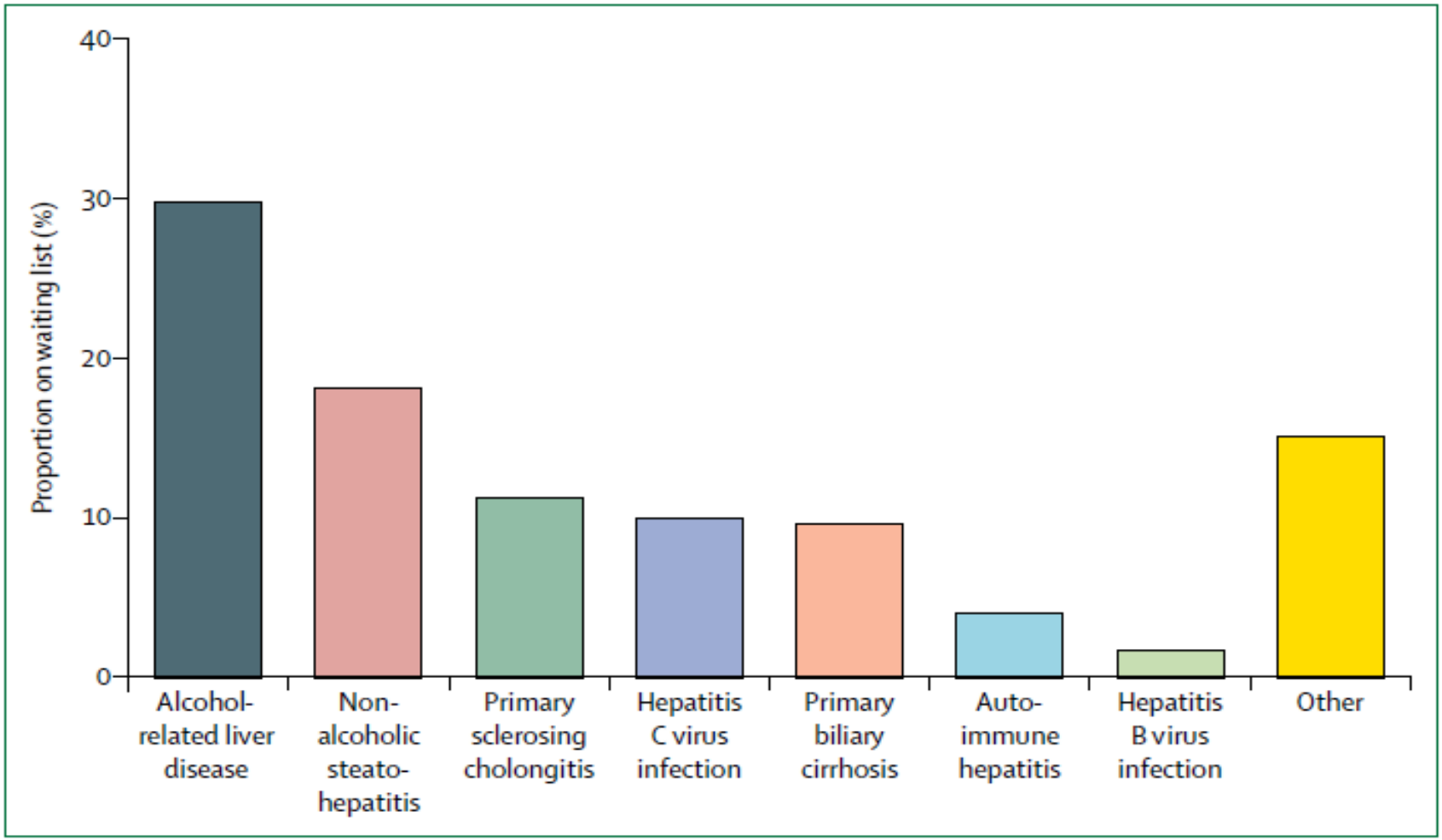

Figure 6: Causes of liver disease in patients on liver transplantation waiting list as of January, 2017

Williams et al, The Lancet, Vol 391 March 17, 2018

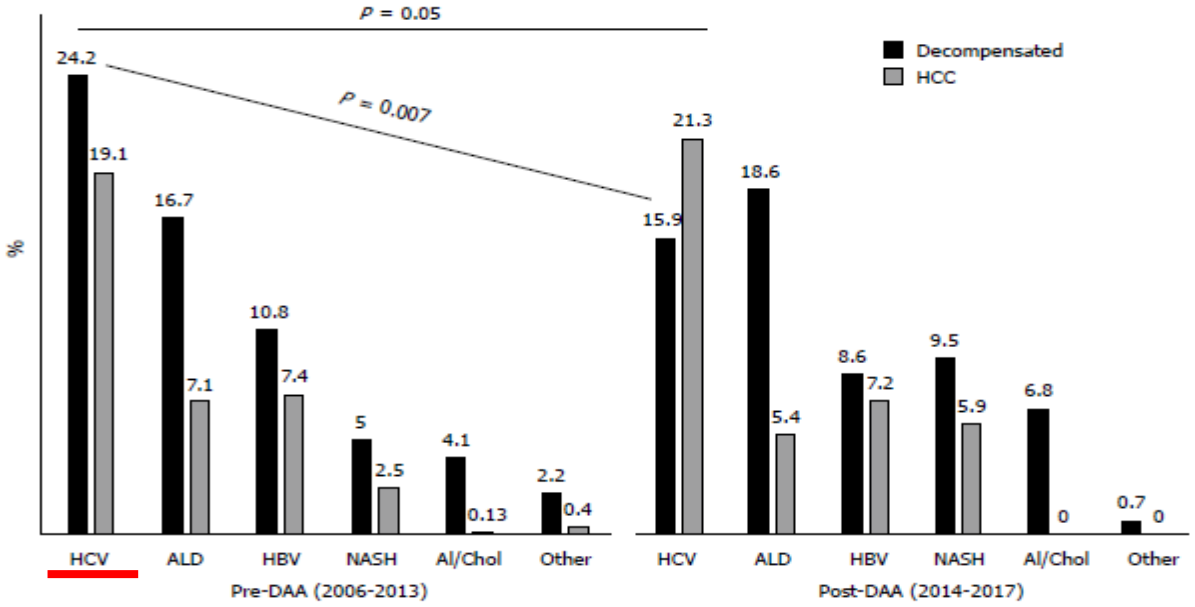

Figure 2 Trends in waiting list registration before and after direct-acting antiviral introduction. ALD: Alcoholic liver disease; DAA: Direct-acting antivirals; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; NASH: Non-alcoholic steatohepatitis.

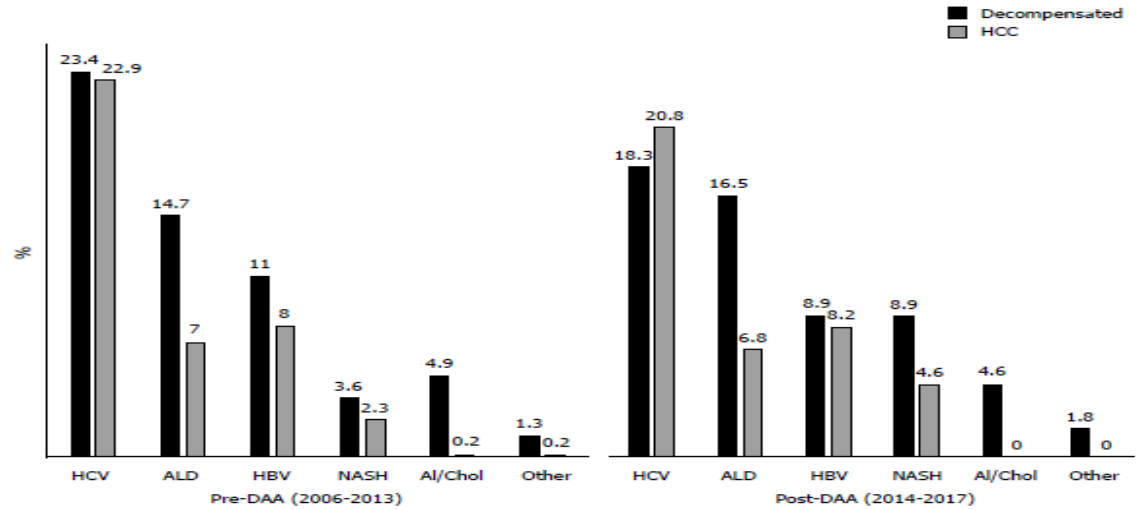

Figure 3 Trends in liver transplantation before and after direct-acting antiviral introduction. ALD: Alcoholic liver disease; DAA: Direct-acting antivirals; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; NASH: Non-alcoholic steatohepatitis.

Ferrarese et al, World J Hepatol 2018; doi: 10.378/wjg.v24.i38.4403

Cirrosi Epatica Alcol Correlata e Trapianto: Sopravvivenza

Europe:

84% at 1 year; 78% at 3 years; 73% at 5 years

Burra et al, Am J Transplant 2010

USA:

92% at 1 year; 86% at 3 years; 86% at 5 years

Japan:

81.3% at 1 year; 78.5% at 3 years; 75.7% at 5 years

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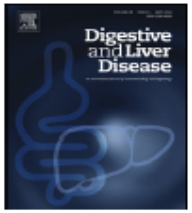

Guidelines

Management of end-stage alcohol-related liver disease and severe acute alcohol-related hepatitis: position paper of the Italian Society on Alcohol (SIA)

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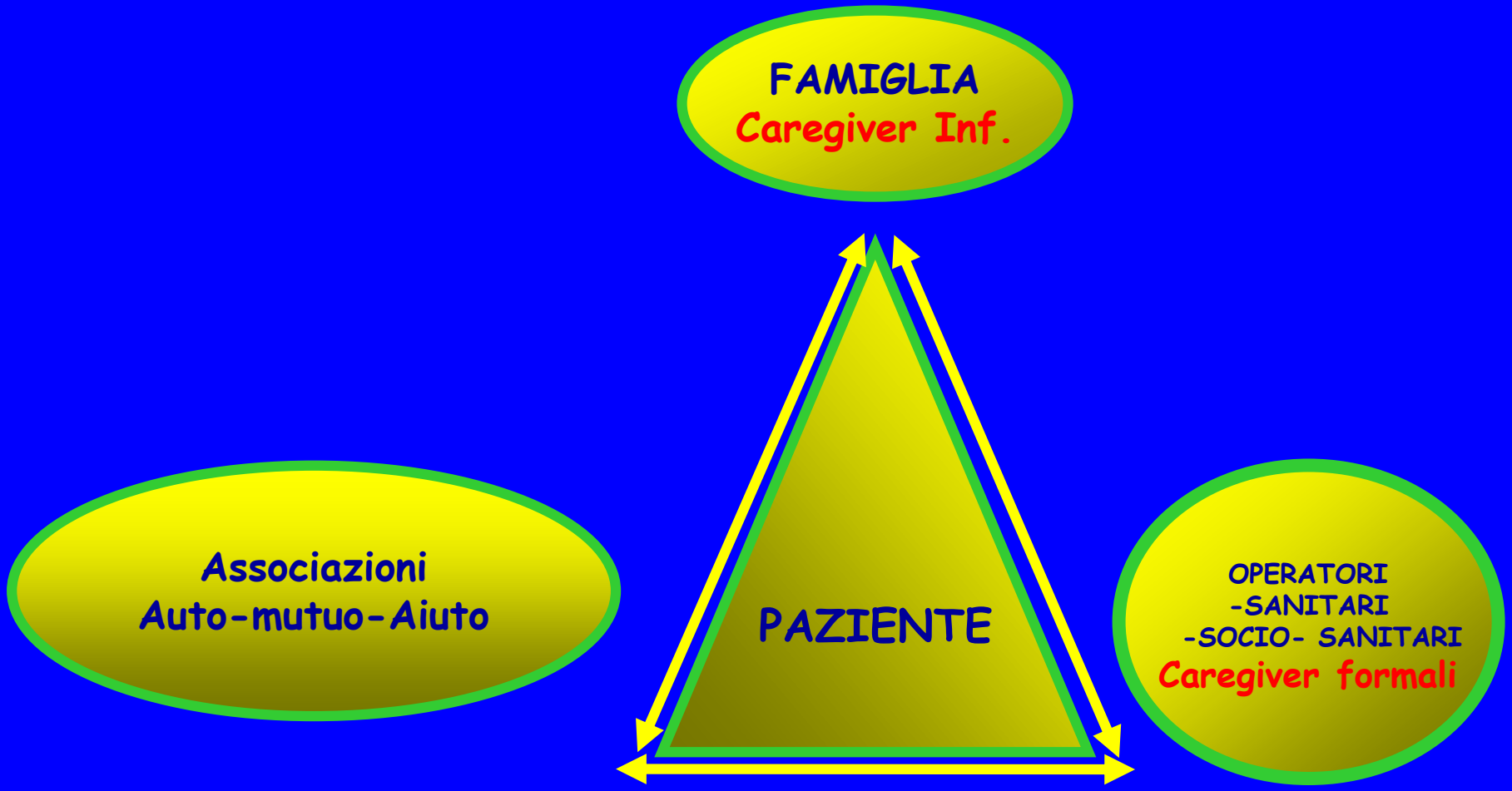
ABSTRACT

Worldwide, the prevalence of alcohol use disorder (AUD) is 20–30% in men and 10–15% in women, and cirrhosis due to alcohol-related liver disease (ALD) is responsible for 0.9% of global deaths and 47.9% of cirrhosis-related deaths. End-stage ALD (ESALD) is the final condition of alcohol-related cirrhosis, and severe acute alcohol-related hepatitis (SAAH) is a distinct clinical syndrome associated with the consumption of large amounts of alcohol. In some cases, ESALD, and SAAH may need liver transplantation (LT). Thus, the management of ESALD and SAAH in patients affected by AUD may be an essential part of the clinical skills for hepatologists. For these reasons, the national board of the Italian Society on Alcohol have reviewed the most recent data on the management of ESALD, SAAH and LT for ALD in patients with AUD, formulating a position paper with related recommendations regarding four issues of specific clinical interest in this field: (a) the management of hepatic encephalopathy in patients with AUD, and LT in patients with ESALD; (b) the management of SAAH; (c) the management of AUD in patients with ESALD and SAAH; (d) special populations: polydrug addicts.

GESTIONE CIRROSI EPATICA




Grazie