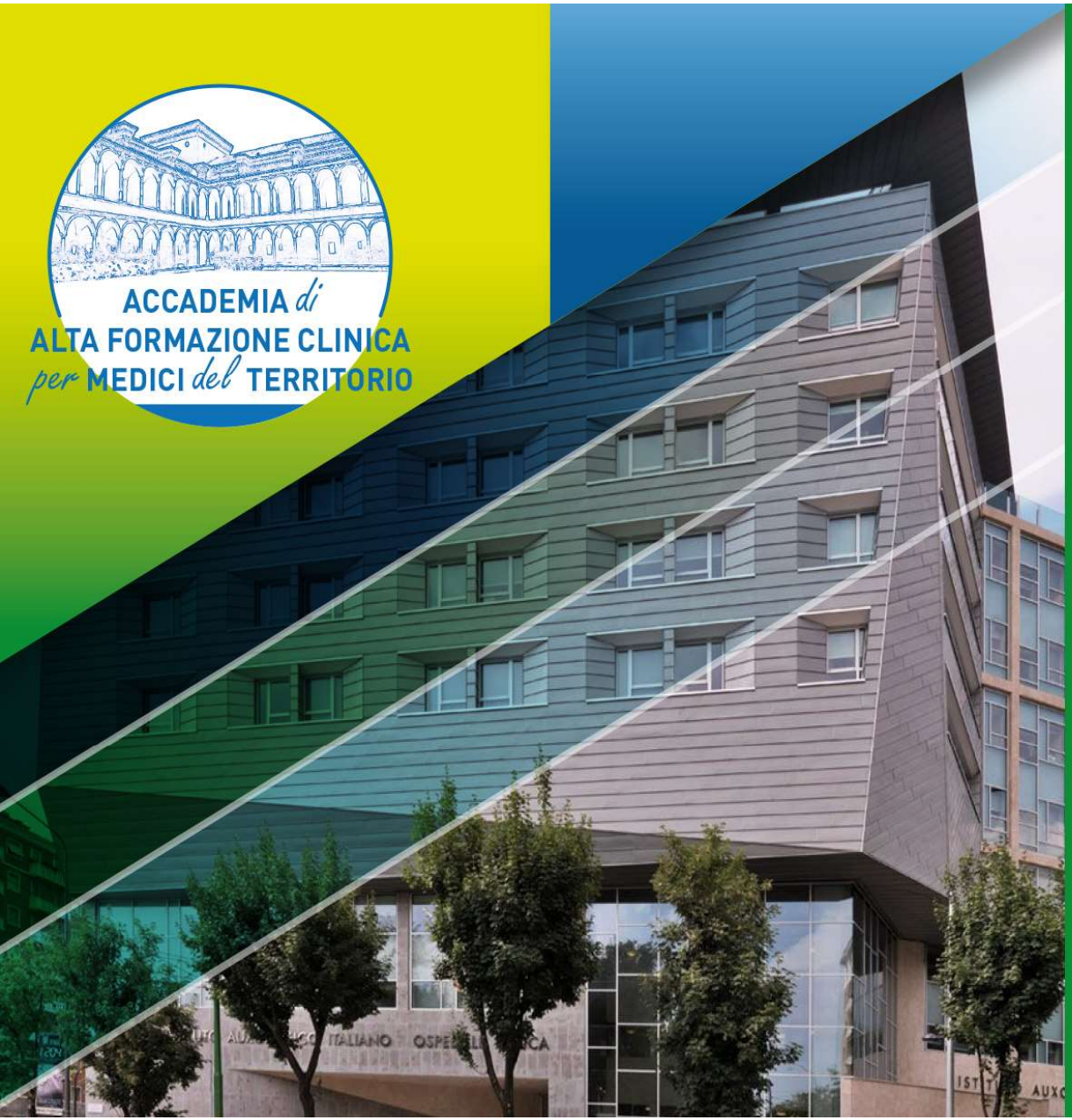
ACCADEMIA di
ALTA FORMAZIONE CLINICA
per MEDICI del TERRITORIO



Accademia di Alta Formazione Clinica per Medici del Territorio

In memoria del Maestro Alberto Zanchetti

TERZO PERCORSO FORMATIVO - ANNO 2024

Responsabile Scientifico
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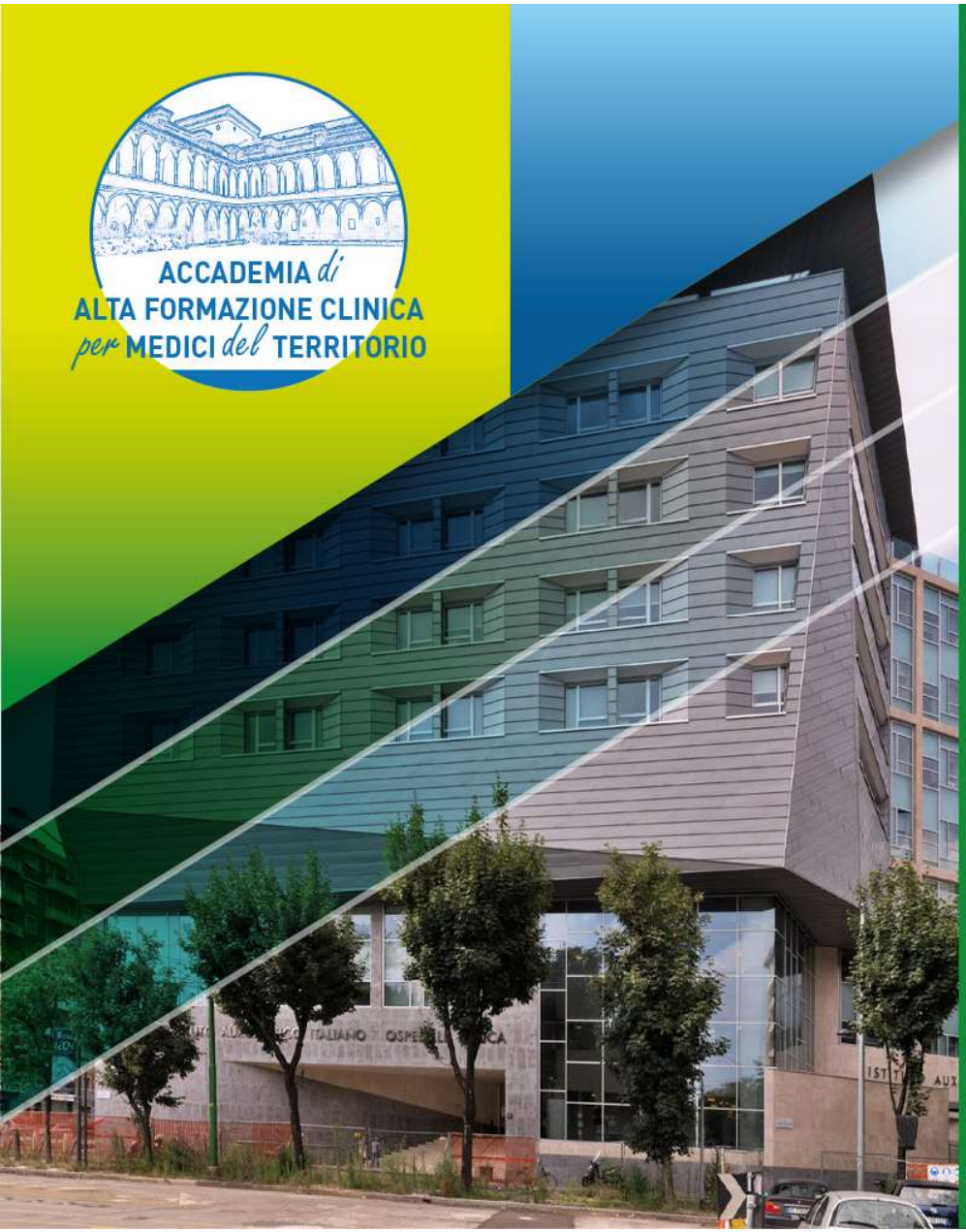
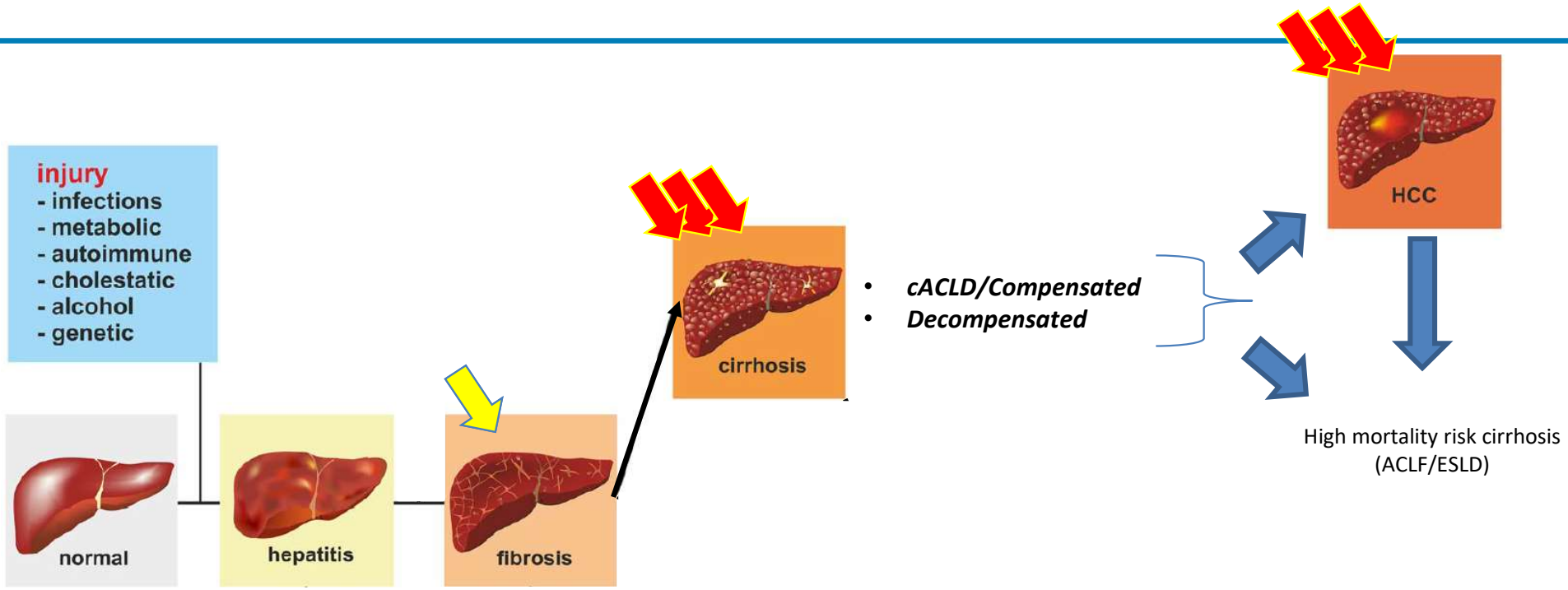


Prevenzione, Diagnosi e Terapia della Cirrosi: dall'ambulatorio di medicina generale alla epatologia ospedaliera

Prof. Vincenzo La Mura
Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico
S.C. Medicina - Emostasi e Trombosi
Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti
Università degli studi di Milano

FROM HEALTHY LIVER TO HIGH MORTALITY RISK CIRRHOSIS



***cACLD**: compensated advanced chronic liver disease; **ACLF**: Acute on Chronic Liver Failure; **ESLD**: end-stage liver disease*

AGENDA

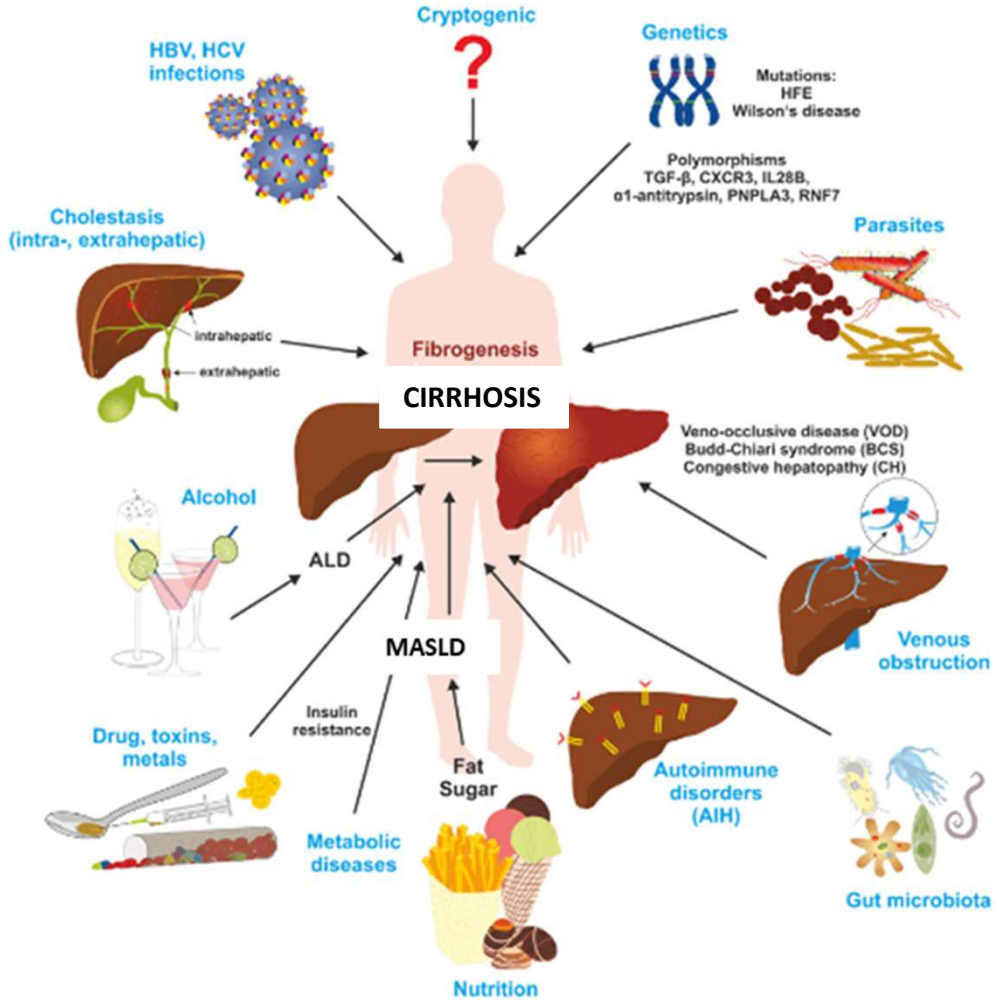
obiettivi pratici

- **EPIDEMIOLOGIA** → *Individuare le categorie a rischio di epatopatia cronica*
  Effettuare la diagnosi di epatopatia cronica

- **REFERRAL** → *Riconoscere la fibrosi avanzata/cirrosi (cACLD) in chi ha una epatopatia cronica*
  Evitare le complicanze in chi ha già una fibrosi avanzata/cirrosi (cACLD) (es. HCC, ipertensione portale)
  Gestire la cirrosi scompensata

- **LE URGENZE** → *Sanguinamento acuto da ipertensione portale*
  Encefalopatia epatica
  Infezioni (e ACLF)

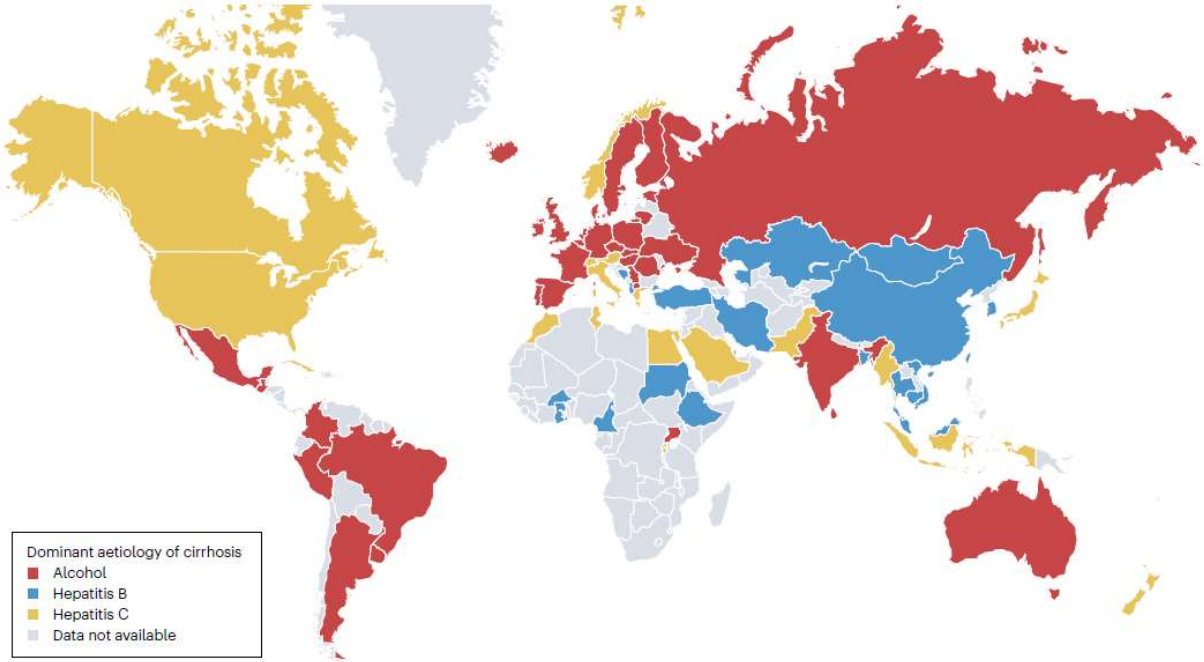
MAJOR CAUSES OF CHRONIC LIVER DISEASES



modified from Weiskirchen R, Weiskirchen S and Tacke F. Recent advances in understanding liver fibrosis: bridging basic science and individualized treatment concepts [version 1]. F1000Research 2018, 7:921 (doi: 10.12688/f1000research.14841.1)

EPIDEMIOLOGY

Dominant reported aetiology of cirrhosis from 1993-2021



Huan et al. Nature Reviews Gastroenterology & Hepatology 2023

Global burden of liver disease: 2023

- Alcohol is one of the leading causes of cirrhosis globally and its prevalence is even higher in high-income countries.
- Non-alcoholic fatty liver disease affects a quarter of the global adult population and is the second-leading cause of end-stage liver disease and liver transplantation in Europe and America.
- Due to the increase in alcohol consumption, aging of the general population and increase in the prevalence of metabolic risk factors, a dramatic increase in mortality linked to alcohol-associated and non-alcoholic fatty liver disease is anticipated in the following decades.

Devarbhavi et al. JHep 2023

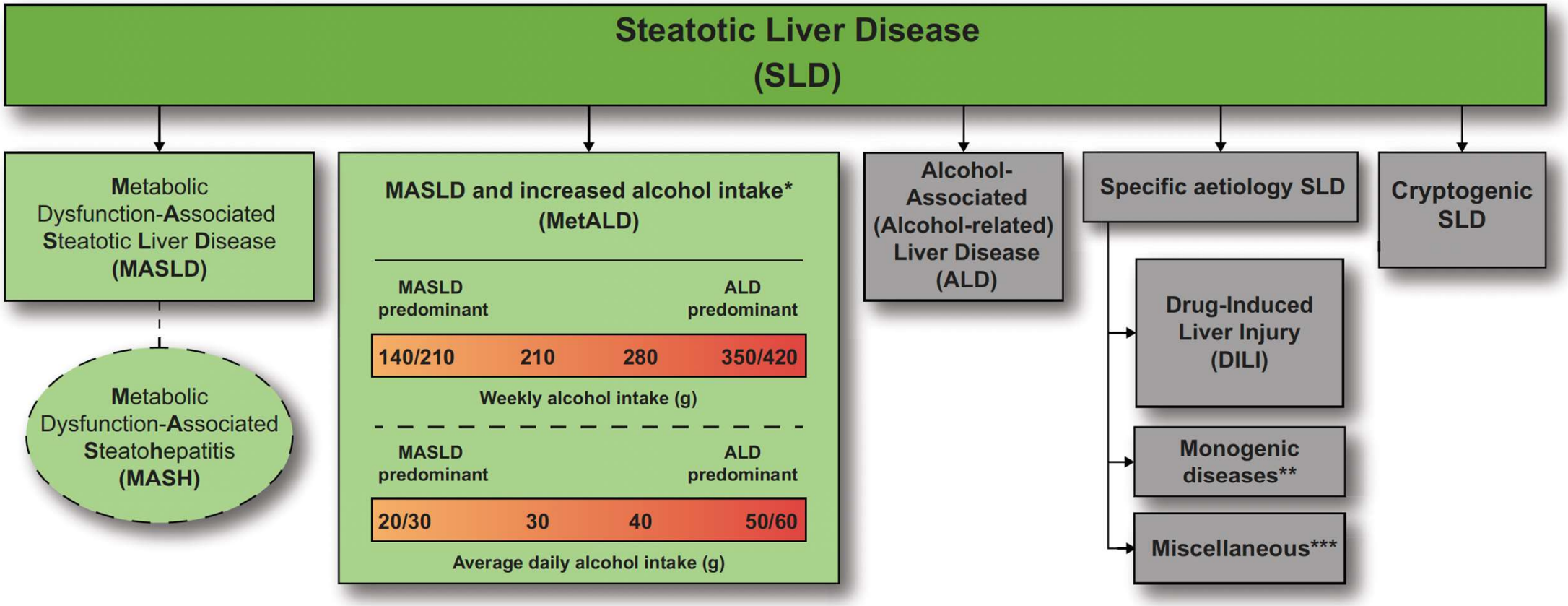
Public health issues: Definitions of “drink” and “drinking”

- Quantification of alcohol consumption is not easy in clinical practice
- Grams of alcohol is more precise, but:
  - Time consuming and frequently difficult to obtain
  - Patients cannot recall the different amounts and types of drink

Term	Definition
One standard drink	10 g of alcohol
Harmful drinking	Where alcohol use is causing damage to either physical or mental health
Heavy episodic drinking	Consumption of more than 60 g of pure alcohol on one occasion
Binge drinking	Consumption within about 2 hours of four or more drinks for women and five or more drinks for men

EASL CPG ALD. J Hepatol 2018;69:154–81

EASL The Home of Hepatology



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

What about markers of chronic liver disease?

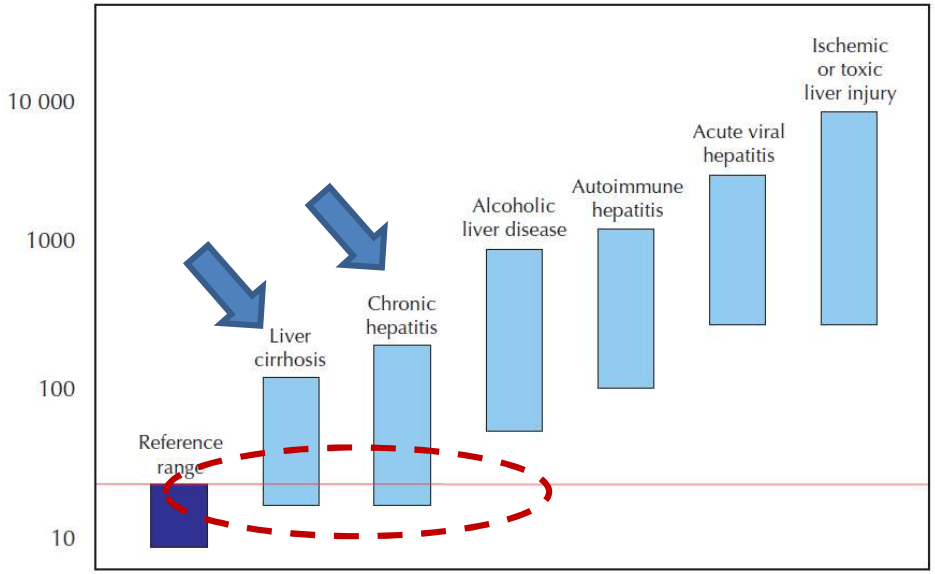
Markers of liver disease-1

Key biochemical markers in hepatic systems and function			
System or function	Marker	Site or significance	Function
HEPATO-CELLULAR DAMAGE	Aspartate aminotransferase	Liver, heart skeletal muscle, kidney, brain, red blood cell	Catabolizes amino acids, permitting them to enter the citric acid cycle.
	Alanine aminotransferase	Liver	
CHOLESTASIS	Alkaline phosphatase	Bone, intestine, liver, placenta	Canicular enzyme that plays a role in bile production.
	γ-Glutamyl-transpeptidase	Correlated levels with alkaline phosphatase indicate hepatobiliary origin	Catalyzes transfer of γ-glutamyl group from peptides to other amino acids.
	Bilirubin	Elevations may indicate hepatic or extrahepatic disorder	Breakdown product of hemolysis taken up by liver cells and conjugated to water-soluble product excreted in bile.
LIVER DYSFUNCTION	Serum albumin	Diet or liver	Liver synthesizes albumin
	Prothrombin time	Liver synthesizes vitamin K-dependent clotting factors	Bile salts are synthesized in the liver and necessary for vitamin K absorption

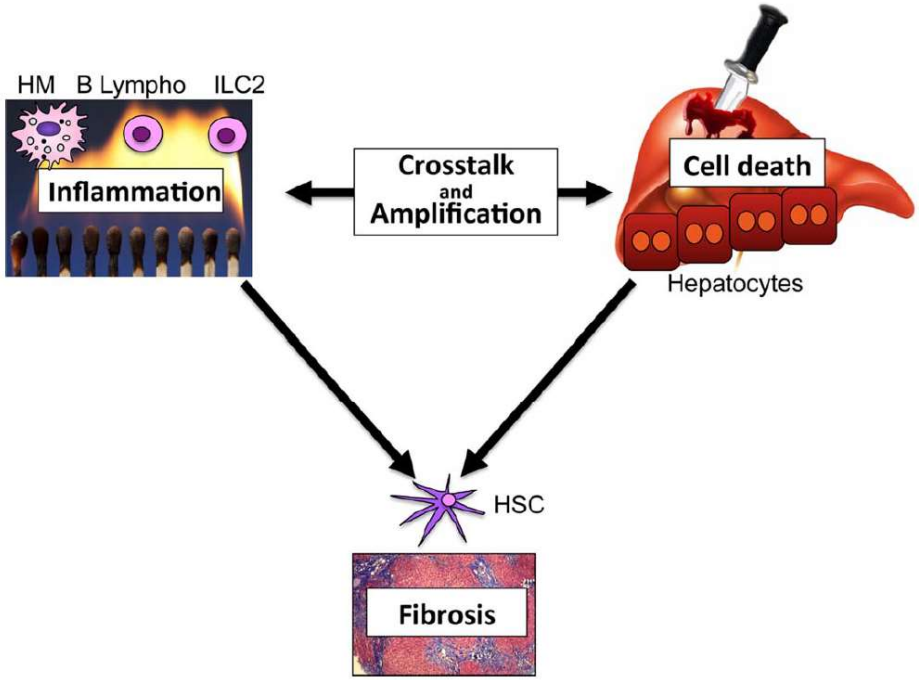
Giannini et al. CMAJ 2005

Markers of liver disease-2

Aminotransferase levels (AT)



AT are not accurate markers of chronic hepatitis
Giannini et al. CMAJ 2005



E. Seki and R.F. Schwabe Hepatology 2015

Fibrosis is the real marker of chronic hepatitis

Chronic hepatitis: when to screen

- If there's chronic exposure to risk factors (*anamnesis is the key!*)

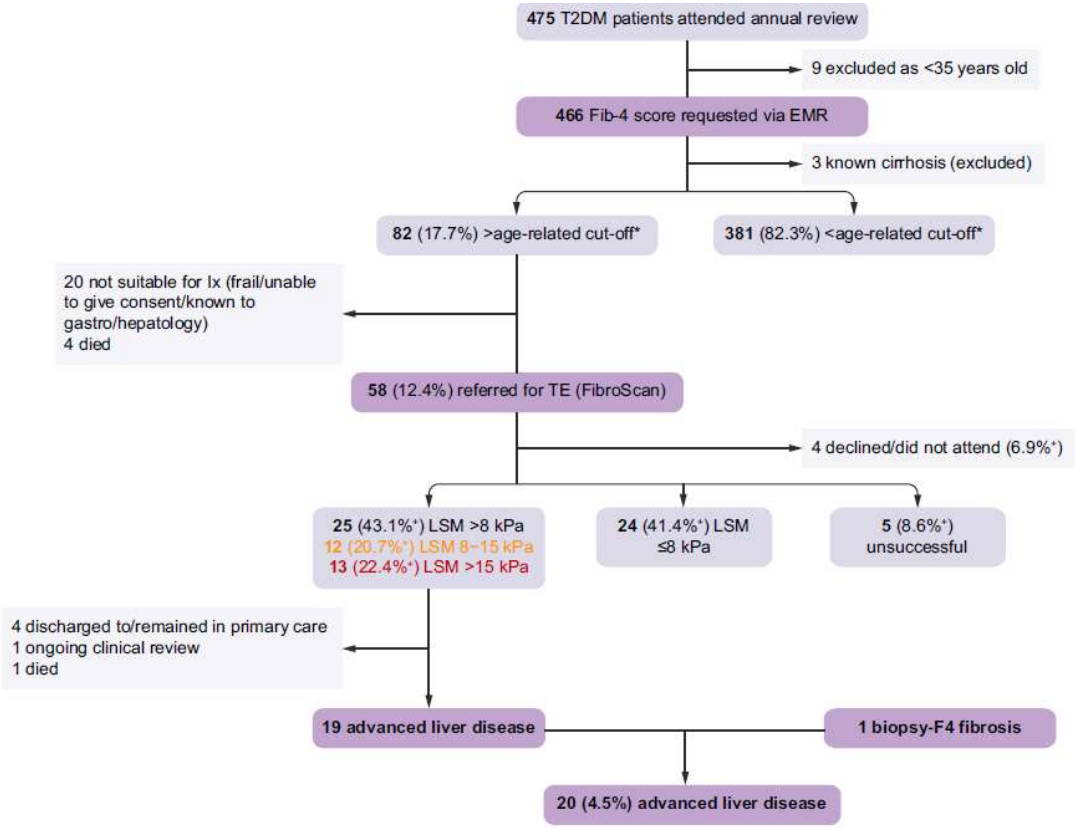
and/or

- If there's chronic impairement (*e.g. 6 months*) of biochemistry

Research article JHEP|Reports

Embedding assessment of liver fibrosis into routine diabetic review in primary care

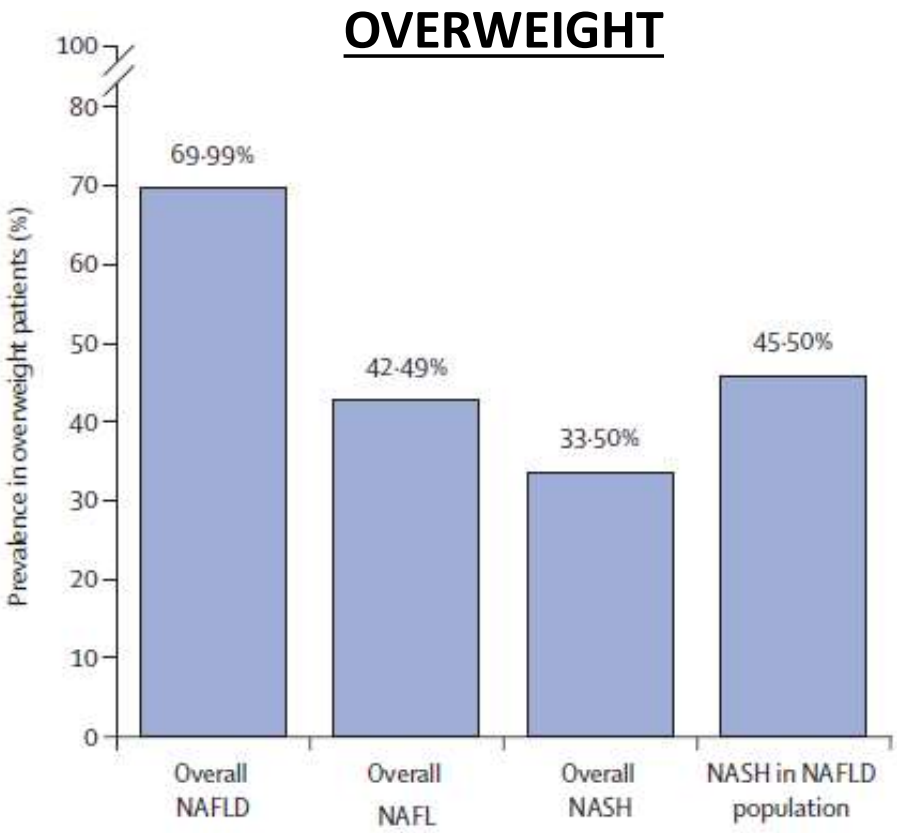
Dina Mansour,[1,2,*] Allison Grapes,[1] Marc Herscovitz,[3] Paul Cassidy,[4] Jonathan Vernazza,[1] Andrea Broad,[5] Quentin M. Anstee,[2,6] Stuart McPherson[2,6]

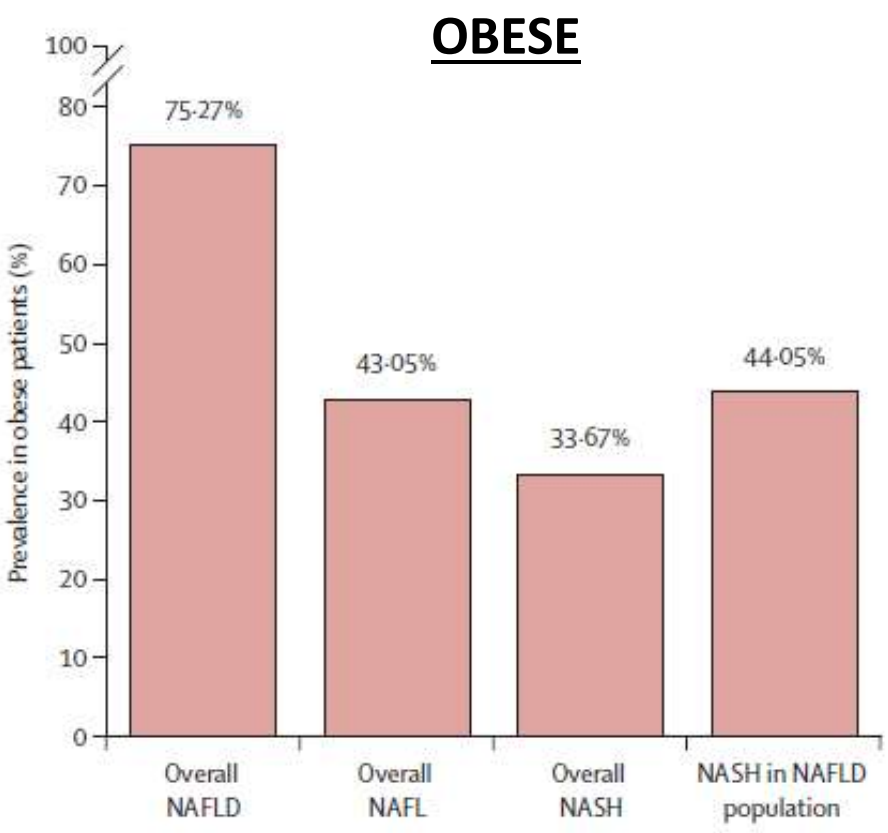


"…Overall, 45.5% of patients with advanced disease in this study had a normal ALT, and so would have been missed if only the presence abnormal ALT was used to identify liver disease"

Mansour et al JHEP Rep 2021

Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis





Quek et al Lancet Gastro Hep 2022

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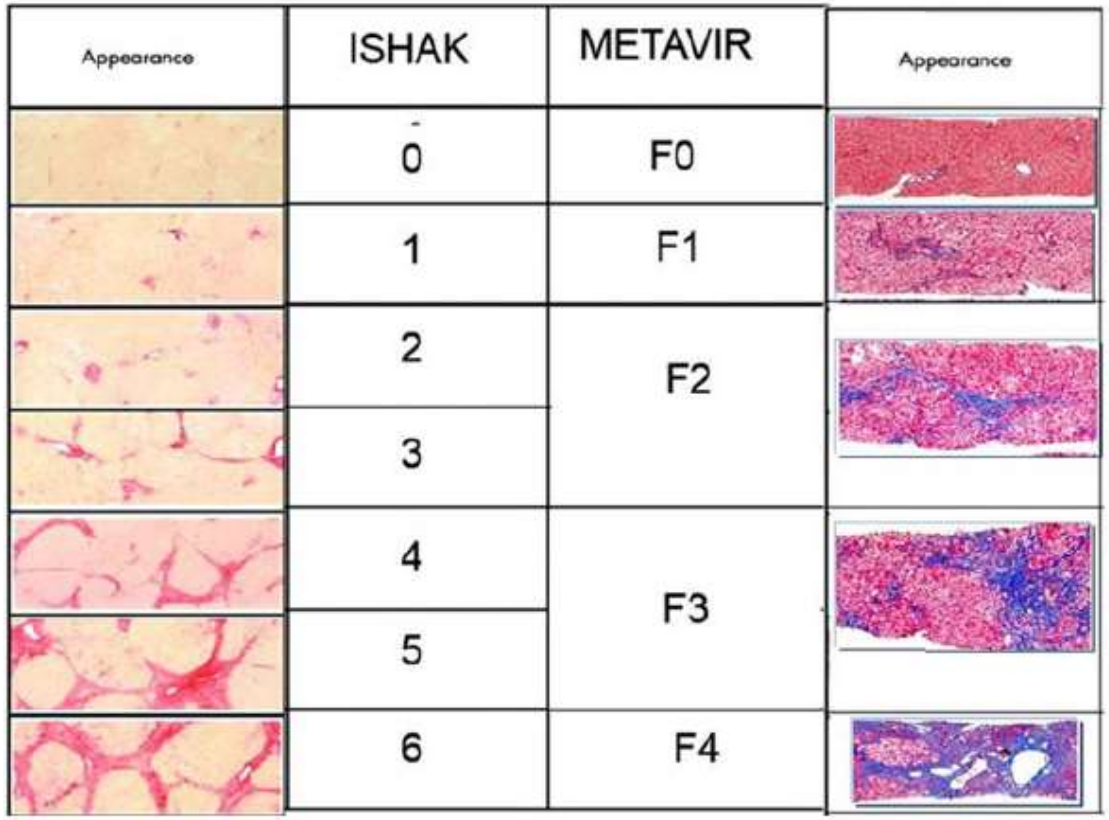
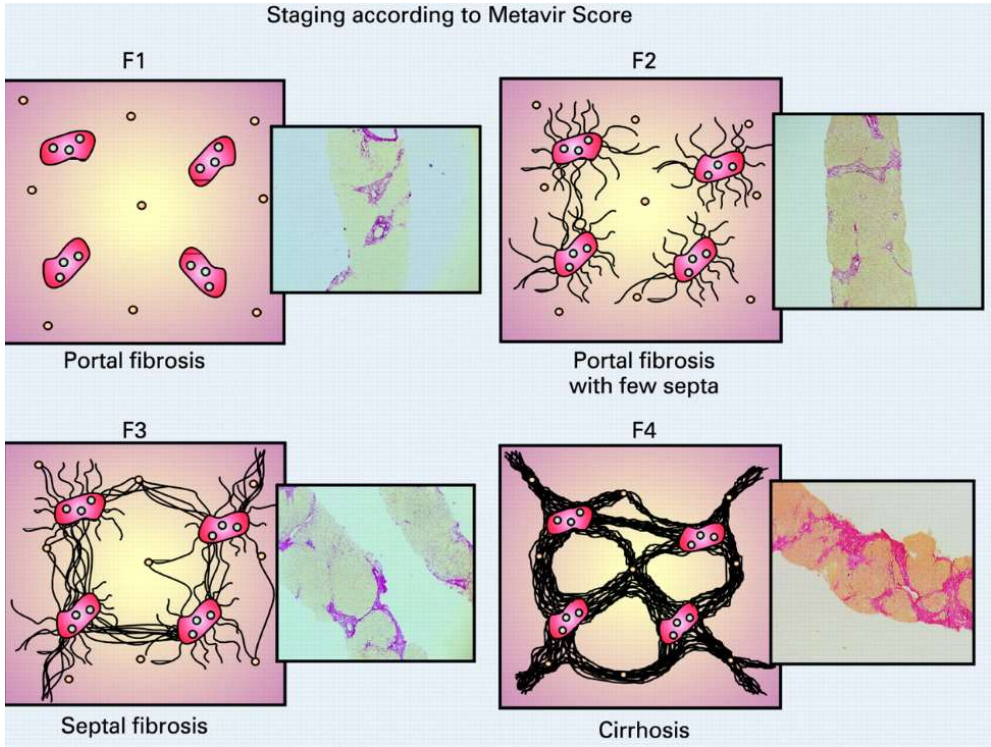
  Infezioni (e ACLF)

Fibrosis: liver biopsy-the “gold” standard





Bedossa et al CLD 2015

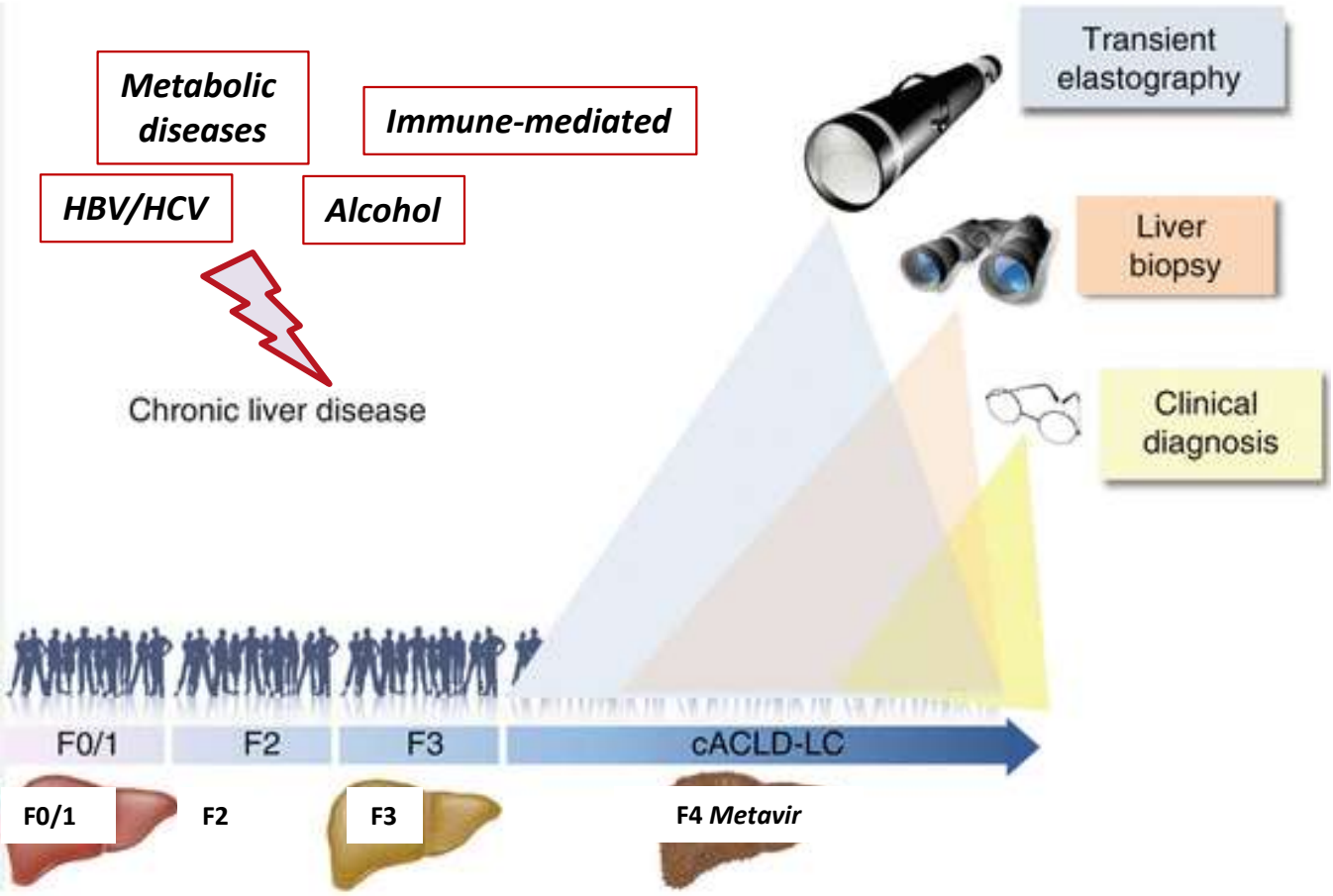
fibrosis: non-invasive tests (NITs)

Test	Description	Ref.
Indirect fibrosis biomarker panels		
AST:ALT ratio (AAR)	AST (IU/L)/ALT (IU/L)	34 36
AST-to-platelet ratio index (APRI)	(AST (IU/L)/(ULN))/platelet count ($\times 10^9$/L) × 100	36
BARD score	Weighted sum of BMI ≥28 = 1 point, AST/ALT ratio ≥0.8 = 2 points, T2DM = 1	40 36
Fibrosis-4 index	Age × AST (IU/L)/platelet count ($\times 10^9$/L) × √ ALT (IU/L)	174 36
NAFLD fibrosis score	-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG or T2DM (yes = 1, no = 0) + 0.99 × AST/ALT ratio - 0.013 × platelet count ($\times 10^9$/L) - 0.66 × albumin (g/dl)	42 36
Direct fibrosis biomarker panels		
ELF	ELF = -7.412 + (ln(HA)*0.681) + (ln(PIIINP)*0.775) + (ln(TIMP1)*0.494)	32,59
FibroTest	Patented algorithm combining total bilirubin, GGT, α2-macroglobulin, apolipoprotein A1, and haptoglobin, corrected for age and gender	29,60,61
FibroMeter NAFLD	Patented algorithm combining age, body weight, glucose, AST, ALT, ferritin and platelet count	30,38
Hepascore	Algorithm containing age, gender, α2-macroglobulin, hyaluronic acid and bilirubin	175
ADAPT	ADAPT = exp($\log_{10}$((age × PRO-C3)/√(platelet count))) + T2DM	27,57,62
FIBC3	FIBC3 = -5.939 + (0.053*age) + (0.076*BMI) + (1.614*T2DM) – (0.009*platelet count) + (0.071*PRO-C3)	27,57
ABC3D	Age >50 = 1 point, BMI >30 = 1 point, platelet count <200 = 1-point, PRO-C3 >15.5 = 1 point, T2DM = 2 points	27,57

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; GGT, gamma-glutamyltransferase; HA, hyaluronic acid; IFG, impaired fasting glucose; NPV, negative predictive value; PIIINP, N-terminal peptide of pro-collagen III; PPV, positive predictive value; PRO-C3, pro-collagen 3 neoepitope; Se, sensitivity; Sp, specificity; T2DM, type 2 diabetes mellitus; TIMP1, tissue inhibitor of metalloproteinase 1; ULN, upper limit of normal.

Anstee et al JHEP 2022

From Histological Staging to a Non-invasive Clinical Staging of Chronic Liver Disease (CLD)



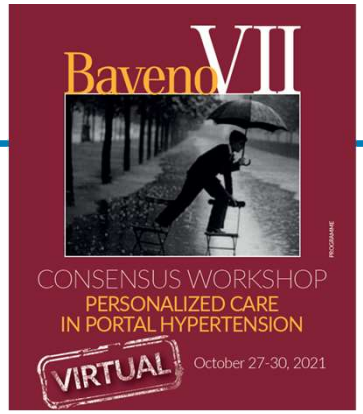
"…a new clinical scenario derived from the extensive use of TE as an important staging method for CLD, also reflecting that, in the absence of a liver biopsy, it was <u>not possible to distinguish between severe fibrosis and cirrhosis</u>"

cACLD

compensated advanced chronic liver disease

Pons M, Barreira A, and Genescà J-"Portal Hyeprtension VII", Chapter 8-Springer

fibrosis: liver stiffness measurement



TE values

- < 10 kPa → cACLD-rule out
- 10-15kPa → cACLD: grey zone
- > 15 kPa → cACLD-rule in

***cACLD**: compensated advanced chronic liver disease*

…BUT

Fibrosis measurement after HCV clearance

EASL 2021

European Association for the Study of the Liver

Statement

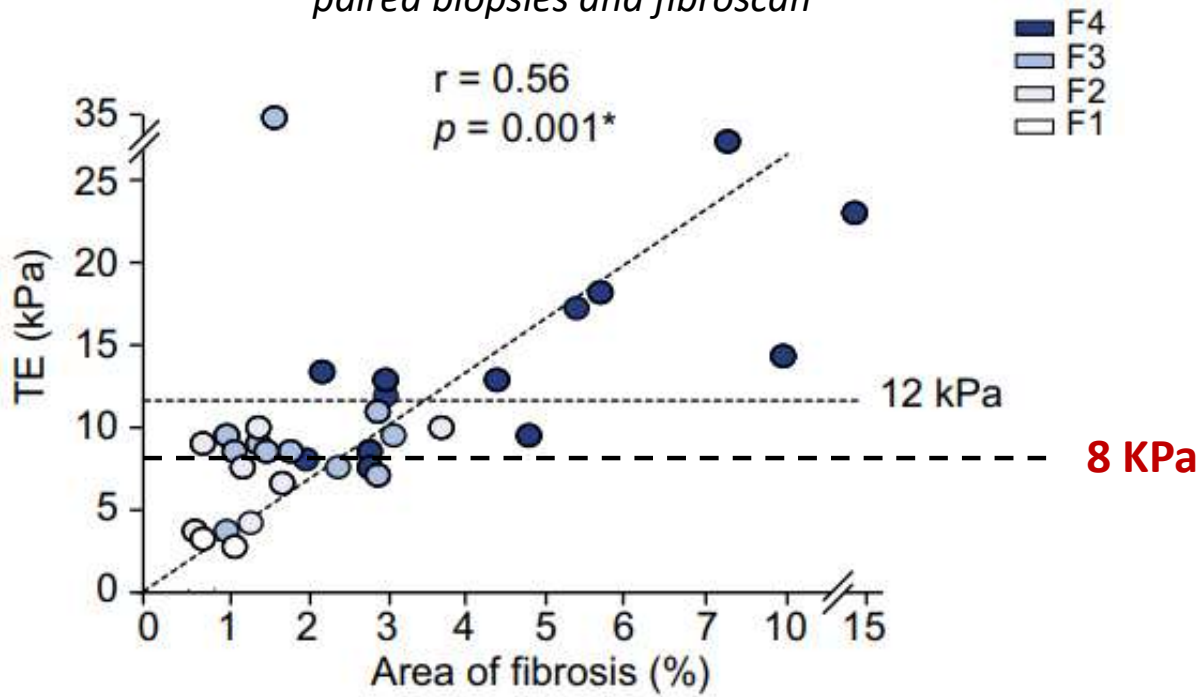
- Non-invasive scores and LSM by TE and other elastography methods are not accurate in detecting fibrosis regression after SVR in HCV patients diagnosed with cACLD prior to antiviral therapy **(LoE 3)**.

Recommendations

- The routine use of non-invasive scores and LSM by TE and other elastography methods is currently not recommended to detect fibrosis regression after SVR in HCV patients **(LoE 3; strong recommendation).**
- Cut-offs of LSM by TE used in patients with untreated HCV should not be used to stage liver fibrosis after SVR **(LoE 4; strong recommendation).**

N=33 HCV-pts without hemophilia

paired biopsies and fibroscan



D'Ambrosio et al JHEP 2013

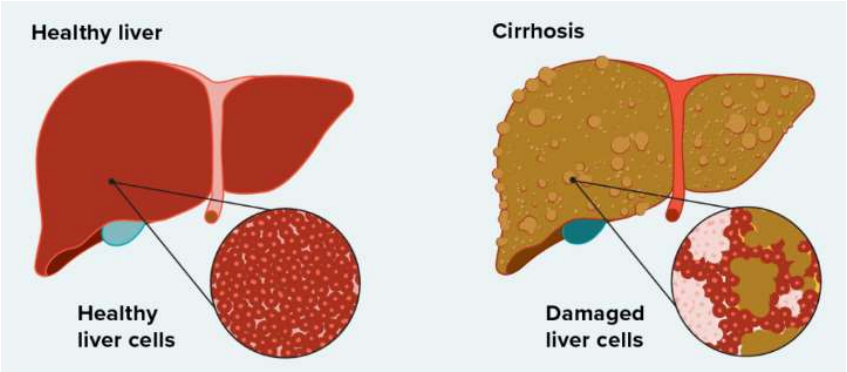
It would be necessary to validate new lower cut-offs in larger studies

Cirrhosis is not just fibrosis!

Main ultrasonographic signs of cirrhosis and portal hypertension

		Refs	Sensitivity	Specificity
US signs of cirrhosis				
Liver	Nodular liver surface	(42;45;79;80)	55–91%	82–95%
	Coarse echopattern	(81;82)	20% overall 51% HBV-HDV	90%
	Left lobe/ right lobe ratio > 1.30	(83)	74%	100%
	Caudate lobe/ right lobe ratio ⩾ 0.65 (hypertrophy of caudate lobe)	(84)	43–84%	100%
	Reduction of the medial segment of left hepatic lobe	(85)	74%	100%
Hepatic veins	Narrowing and loss of normal phasicity of flow by Doppler	(86)	Not reported	Not reported
	Altered straightness	(87)	97%	91% 86%
	Nonuniformity of hepatic vein wall echogenicity		88%	
Hepatic artery	Increased diameter	(88)	Not reported	Not reported
US signs of portal hypertension				
Portal venous system	Dilatation of portal vein (⩾ 13 mm)	(16;47)	< 50%	90–100%
	Reduction of portal vein blood flow velocity (Max vel < 16 cm/s;) mean vel < 13 cm/ s	(89;90)	80–88%	80–96%
	Inversion of portal vein blood flow	(91)d}2}	Not reported; sign prevalence: 8.3% of unselected pts	100%
	Increased portal vein congestion index (⩾ 0.08)	(49;90)	67–95%	100%
	Dilatation of splenic vein (SV) and superior mesenteric vein (SMV) (⩾ 11 mm)	(92;93)	72%	100%
	Reduction of respiratory variation of diameter in SV or SMV (< 40%)	(47)	79.7%	100%
Spleen	Splenomegaly (diameter > 12 cm and/or area ⩾ 45 cm^2	(3)	93%	36%
Splenic artery	Increased resistive index of the intraparenchymal branches (⩾ 0.60)	(94)	84.6%	70.4%
Hepatic artery	Increased resistive index of artery at the porta hepatis (> 0.78) Increased resistive index of the intrahepatic branches	(95)	50%	100%
Renal artery	Increased resistive index of the right interlobar renal artery (⩾ 0.65)	(94)	79.5%	59.3%
SMA	Decrased pulsatility index (⩽ 2.70)	(94)	85.7%	65.2%
Presence of porto-systemic collateral circulation		(58)	83%	100%

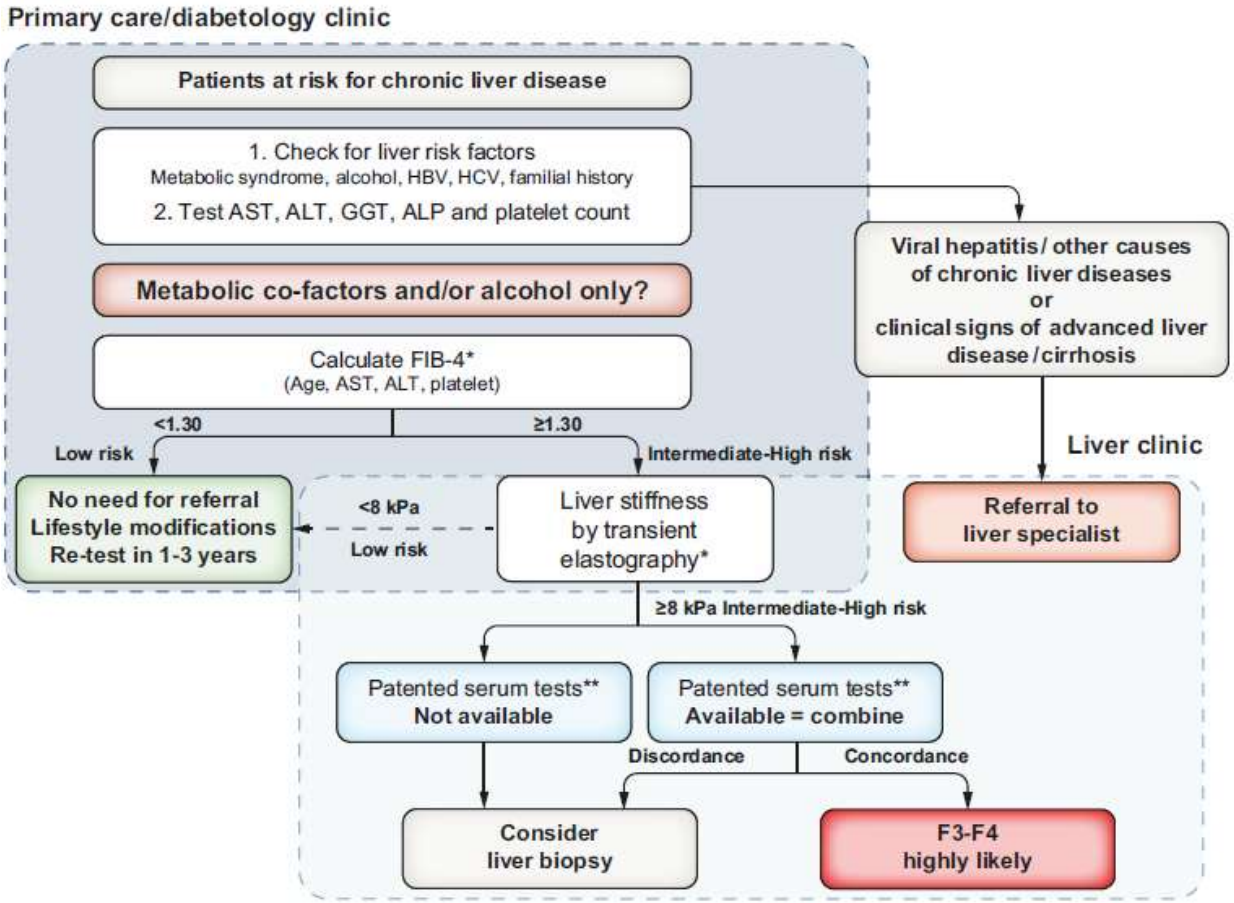
Berzigotti et al Disease Markers 2011



- **Morphology could be useful to suspect cirrhosis even after HCV clearance** *(speaker's opinion)*

What are the recommended screening programmes for cirrhosis (cACLD)?

MASLD (ex NAFLD)



ALD

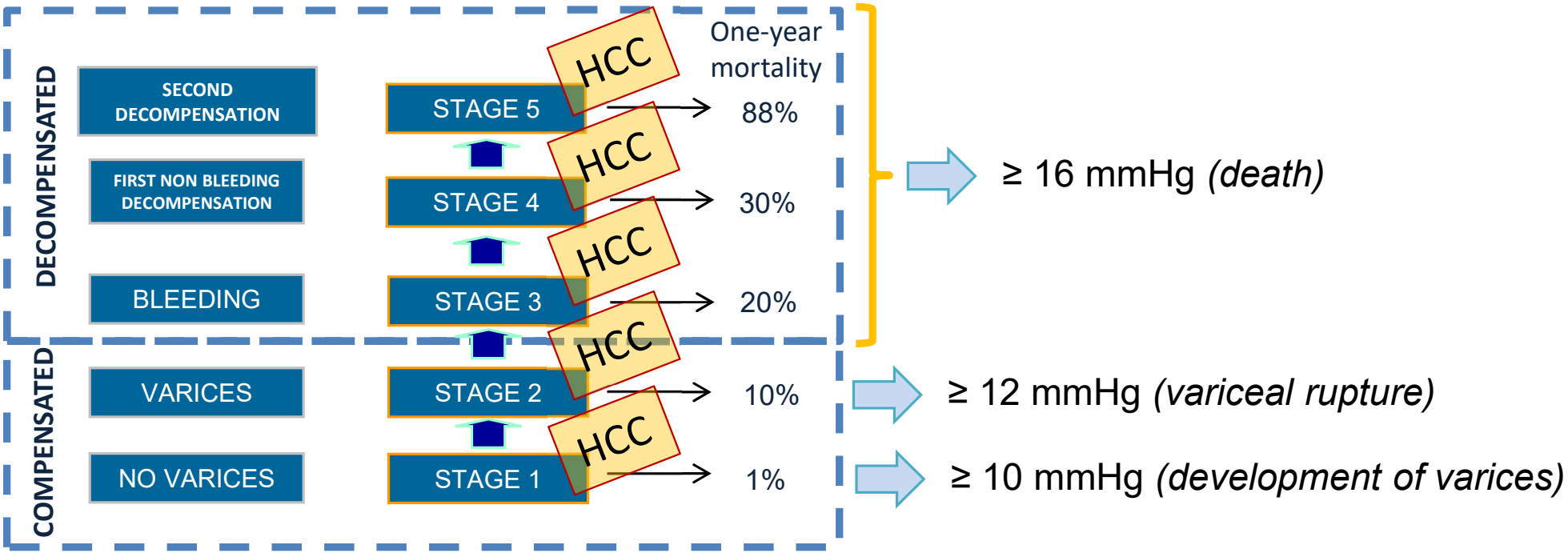
Recommendations

- In patients with ALD, LSM by TE <8 kPa is recommended to rule-out advanced fibrosis in clinical practice, with the following NITs as alternatives, if TE is not available (**LoE 3; strong recommendation**).
  - Patented tests: ELF™ <9.8 or FibroMeter™ <0.45 or FibroTest® <0.48
  - Non-patented tests: FIB-4 <1.3
- Upon referral of patients at risk of ALD, LSM by TE ≥12-15 kPa is recommended to rule-in advanced fibrosis, after considering causes of false positives (**LoE 2; strong recommendation**).
- In patients with elevated liver stiffness and biochemical evidence of hepatic inflammation (AST or GGT >2xULN), LSM by TE should be repeated after at least 1 week of alcohol abstinence or reduced drinking (**LoE 3; strong recommendation**).

EASL CPG JHEP 2021

Why does cirrhosis matter?

Cirrhosis: a multistage disease



The higher the portal pressure (HVPG) the higher the risk

Can we manage the risk of HCC and/or portal hypertension?

- Etiologic therapies: they may ameliorate the ouctome
- Adequate screening for HCC: erly detection→best chance of cure
- Stratification for the risk of first decompensation: we have efficiacious options

Etiologic therapies may ameliorate the outcome-1

Epidemiology and risk factors

- Incidence of HCC has been rising
  - Driven by increases in chronic viral infections and lifestyle-related risk factors
- **Cirrhosis is an important risk factor for HCC**
  - Multiple causes, including viral hepatitis, chronic alcohol use, NAFLD
  - Up to 90% of HCC arises on a background of cirrhosis in the Western world[1]

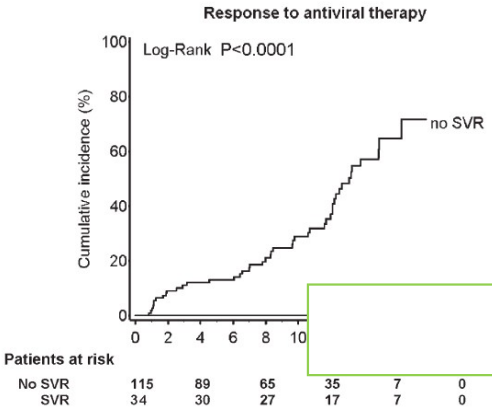
Recommendations	Level of evidence	Grade of recommendation
The **incidence of HCC is increasing** both in Europe and worldwide; it is amongst the leading causes of cancer death globally	High	
Chronic liver disease should be treated to avoid progression	High	Strong

1. Forner A, et al. Lancet 2018;391:1301–1314;
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

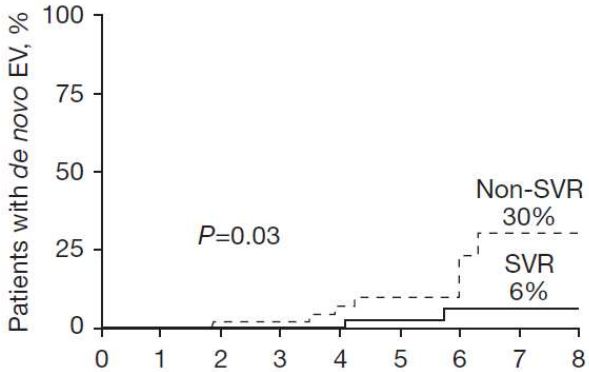
EASL The Home of Hepatology

Etiologic therapies may ameliorate the outcome-2

HCV-patients

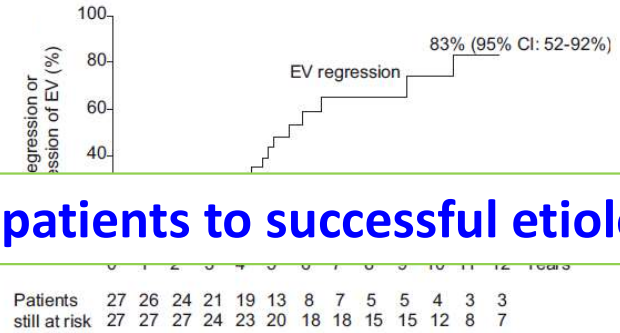


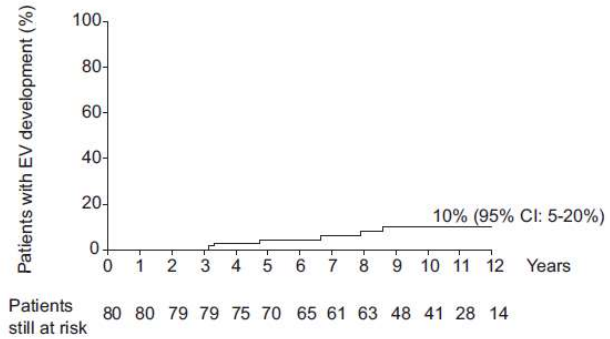
Bruno S et al. Hepatology 2010



D'Ambrosio et al. Antiviral Ther 2011

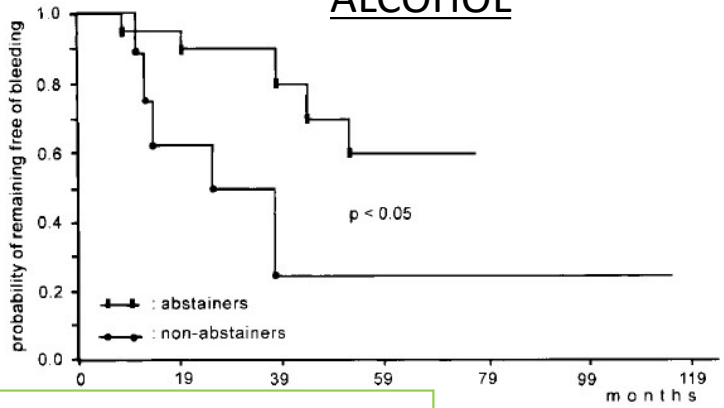
HBV-patients





Lampertico et al. J Hepatol 2015

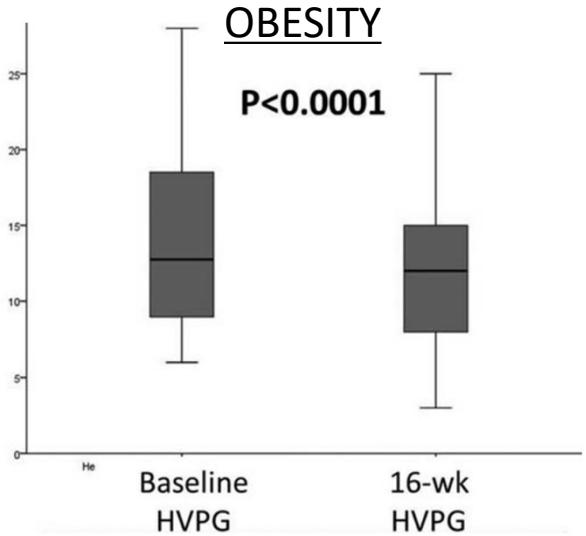
ALCOHOL



Gastro 1996

Address patients to successful etiologic therapies!

OBESITY



Berzigotti A et al. Hepatology 2017

CIRRHOSIS OUTCOME AFTER HCV THERAPY

Study design	Results		
	Median follow-up 51 (range 8-68) months **5-year cumulative incidences of**		
	Liver-related events	Non-liver related events	Mortality
Single-center longitudinal study **636 HCV cirrhotic patients** achieving an SVR to DAA treatment			
Cohort A (n = 480) CPT-A without previous liver-related events	**10.4%** (95% CI 7-13%) HCC 7.7%; ascites 1.4% bleeding 1.3%	**11.7%** (95% CI 8-15%)	Liver-related 0.5%* Non-liver related 4.5%§
	vs.	*vs.*	*vs.*
Cohort B (n = 89) CPT-B or CPT-A patients with prior non-HCC liver-related events	**32.0%** (95% CI 20-44%) HCC 19.7%; ascites 8.6% bleeding 7.8%; PSE 2.5%	**17.9%** (95% CI 6-29%)	Liver-related 16.2%* Non-liver related 8.8%§
	vs.	*vs.*	*vs.*
Cohort C (n = 67) Prior HCC	**71%** (95% CI 56-85%) HCC only	**17.5%** (95% CI 7-27%)	Liver-related 12.4%* Non-liver related 7.7§
	***p* <0.0001**	*p* = 0.32	***p* <0.0001** §*p* = 0.12

SVR: Sustained virological response; DAA: direct-acting antivirals; CPT: Child-Pugh-Turcotte; HCC: hepatocellular carcinoma; PSE: porto-systemic encephalopathy

If under regular follow-up
(US+/-NSBBs/carvedilol/EBL etc)

HCC (10-71%)

PHT-related events (1-9%)

Liver-related Death (1-12%)

Non-liver related Death (5-9%)

D'Ambrosio et al JHEP 2023

A non-negligible proportion of patients after successful etiologic therapies still need of new pathophysiological targets of therapy *(point of no return)*

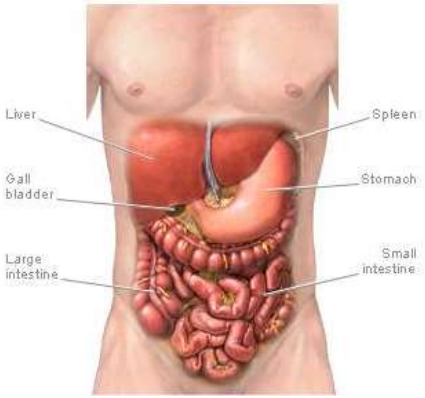
STRATIFICATION FOR THE RISK OF FIRST DECOMPENSATION

because

WE HAVE EFFICIACIOUS OPTIONS

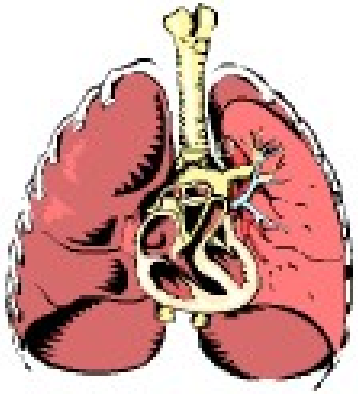
Complications of portal hypertension

GI tract



Varices
Gastropathy
Bacterial Translocation
Haemorrhage

Lungs

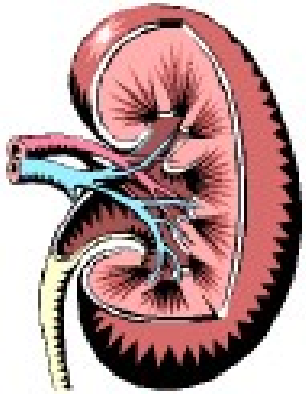


H-P syndrome

P-P hypertension

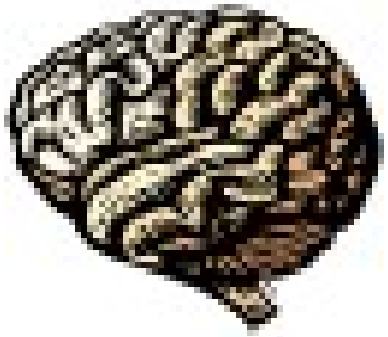
Hepatic hydrothorax

Kidney

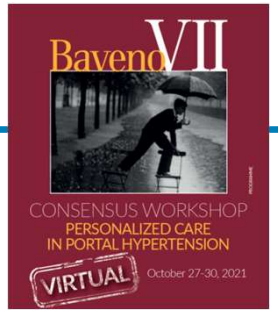


Ascites
AKI/HRS

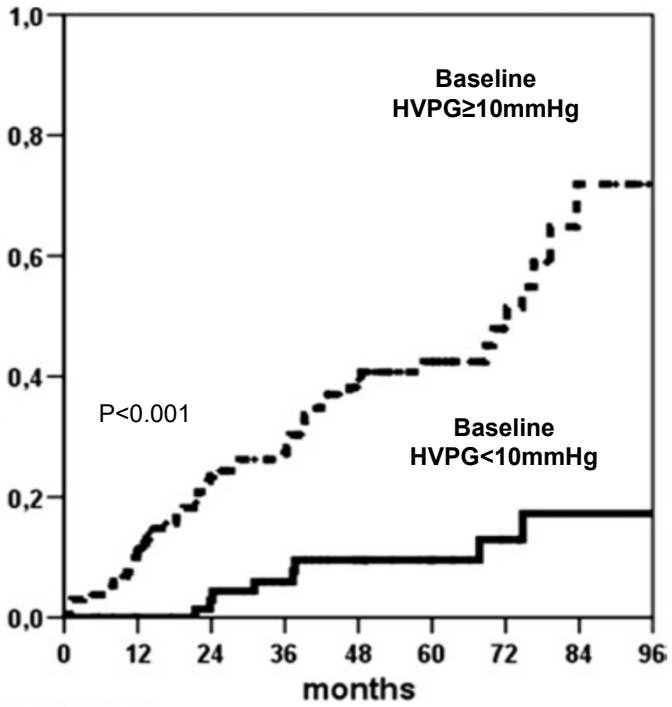
Brain



Hepatic encephalopathy
(coma)



FIRST DECOMPENSATION



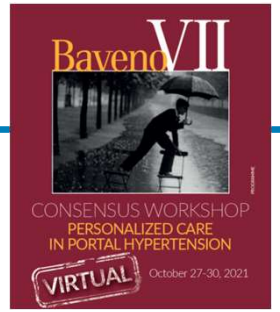
Ripoll et al Gastroenterology 2007

HVPG≥10mmHg (CSPH): high risk of first decompensation in cACLD

CSPH: clinically significant portal hypertension (risk of decompensation)

- **Compensated cirrhosis is defined by the absence of present or past complications of cirrhosis. The transition from compensated to decompensated cirrhosis leads to an increased mortality risk.** *(A1) (New)*

- **Compensated cirrhosis can be divided in 2 stages, based on the absence or presence of clinically significant portal hypertension (CSPH). Patients with CSPH have increased risk of decompensation. The goal of treatment in compensated cirrhosis is to prevent complications that define decompensation.** *(A1) (Changed)*



NSBBs/carvedilol: disease modifying drugs

HVPG>10mmHg *(hyperdynamic circulation)*

VARICES

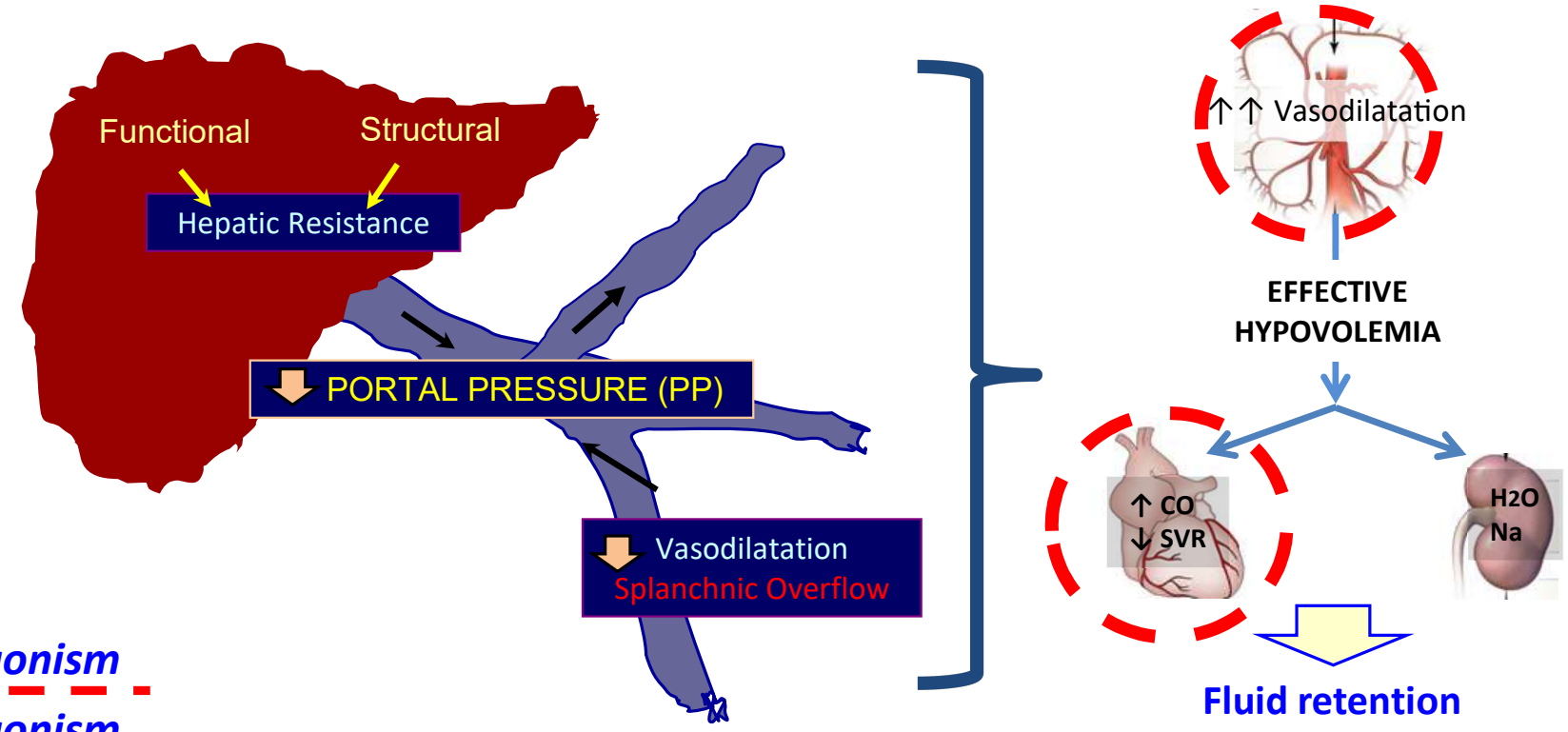
traditional indication

NON-INVASIVE STRATEGIES

- Liver/spleen stiffness (fibroscan, ARFI etc.)+/-platelets
- Porto-systemic shunts (imaging TC/RM)

Pathophysiological indication

FROM PATHOPHYSIOLOGY TO THERAPY



- *β1 antagonism*
- *β2 antagonism*
  (unopposed α-Adr tone)

We need beta-1 beta-2 block: consider NSBB/carvedilol to reduce the risk of (any) decompensantion

Preventing first bleeding: *prophylaxis*

EVL vs NSBBs/carvedilol-*why we should prefer tablets*

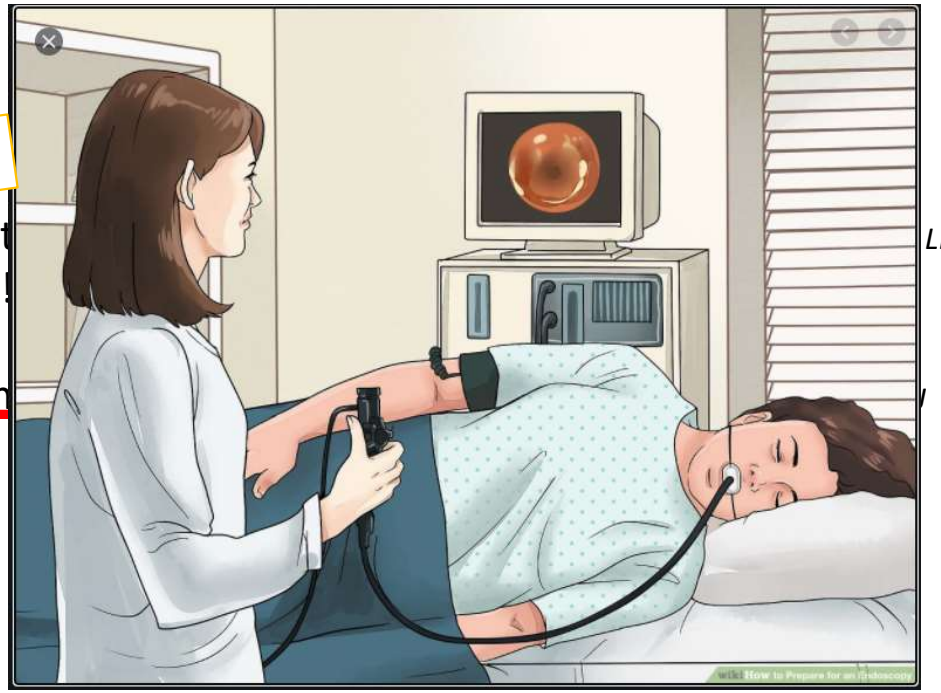
1.The *es Am J Gastro 2006)* while EVLs are a local treatment and need repet

2.The

3. Ad VL but *LL*
Cochr age!!

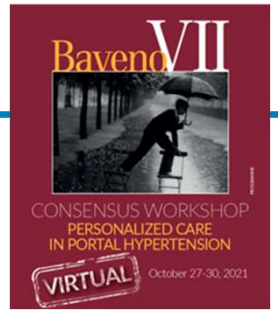
4. Co dition
Gastro

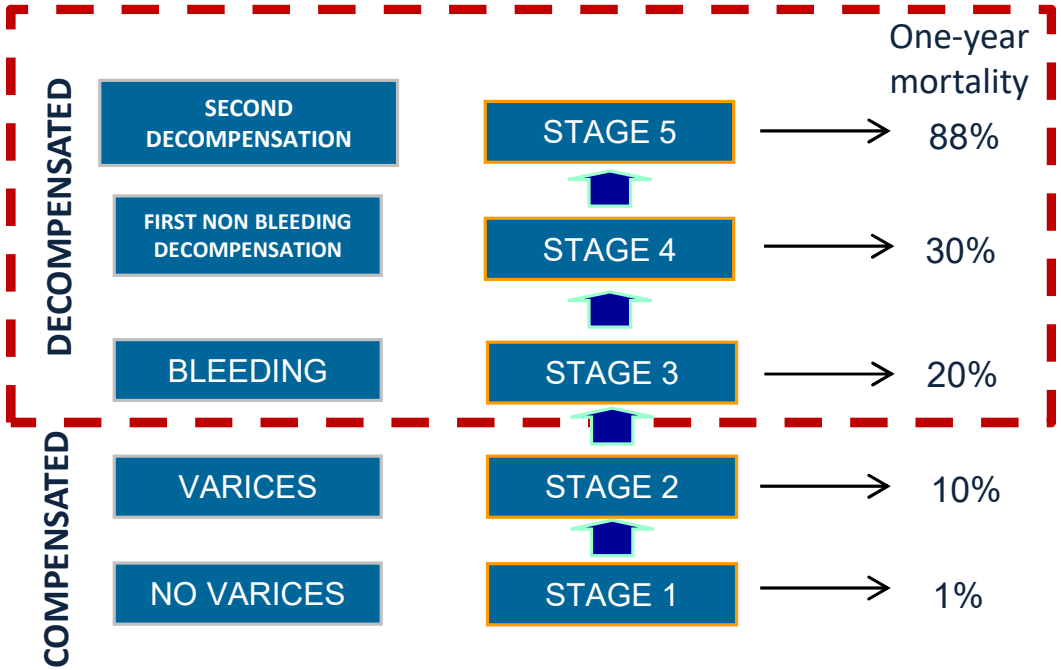
A key-strategy in decompensated cirrhosis (*Tellez JHEP2020*)



MANAGEMENT OF DECOMPENSATED CIRRHOSIS

Cirrhosis: a multistage disease





Patients with decompensated cirrhosis should be considered for liver transplantation. (A1) *(New)*

Need for network!!

AISF
ASSOCIAZIONE ITALIANA PER LO STUDIO DEL FEGATO
Riconosciuta con D.M. del 7.5.1998, G.U. del 20.6.1998
Iscritta nell'Elenco di cui all'art. 1, comma 353, della Legge 23.12.2005 n. 266, D.P.C.M. 15.4.2011
Iscritta nell'Elenco di cui all'art. 14, comma 1, del D.L. 14.3.2005, n. 35, convertito nella Legge 14.5.2005 n. 80, D.P.C.M. 15.4.2011

Modello Ragionato Di Rete Clinico-assistenziale Epatologica

2.A.5. Aspetti di integrazione ospedale-territorio

La Rete clinico-assistenziale epatologica, anche attraverso, fra ospedale e territorio La Rete clinico-assistenziale epatologica deve assicurare una integrazione fra ospedale e territorio e con il coordinamento regionale dell'emergenza-urgenza, basata sulla generazione di Team multidisciplinari inter-ospedalieri, intra-ospedalieri e fra specialisti ospedalieri e professionisti che invece lavorano sul territorio, e sulla definizione di protocolli e procedure per l'integrazione organizzativa e professionale tra i singoli nodi della Rete . La creazione di una cartella clinica elettronica condivisa fra ospedali e territorio nonché l'istituzione della figura del Case Manager rappresentano ulteriori strumenti per realizzare l'integrazione ospedale-territorio;

May it be reality?

Tale attività nel suo insieme

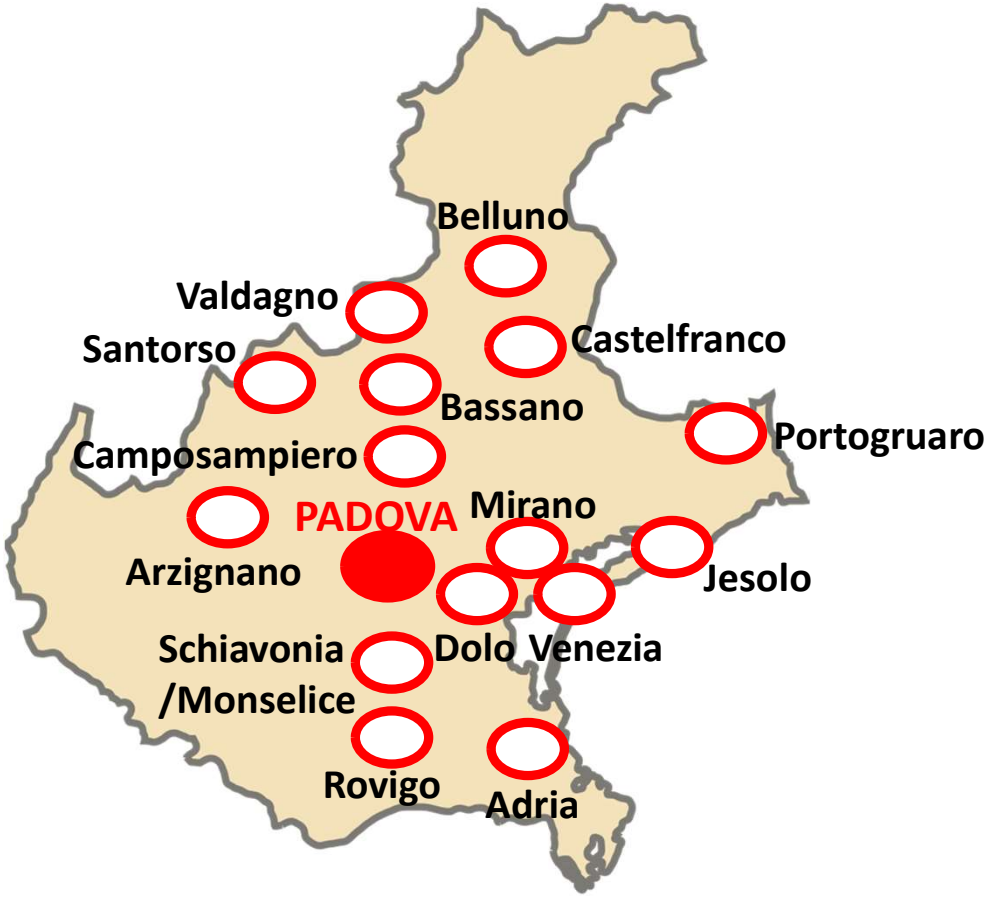
- garantisce l'appropriata presa in carico dei pazienti;
- assicura la continuità assistenziale tra i diversi professionisti intra- ed extra-ospedalieri, tenendo conto che a livello territoriale non è prevista la figura professionale dell'epatologo;
- elabora ed implementa i PDTA, ai quali devono essere conformati i Piani di Assistenza Individuale (PAI) dei singoli assistiti.

La Rete epatologica assicura la continuità assistenziale considerata dal Piano Nazionale della Cronicità perché:

- La logica di rete valorizza il ruolo dei MMG e dei professionisti territoriali, realizzando un modello d'integrazione tra coloro che operano nell'ospedale e nel territorio.
- Il modello assistenziale orientato alla continuità assistenziale, prevede il disegno di appositi percorsi e la presa in carico, costante nel tempo, da parte di un team multiprofessionale e multidisciplinare, caratterizzato da

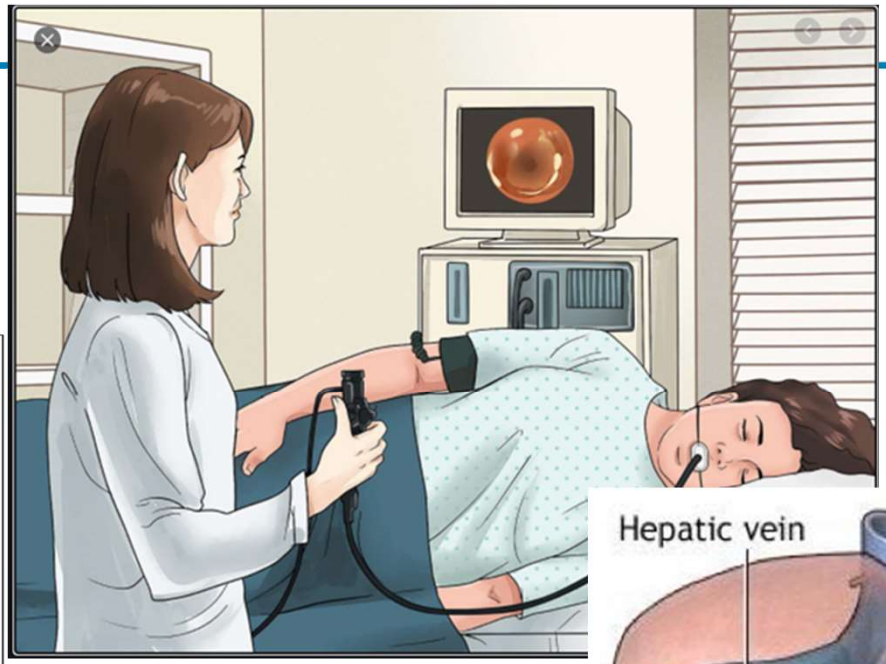
Rete Referral Morando

Discussione settimanale



Epatophone / contatti diretti

ENDOSCOPY



PARACENTESIS

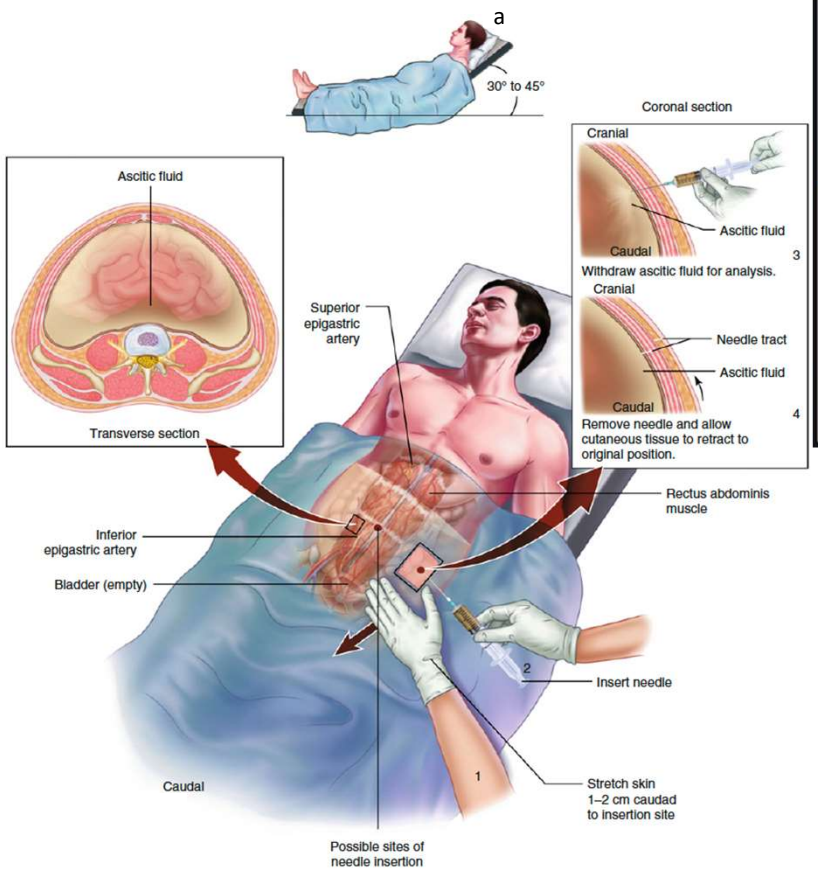
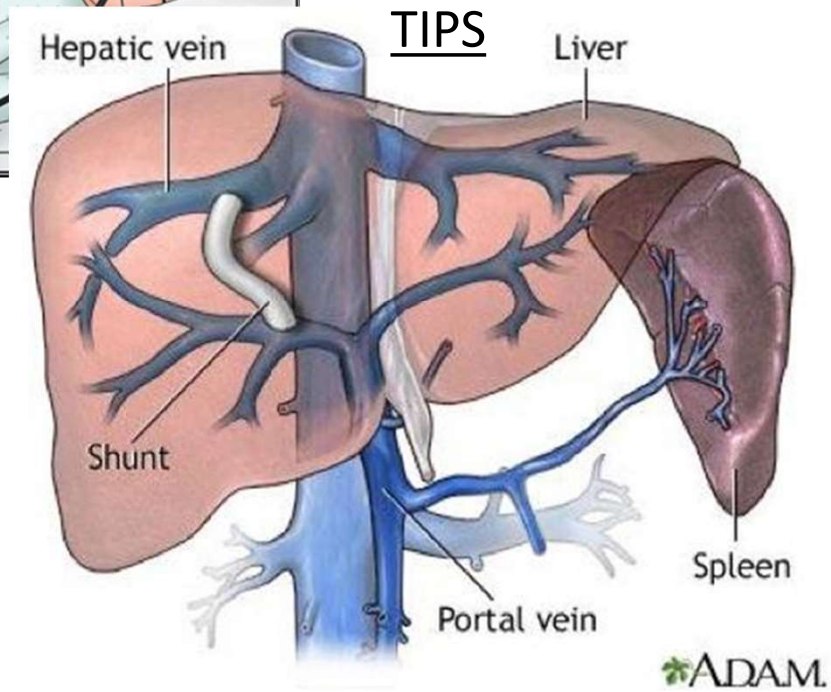


Fig. 79.1 Paracentesis procedure

TIPS



CHEMOEMBOLIZATION
RADIOFREQUENCY
TRANSPLANTATION
SURGERY
…

AGENDA

obiettivi pratici

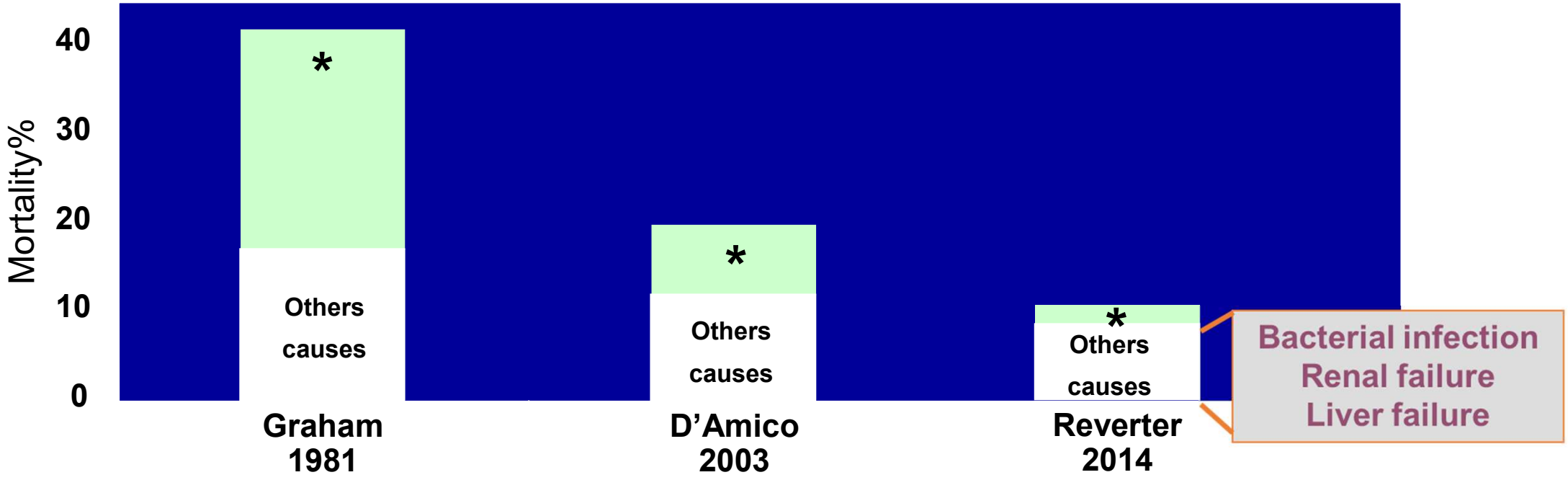
- **EPIDEMIOLOGIA** → *Individuare le categorie a rischio di epatopatia cronica*
  Effettuare la diagnosi di epatopatia cronica

- **REFERRAL** → *Riconoscere la fibrosi avanzata/cirrosi (cACLD) in chi ha una epatopatia cronica*
  Evitare le complicanze in chi ha già una fibrosi avanzata/cirrosi (cACLD) (HCC, ipertensione portale)
  Gestire la cirrosi scompensata

- **LE URGENZE** → *Sanguinamento acuto da ipertensione portale*
  Encefalopatia epatica
  Infezioni (e ACLF)

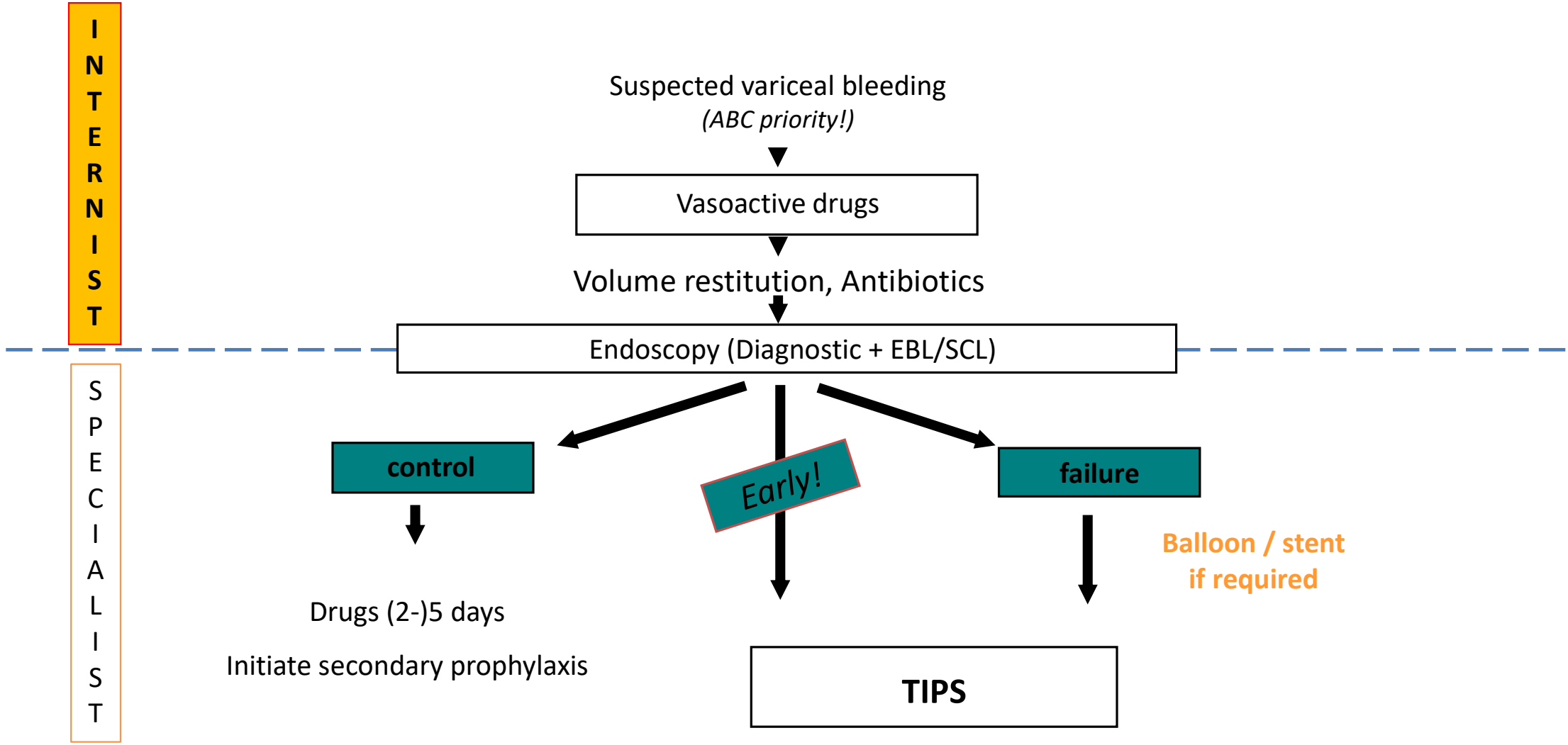
Bleeding Related Mortality

6-week mortality



**depending on portal hypertension lowering effect (e.g.: vasoactive drugs and TIPS)*

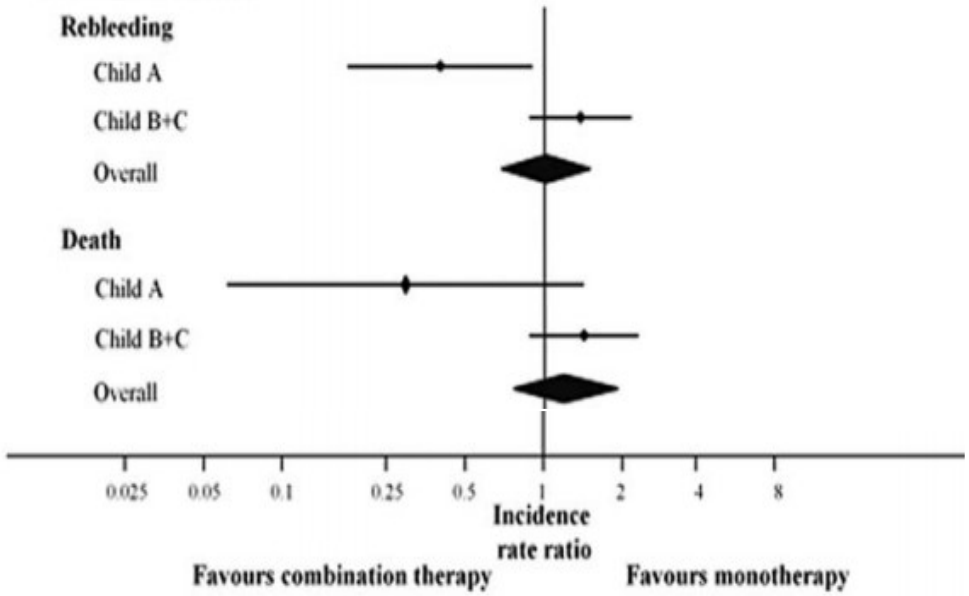
Treating acute bleeding-*the algorithm*



NSBBS + EVL THE STANDARD OF CARE

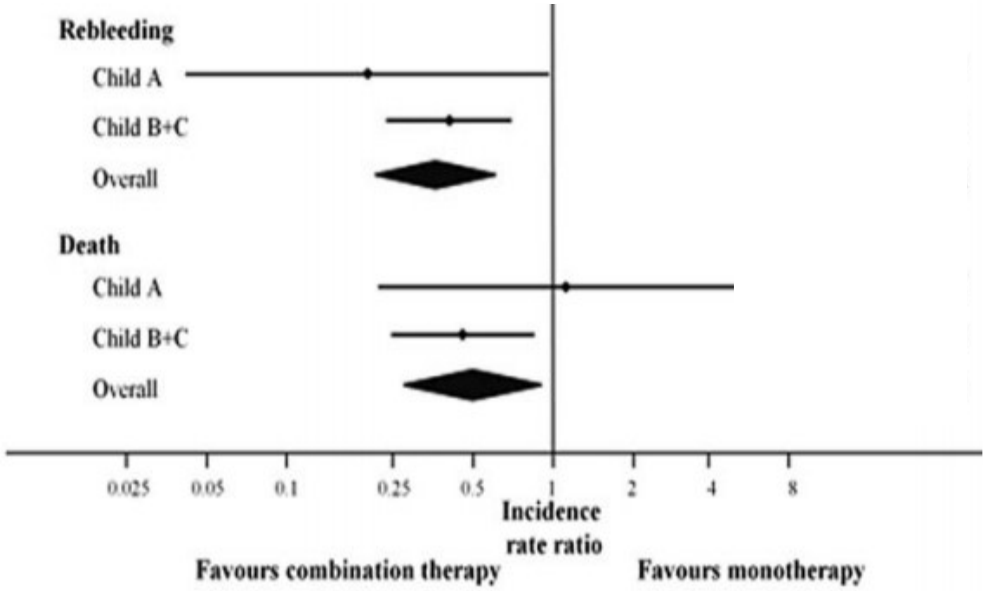
389 patients from three trials

EVL+NSBBs vs NSBB



416 patients from four trials

EVL+NSBBs vs EVL



Albillos Hepatology 2017

NSBB is the key element of combination therapy (*individual data meta-analysis*)

HEPATIC ENCEPHALOPATHY

Need for Differential Diagnosis

			Facilitating and	Ammonia
Acut				ring nts
Portal- (no si				
Liv (both l portal-				Yes all ions)
Acut Li				

List of disorders that could mimic or associate with HE, and should be considered for purposes of differential diagnosis.

- Alcohol/opioids withdrawal syndromes
- Electrolyte-related encephalopathy (*i.e.* hyponatremia, hyper/hypocalcemia *etc.*)
- Encephalopathy of endocrine origin (*i.e.* hypothyroidism and hypocorticism)
- Hypercapnic encephalopathy
- Hyperosmotic encephalopathy
- Hypo/hyperglycaemic encephalopathy
- Intoxication with alcohol or other recreational drugs
- Intoxication with benzodiazepines or other psychoactive drugs (*i.e.* anticonvulsants, sedative antidepressants, opioids, fluoroquinolones)
- Intracranial structural injury (*i.e.* subarachnoid haemorrage, ischaemic or haemorragic stroke, brain neoplasms)
- Meningoencephalitis
- Non convulsive status epilepticus
- Septic encephalopathy
- Simulation
- Uraemic encephalopathy
- Vitamin deficiencies or complex malnutrition-related syndromes
- Wernicke's encephalopathy

Montagnese, et al. Dig Liver Dis. 2019

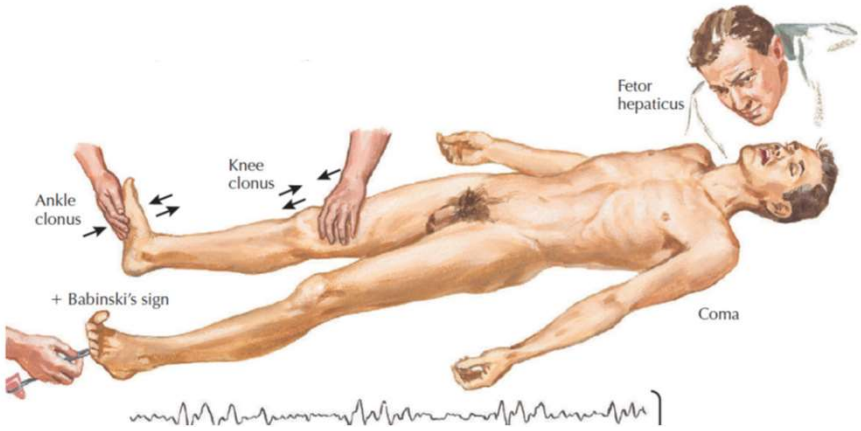


Table 3. Precipitating Factors for OHE by Decreasing Frequency

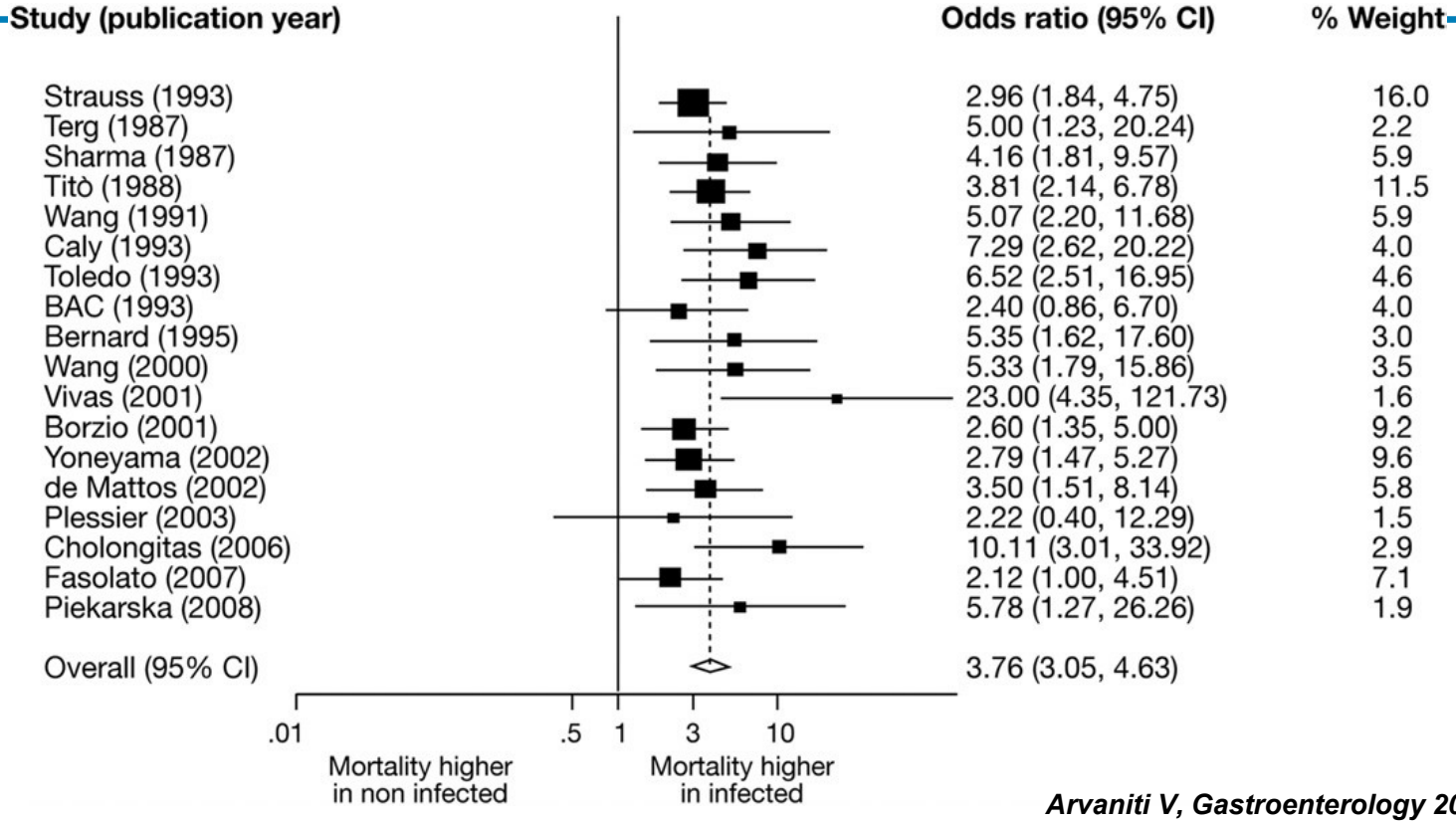
Episodic	Recurrent
Infections*	Electrolyte disorder
GI bleeding	Infections
Diuretic overdose	Unidentified
Electrolyte disorder	Constipation
Constipation	Diuretic overdose
Unidentified	GI bleeding

Modified from Strauss E, da Costa MF. The importance of bacterial infections as precipitating factors of chronic hepatic encephalopathy in cirrhosis. Hepatogastroenterology 1998;45:900-904.

*More recent unpublished case series confirm the dominant role of infections.

Vilsrup et al Hepatol 2014

ACUTE BACTERIAL INFECTION



Arvaniti V, Gastroenterology 2010

- **Prevalence: 30% of pts with cirrhosis are infected**

- **Risk Factors: Child-Pugh, variceal bleeding, low proteins in ascitic fluid, previous s.b.p**

- **<u>Mortality</u>: up to 40% at one month after admission, up to 60% at 1 year**

ACLF: EASL-CLIF definition is based on clinical evidence

2013, **CANONIC Study**: 1343 hospitalized cirrhotic pts with acute decompensation (29 liver units across Europe)

ACUTE ON CHRONIC LIVER FAILURE

Acute decompensation of cirrhosis

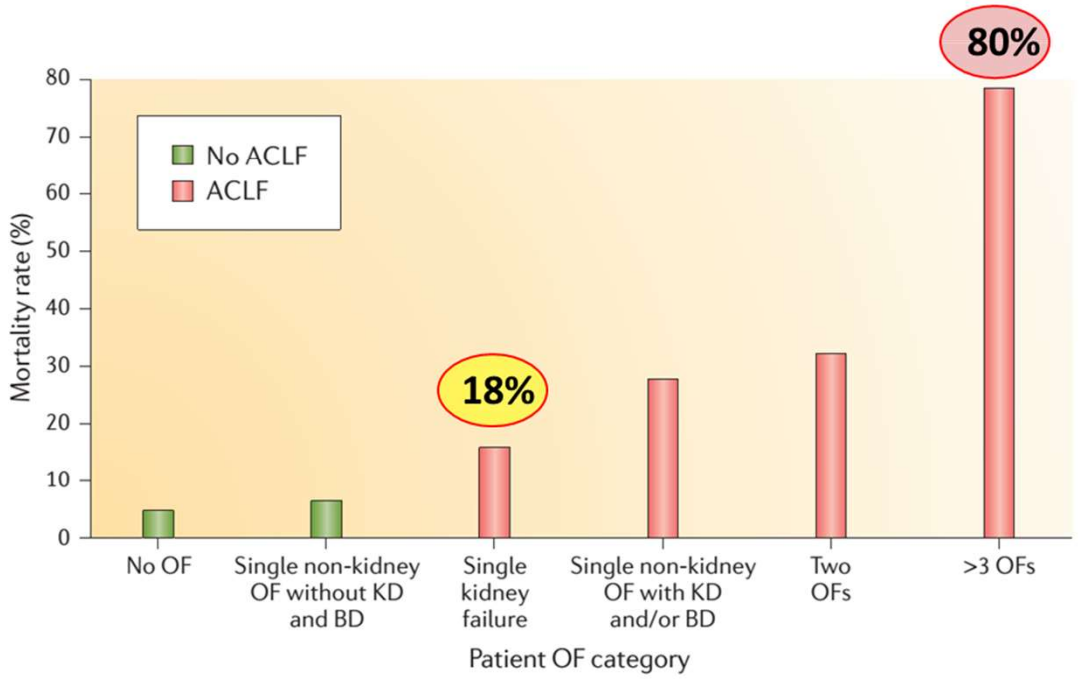
Development of:
-Ascites
-Encephalopathy
-Gastrointestinal haemorrhage
-Bacterial infection

+

Single or multiple organ failure

Single renal failure or other single non-renal organ failure if associated with renal and/or brain dysfunction

High 28 days mortality



Moreau et al. Gastroenterology 2013; Arroyo et al. Nat rev 2016, EASL CPG. J Hepatol 2018

PRECIPITATING FACTORS

Precipitating events	AD without ACLF	ACLF
Bacterial infection	22%-29%	33%-50%
Active alcoholism in the past 3 months (suspected alcoholic hepatitis)	15%-26%	24.5%-43.5%
Gastrointestinal bleeding	16%-17%	13%-20%
Neurotoxic drugs	8%	8%
Paracentesis without albumin	10%	10%
TIPS	5%	4%
DILI	1.5%	2%
Viral hepatitis or other viral infections	1%	1.5%
Drug-induced kidney injury	0.3%	0.5%
Surgery	0.3%	0%
Decompensated cardiopulmonary disease	0.4%	1.5%
Dehydration	0.3%	0.5%
Large hematomas	0.3%	0%
Acute pancreatitis	0.1%	0.5%
Portomesenteric vein thrombosis	0.2%	0.5%
Extrahepatic autoimmune disease	0.2%	0%
Cerebrovascular accident	0%	0.5%
Bowel occlusion	0.1%	0%
Indeterminate precipitating event #	59%-62%	29%-44%
More than one precipitating event	5%-6%	13.5%-25%

Gustot et al JHEP 2020

Bacterial infections and acute alcoholic hepatitis the most frequent precipitating factors associated with ACLF in EU

SUSPECT INFECTIONS ANY TIME YOU HAVE A SIGNIFCANT CHANGE OF YOUR PATIENT!

What else?

- Portal vein thrombosis
- Use of albumin
- AKI/HRS
- Spontaneous bacterial peritonitis
- Anemia/leuco-/thrombocitopenia and transfusion policy
- Cirrhosis regression
- Palliative care

- Portal vein thrombosis
- Aspirin
- Anticoagulation
- Management of atherothrombotic risk
- Hemorrhagic risk associated with invasive procedures
- …….Periprocedural risk

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