PROGRAMMA SCIENTIFICO

SOCIETÀ MEDICA DI SANTA MARIA NUOVA

L'Ospedale dei Fiorentini

Giornate Mediche di Santa Maria Nuova 2015

VII EDIZIONE

L'ECCELLENZA DELLE CURE IN OSPEDALE:
Santa Maria Nuova si confronta con la sua storia e con l'innovazione

2 - 3 Ottobre 2015

Sala Verde - Palazzo Incontri - Banca CR Firenze
Via de' Pucci, 1 - Firenze

La Cirrosi da HCV: che cosa cambia con le nuove terapie

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Consultant for:

Abbvie
Bayer
ViiV Healthcare

Deaths associated with different diseases in Italy

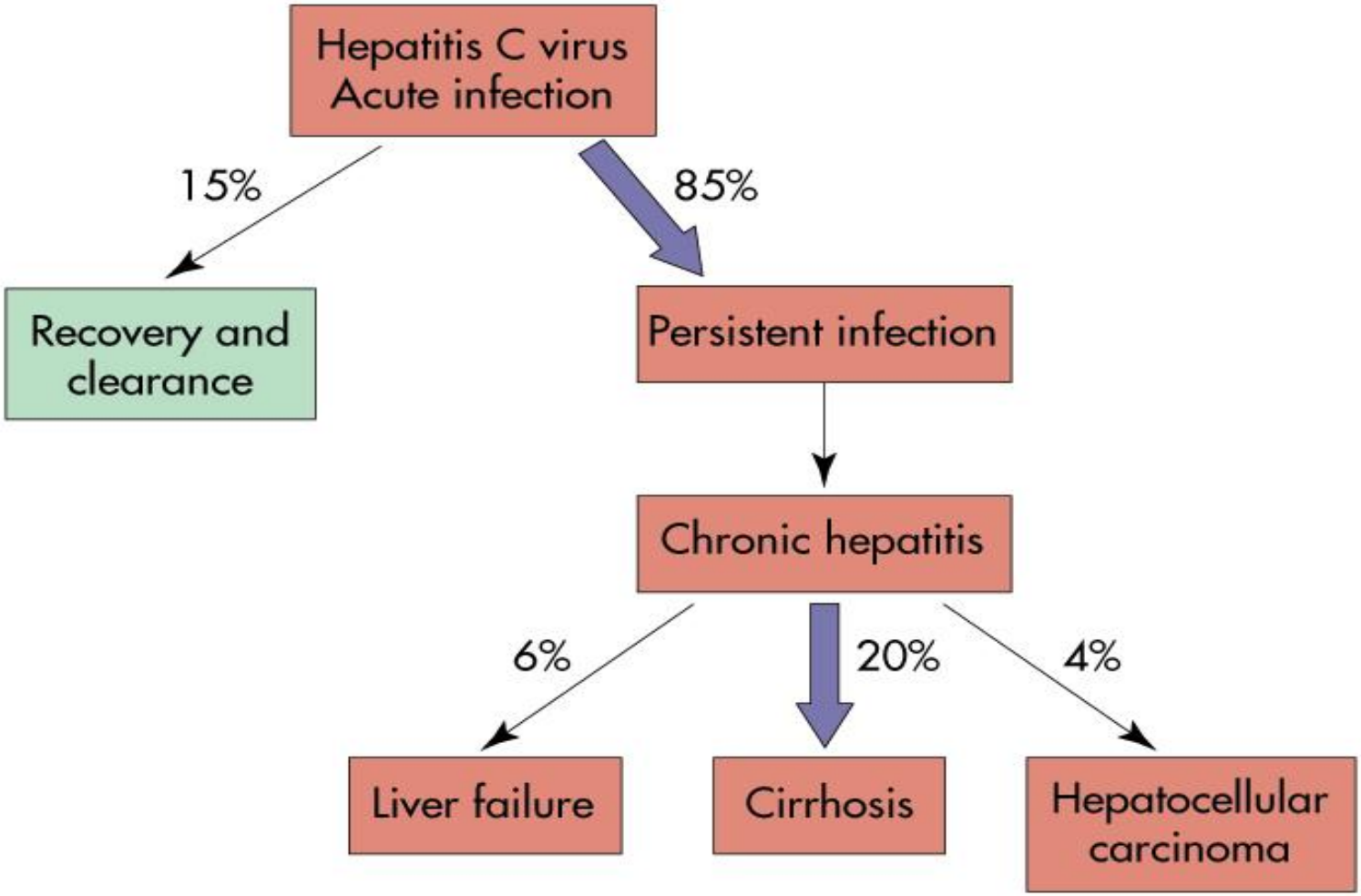
Disease	n. deaths/yr
Colon and rectum cancers	20,269
Breast cancers	13,222
Chronic obstructive pulmonary disease	21,527
Nephritis and nephrosis	8744
Liver cancer	9753
Cirrhosis of the liver	8165

➢ 60% related to HCV

Comparison of the number of deaths associated with selected diseases compared to liver diseases based on death certificates (age-standardized) in Italy (population 59,6 millions)

Blachier et al., J Hepatol 2013

Natural history of HCV infection



Natural history of HCV infection: conflicting views on severity

Worst-case scenario (Tong et al NEJM, 1995)	131 Tx-related chronic hepatitis C (followed for 1-15 yr)	45%	cirrhosis
		11%	HCC
		15%	HCV-related mortality
Best-case scenario (Wiese et al J Hep, 2005)	2867 women treated with HCV1b Rh Ig (followed for 25 yr)	7%	uninfected
		54%	spontanous recovery
		0.5%	cirrhosis
		0.1%	HCC
		0.3%	HCV-mortality

How to explain its heterogeneous and contrasting features ?

Natural History of Hepatitis C

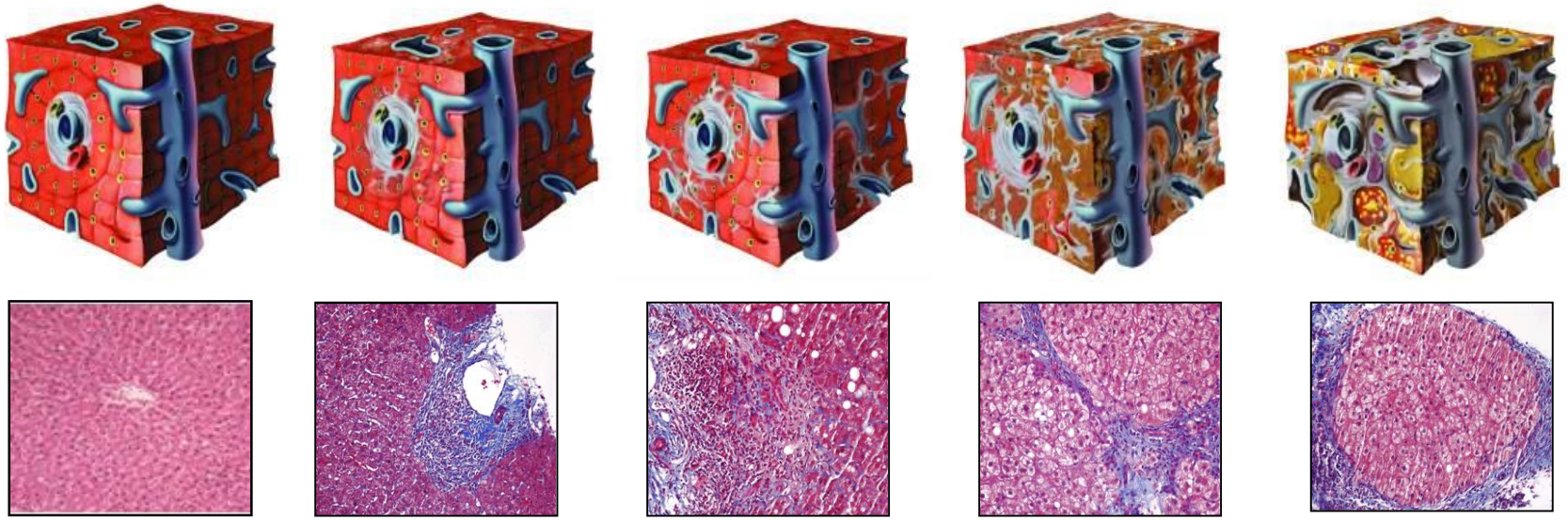
Factors / variables associated with progression

- **Age at infection**
- **Gender**
- **Race**
- **HIV – HBV coinfections**
- **HCV genotype**
- **Alcohol**
- **Smoking**
- **Hemochromatosis**
- **NASH - Obesity**
- **Genetics**
- **ALT profile**

Non-specialist's approach to a newly diagnosed patient

- Does HCV contribute to the problem which led to presentation?
- Recognition and staging of the underlying liver disease
  - *Physical examination, ALT, AST, bilirubin, INR, albumin, ultrasound*
- Exposure to other parenterally-transmitted diseases?
  - *HBsAg, anti-HBs, anti-HBc, HIV*
- Is there an indication to antiviral treatment?
  - *Refer to specialist, HCV-RNA, genotype*

Progression of chronic liver diseases



F0	F1	F2	F3	F4
No fibrosis	Fibrosis without septa	Few septa	Numerous Septa W/O cirrhosis	Numerous Septa WITH CIRRHOSIS

- **Deranged microvascular anatomy**
- **Portal hypertension**
- **Cancer**

Diagnostic approaches to staging

Biopsy

Biomarkers

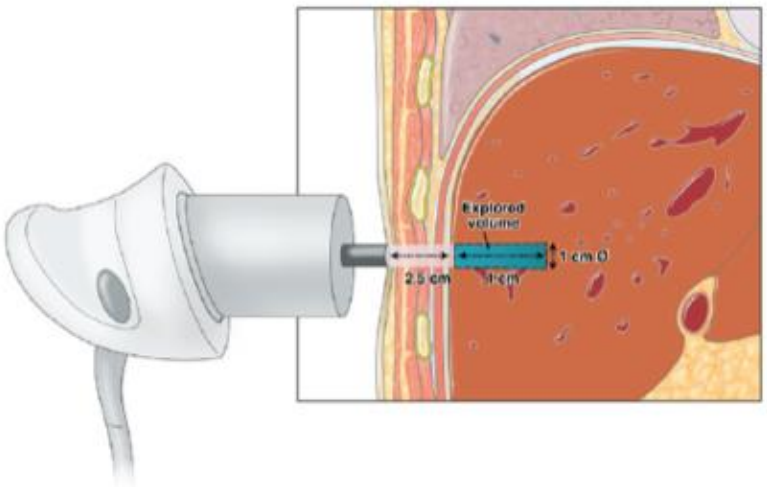
Biopsy

Imaging

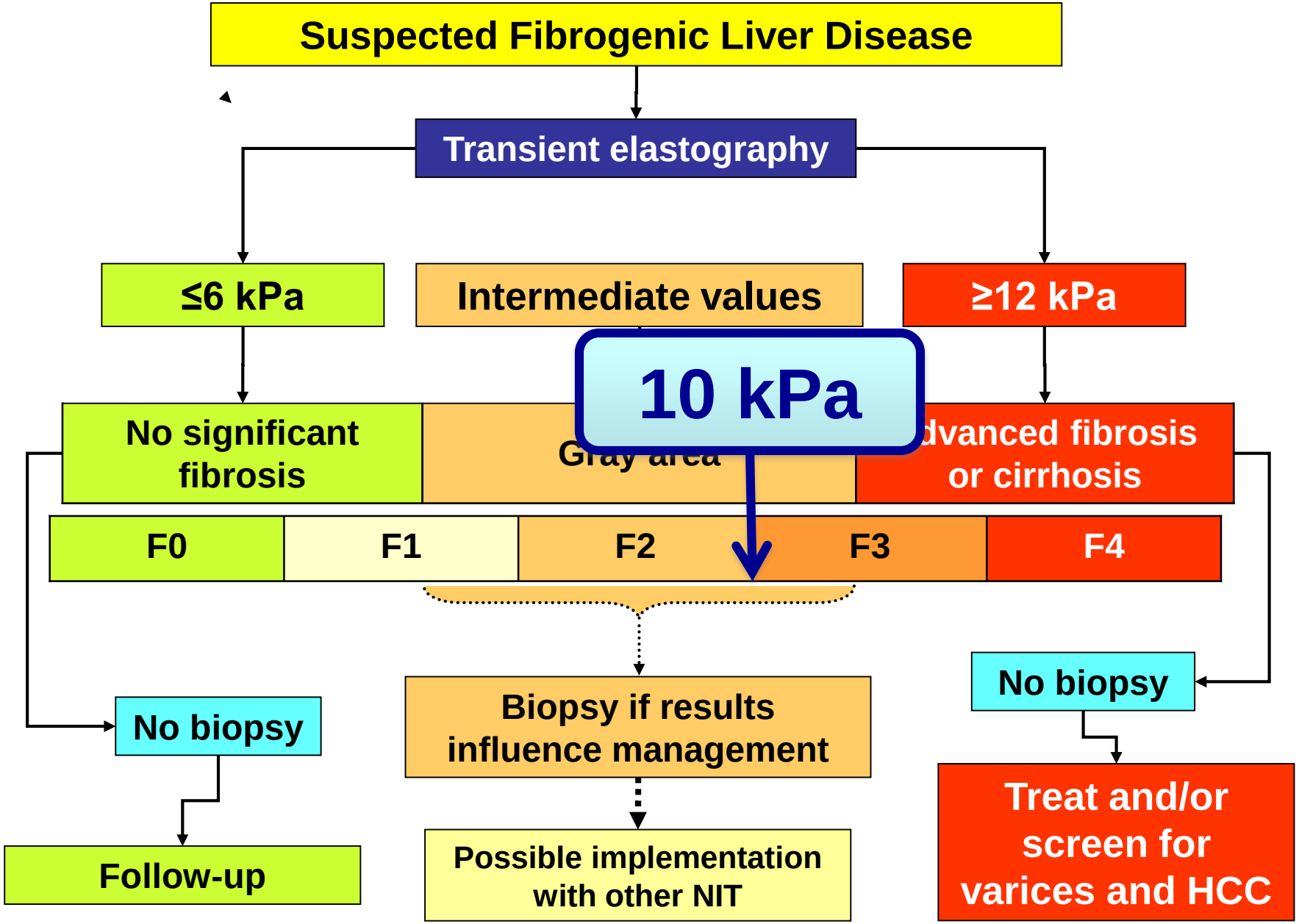
Elastography (Fibroscan®)

HVPG

Transient elastography (Fibroscan®)



- Based on a ultrasound transducer probe mounted on the axis of a vibrator.
- Vibrations induce an elastic shear wave that propagates through the underlying liver tissue.
- The velocity of the wave is directly related to tissue stiffness and to the amount of fibrotic tissue
- Tests approximately 1/500 of the liver
- Not reliable with obesity or ascites



Modified from Vizzutti et al., Gut 2009;58:157

FIBROscan or ‘HEPATOscan’?

Confounding factors:

Inflammation

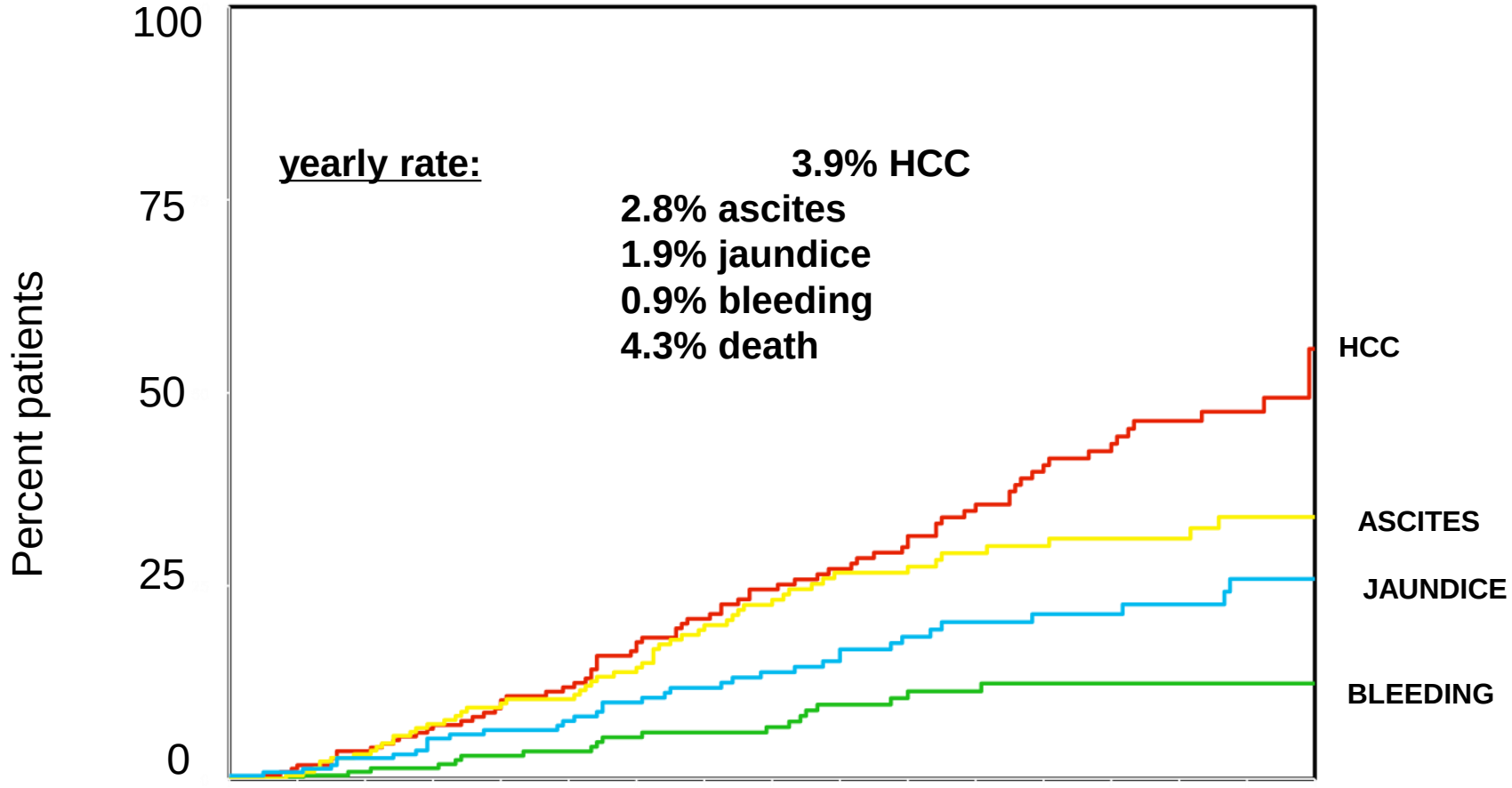
Tissue edema

Extrahepatic cholestasis

Passive congestion

Active blood flow (meal)

Major complications in HCV-related cirrhosis



Patients still at risk

241	222	209	186	169	155	142	127	118	104	97	79	70	60	51	38	6
241	223	206	180	167	156	146	126	116	100	93	78	72	63	54	42	5
241	222	208	182	169	158	147	134	126	110	98	80	74	63	53	43	6
241	224	212	189	176	165	155	140	132	113	101	87	78	67	57	45	6

Sangiovanni et al., Hepatology 2005

N.M. male, 52 yo
Reports no major problems in the past
No medication, social drinker (60 g/day), obese
Works as a dentist

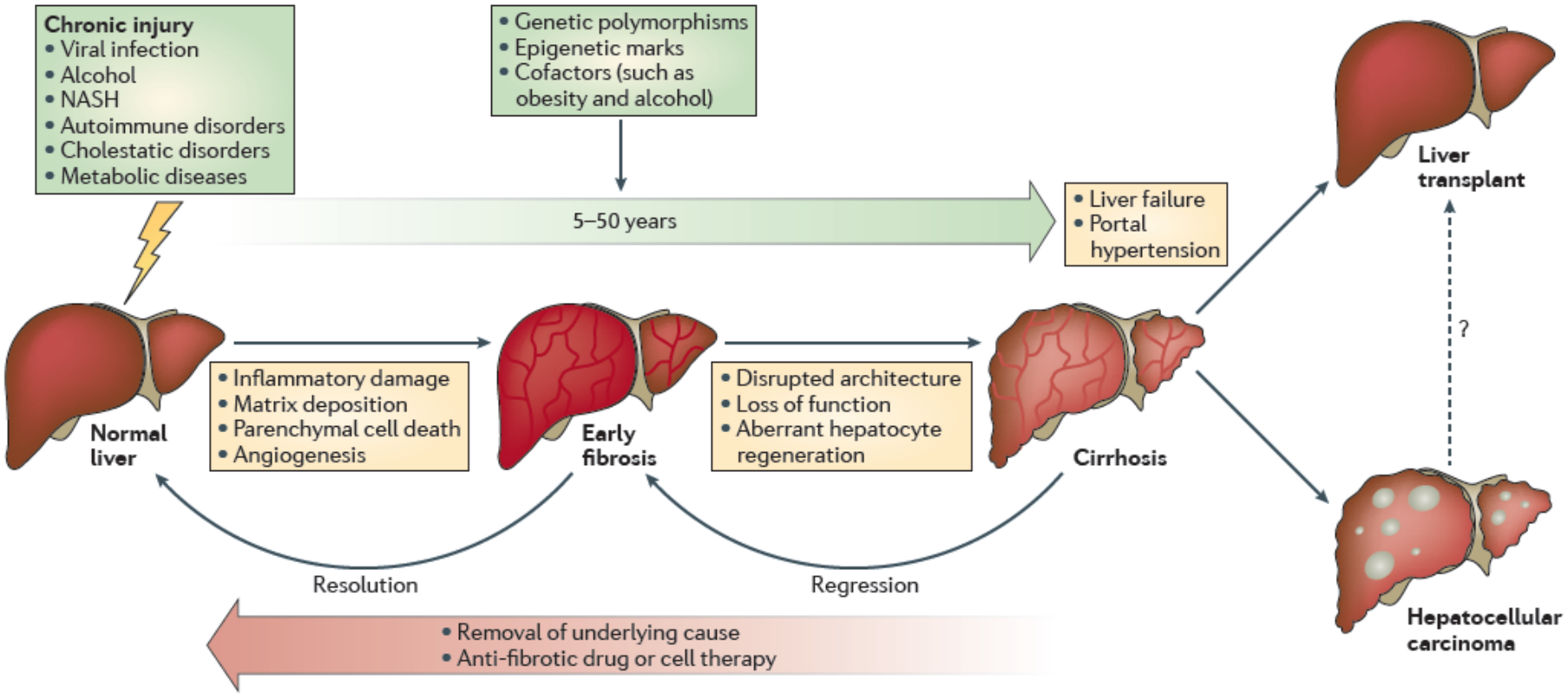
Presents to the ER during a trip in Spain for massive hematemesis after taking NSAIDs for back pain

Upper endoscopy shows actively bleeding varices (F3)

Lab test: hyperbilirubinemia,
HCV positive

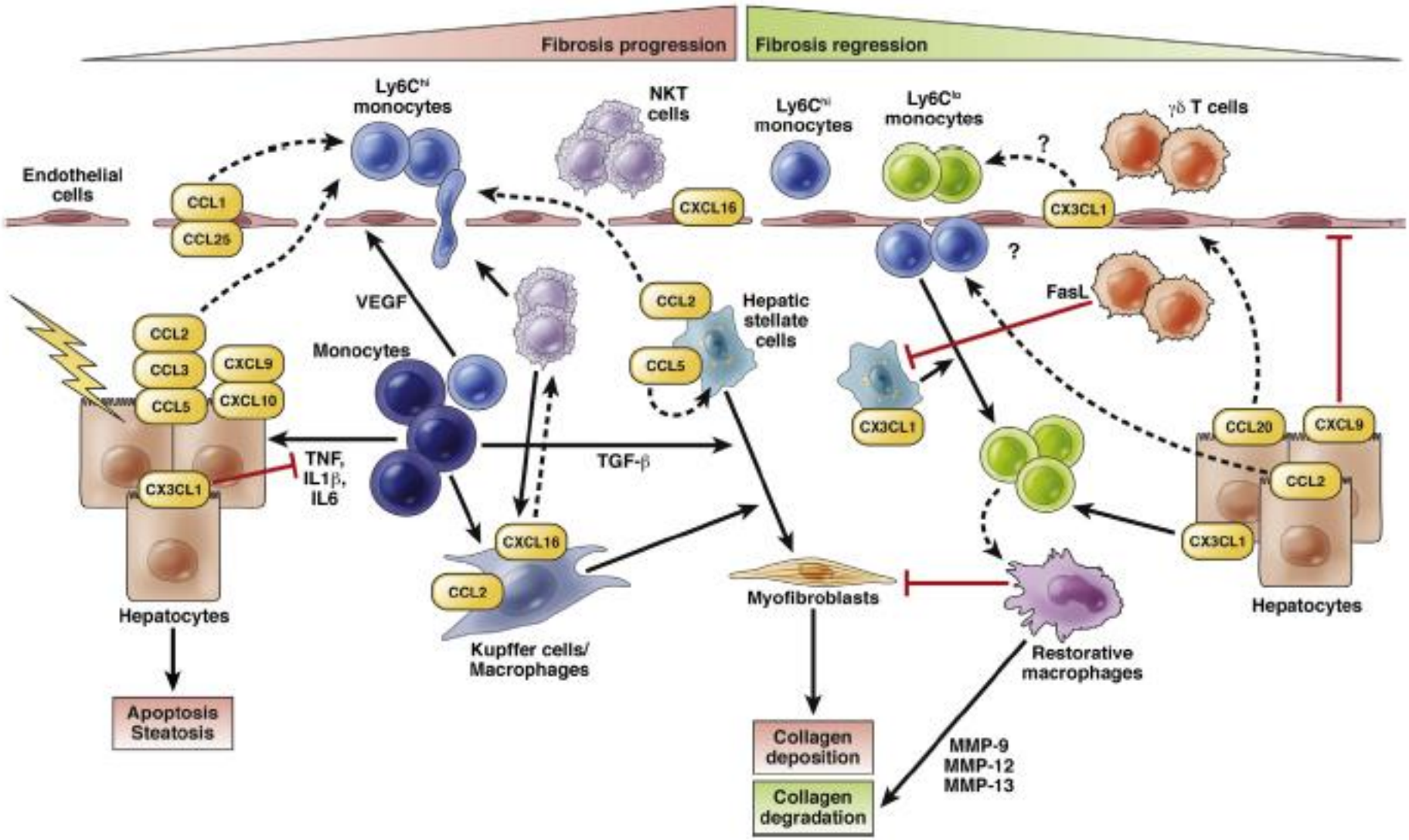
CT scan: single HCC nodule

Cirrhosis – F4



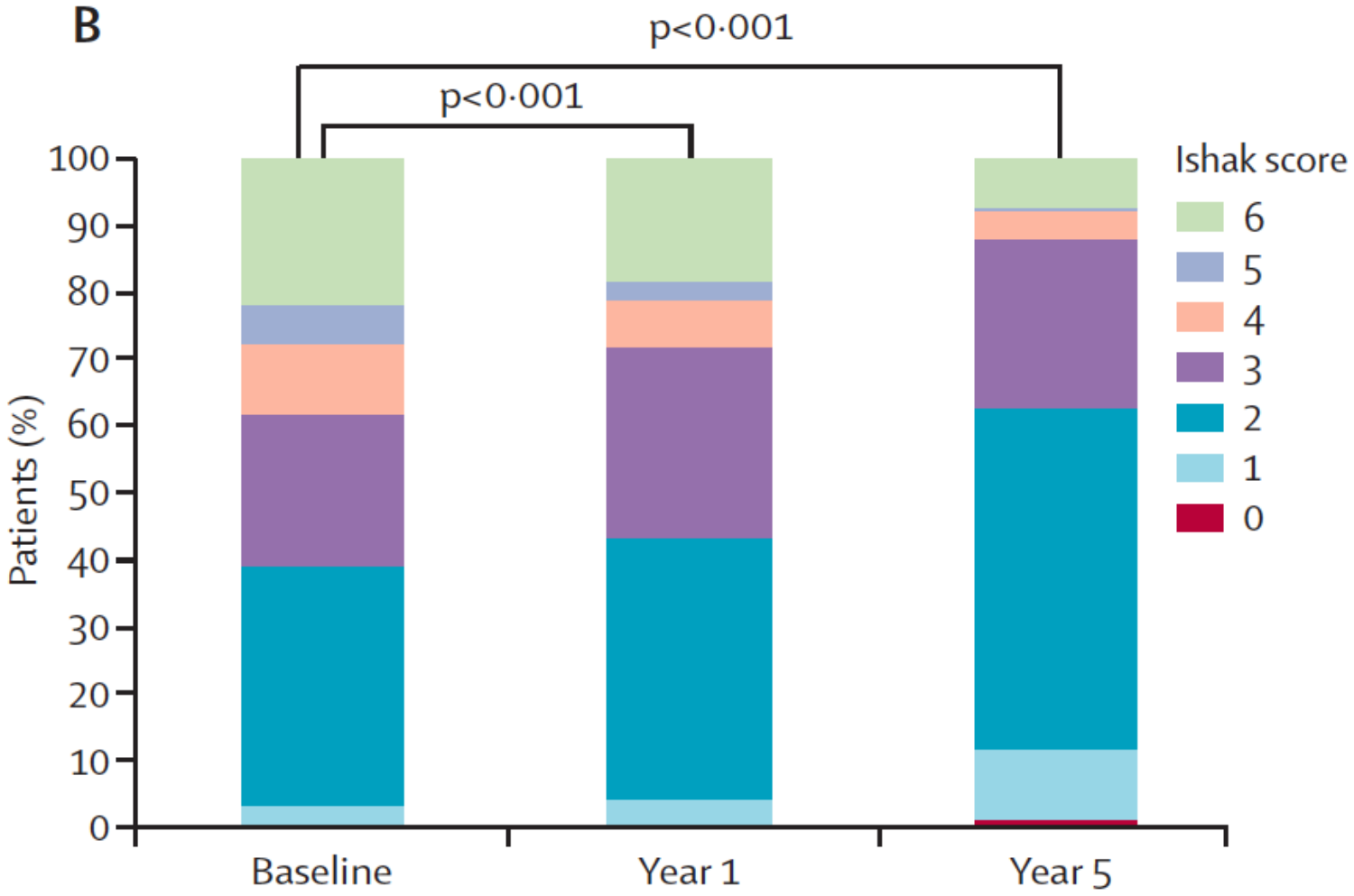
Pellicoro et al., Nat Rev Immunol 2014

Fibrosis and inflammatory cells



Marra & Tacke, Gastroenterology 2014

Regression of fibrosis (and cirrhosis?) after Hep B therapy



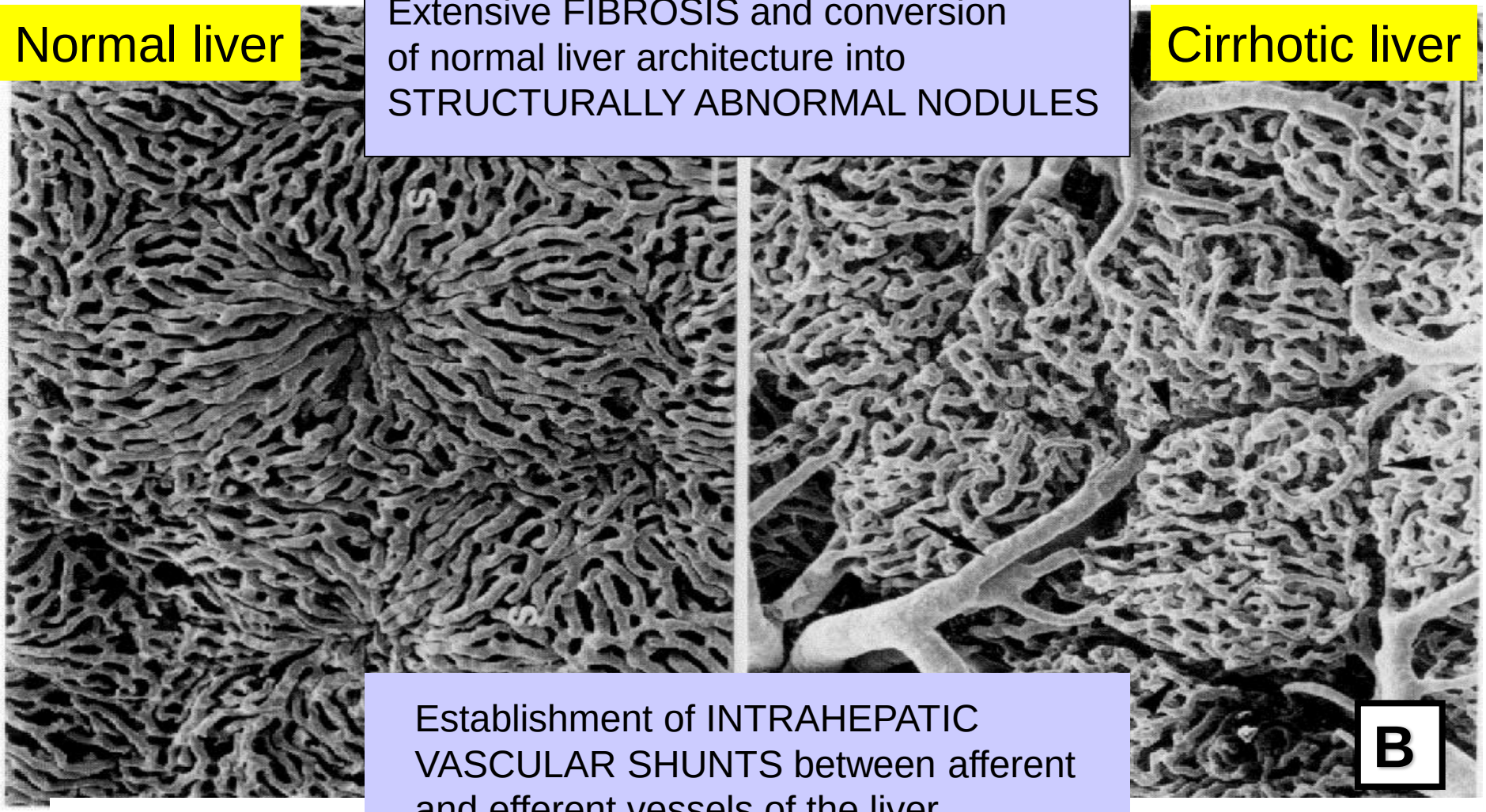
Marcellin et al., Lancet 2013; 381:486

Deranged microvascular anatomy in cirrhosis

Normal liver

Extensive FIBROSIS and conversion of normal liver architecture into STRUCTURALLY ABNORMAL NODULES

Cirrhotic liver

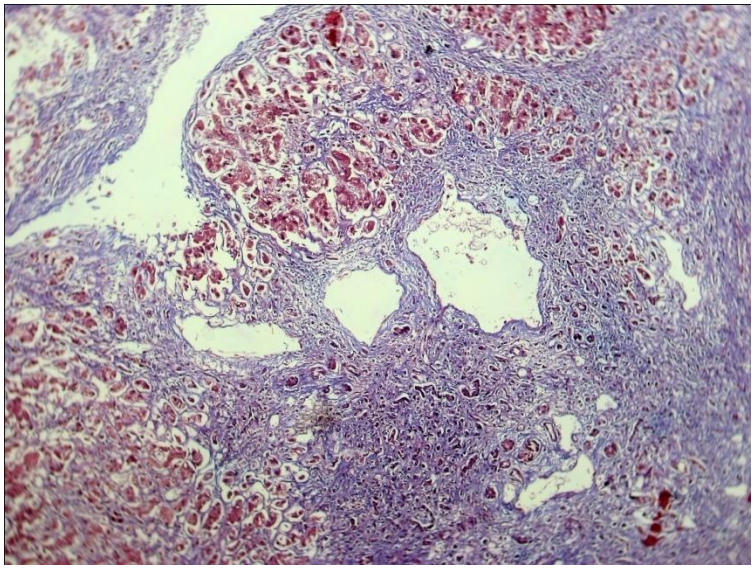


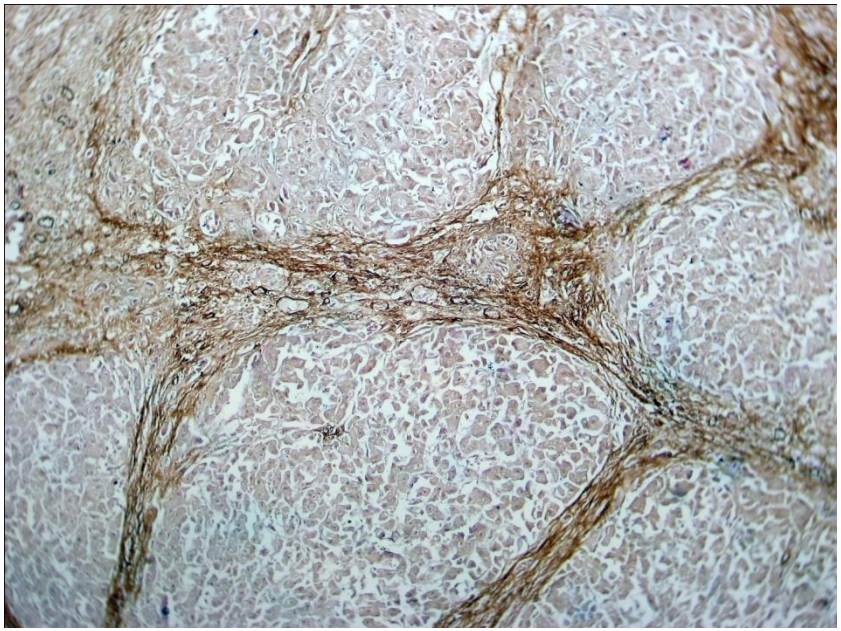
Establishment of INTRAHEPATIC VASCULAR SHUNTS between afferent and efferent vessels of the liver

Onori et al., J Hepatol 2000; 33:555

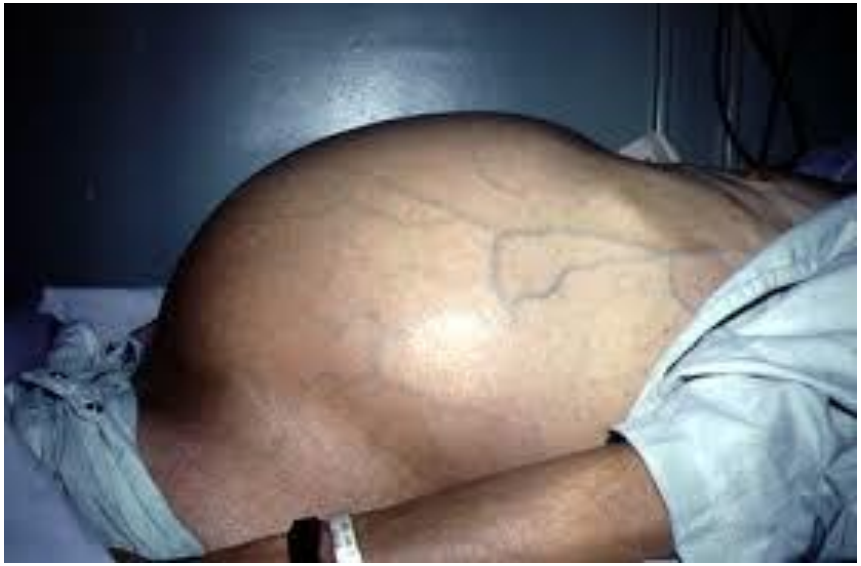
What is not Reversible?

- Parenchymal regenerative nodules
- Vascular anastomosis
- Vascularized septae





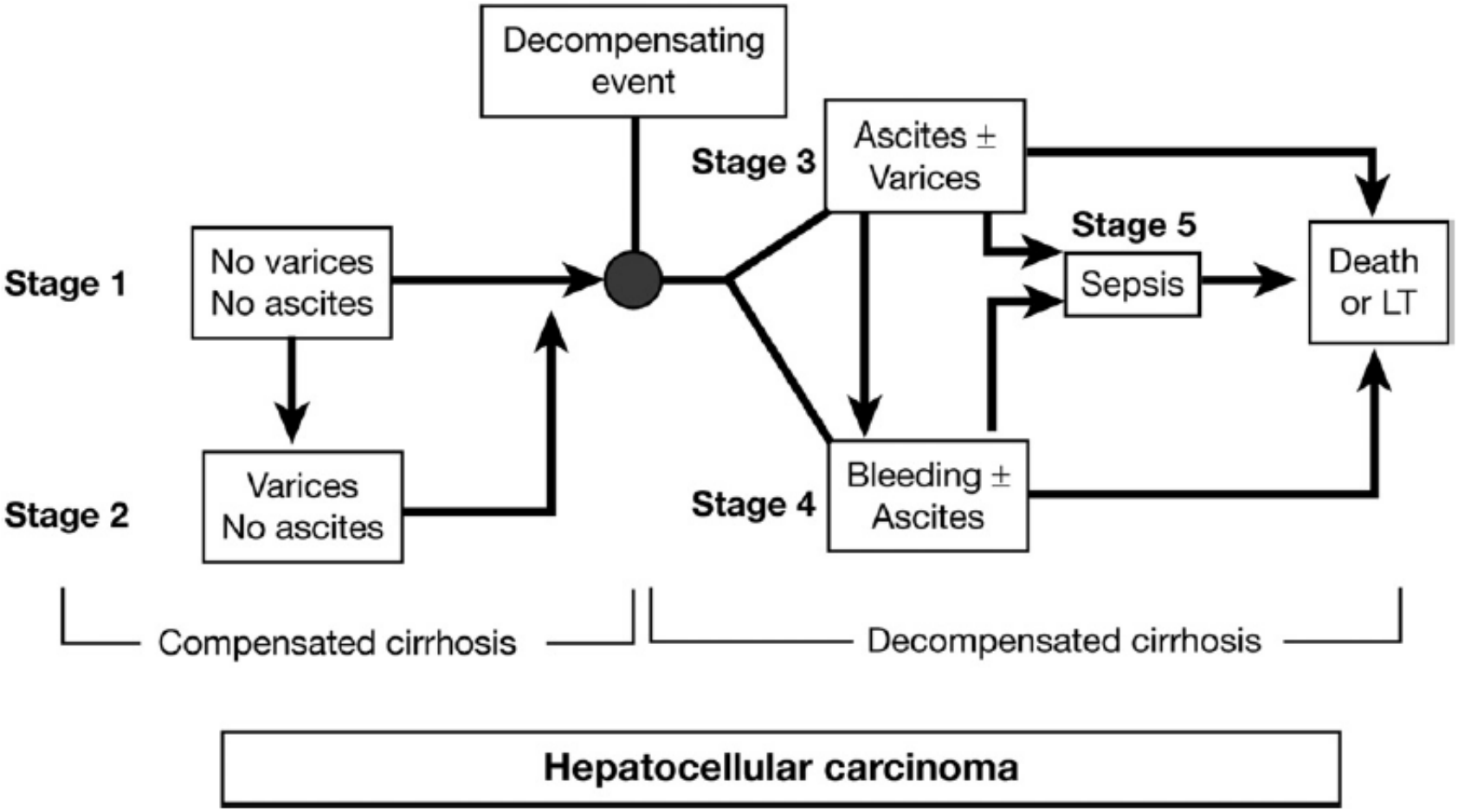
Tell the difference between these two patients



571.5

571.5

Towards a new classification of cirrhosis



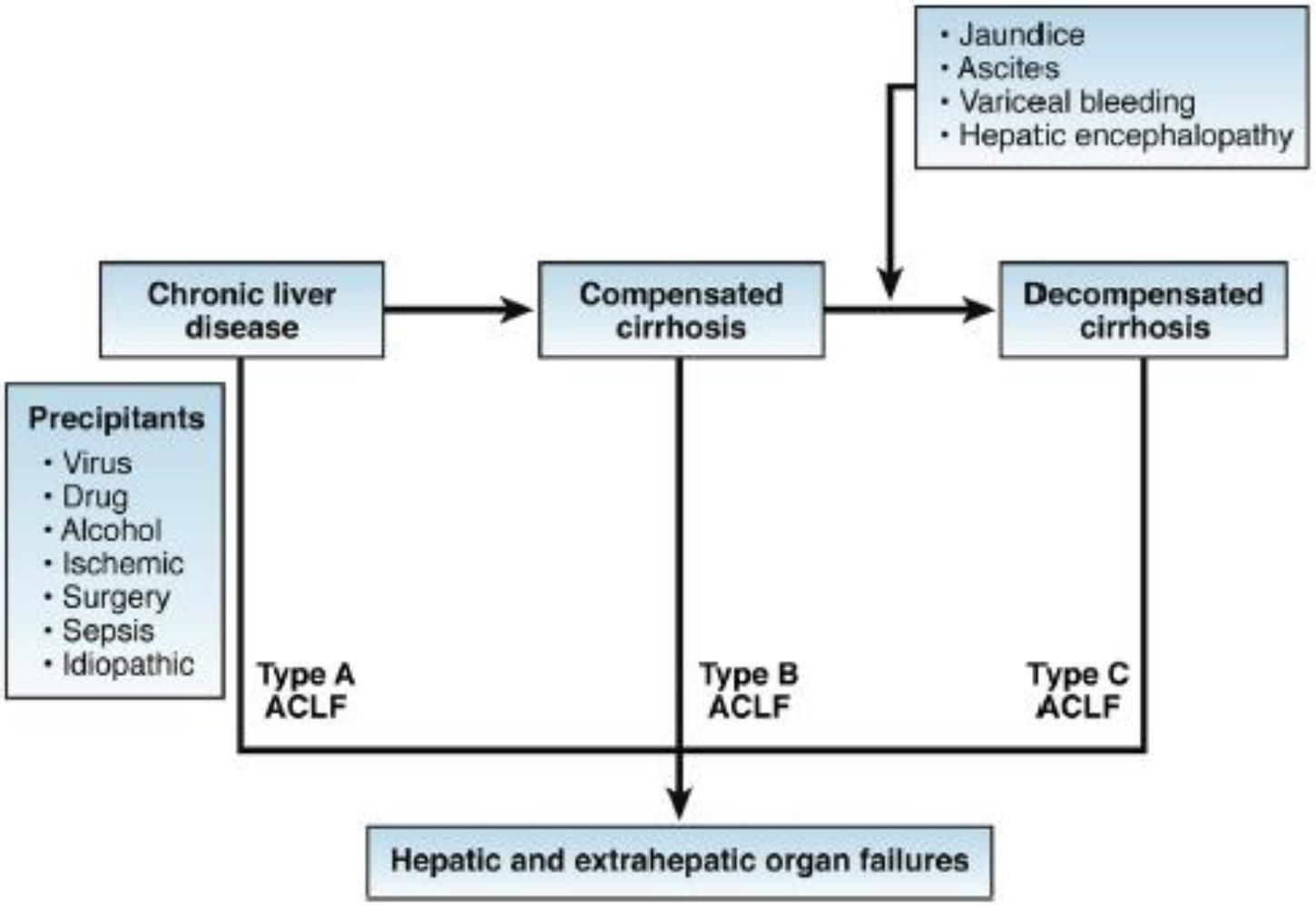
Arvaniti et al., Gastroenterology 2010;139:1246

Definition of acute-on-chronic liver failure (ACLF)

✧ A syndrome characterized by the acute deterioration of liver function in a patient with compensated or decompensated, but hitherto stable, cirrhosis.

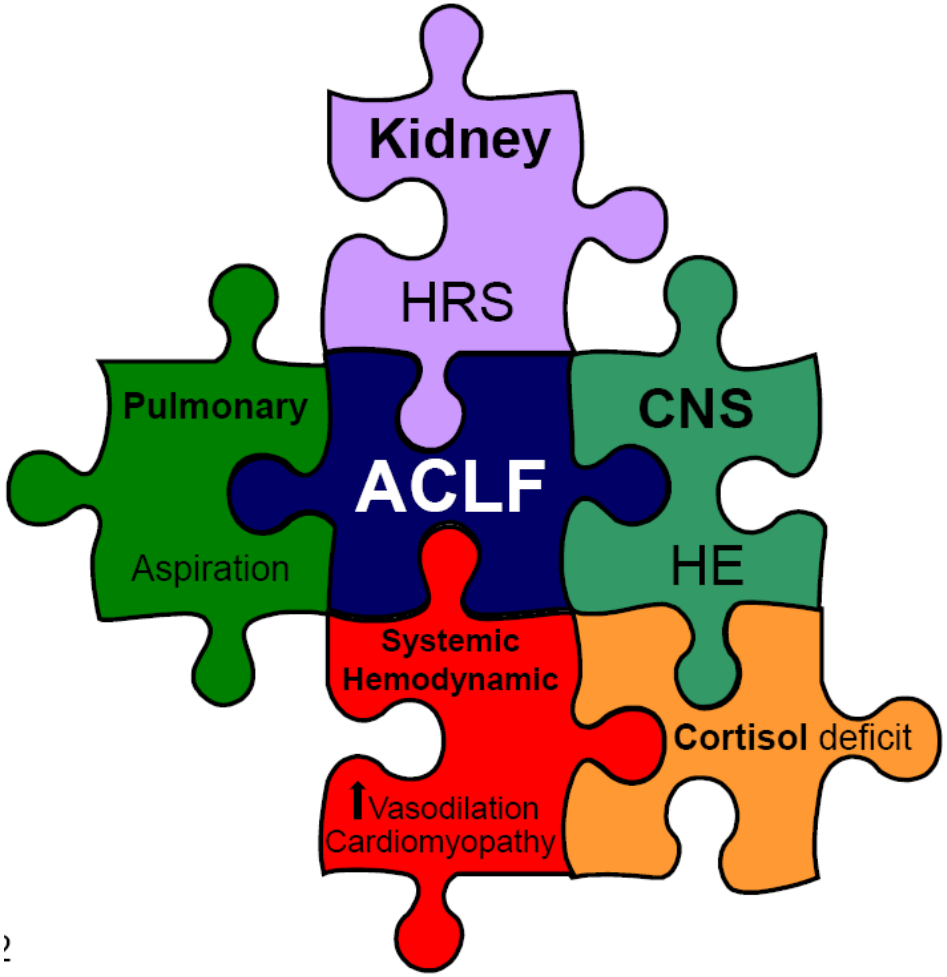
✧ It is commonly precipitated by an acute event (precipitating factor) and associated with failure in the function of extra-hepatic organs.

New classification of ACLF



Jalan et al., Gastroenterology 2014

The liver and other organs in ACLF



Vizzutti et al., Trends Anaest Crit Care 2013

Definition and grades of ACLF

ACLF grade	Definition
No	• No organ failure • Single organ failure (liver, coagulation, circulation, lungs) + creatinine <1.5 mg/dl + no hepatic encephalopathy • Single cerebral failure + creatinine <1.5 mg/dl
1	• Single kidney failure • Single organ failure (liver, coagulation, circulation, lungs) + creatinine 1.5-≤1.9 mg/dl and/or grade 1-2 hepatic encephalopathy • Single cerebral failure + creatinine 1.5-≤1.9 mg/dl
2	• 2 organ failures
3	• 3 organ failures or more

ACLF grade 1

Mortality: 30d: 22.1% - 90d: 40.7%

ACLF grade 2

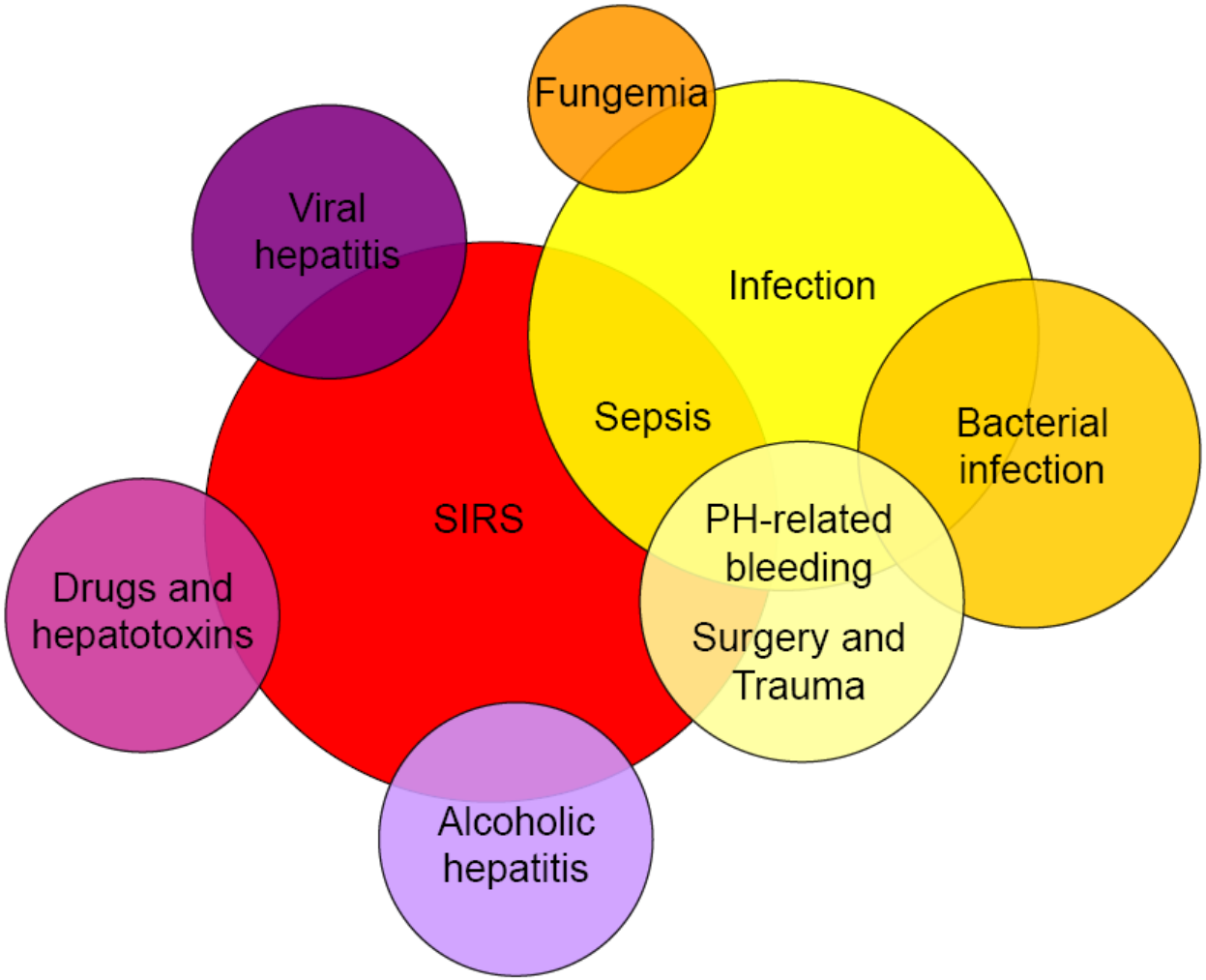
Mortality: 30d: 32.0% - 90d: 52.3%

ACLF grade 3

Mortality: 30d: 76.7% - 90d: 79.1%

Moreau et al., Gastroenterology 2013

Precipitating events in ACLF



Vizzutti et al., Trends Anaest Crit Care 2013


虫草
花旗参
虫草花
雪蛤
黄芪
红参片
白燕窝
元贝
鹿鞭
花旗参
血燕窝
花胶

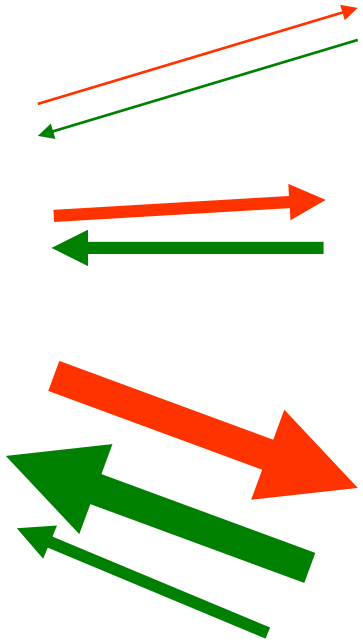
Infections in cirrhosis

- The incidence and severity of infection in cirrhosis is higher
- Infection with multiresistant organisms is common in cirrhosis
- The end-organ damaging effect of bacterial infection is greater, often culminating in acute-on-chronic liver failure
- Delays in the diagnosis and start of treatment results in higher mortality
- In patients with spontaneous bacterial peritonitis, the addition of albumin to antibiotics reduces mortality

“MISSIONE” DEL VALUE FOR MONEY:
massimizzare la salute che si può ottenere con il finanziamento a disposizione

costo

SVR



Freccia rossa = entità della spesa per quell’intervento

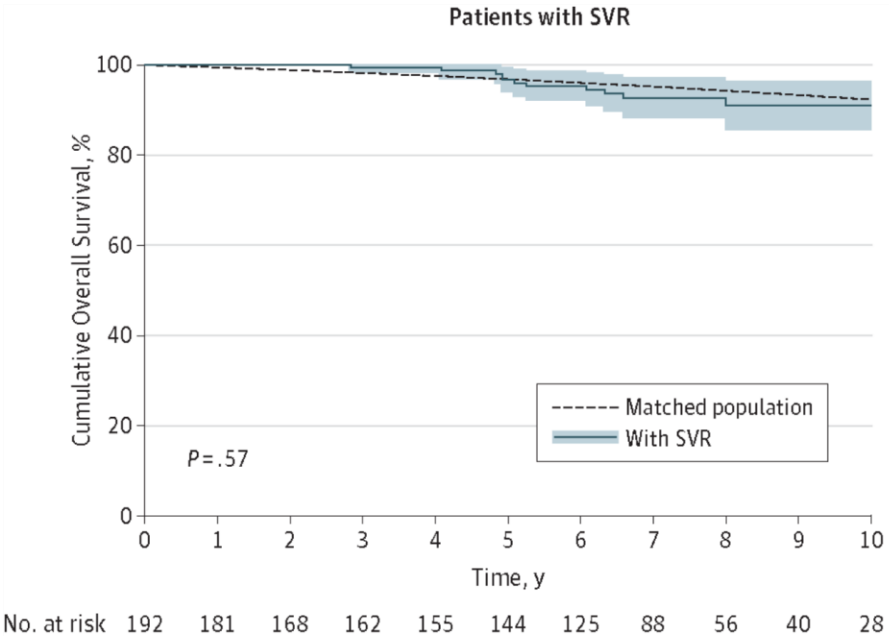
Freccia verde = quantità di salute acquistata o ritorno di salute

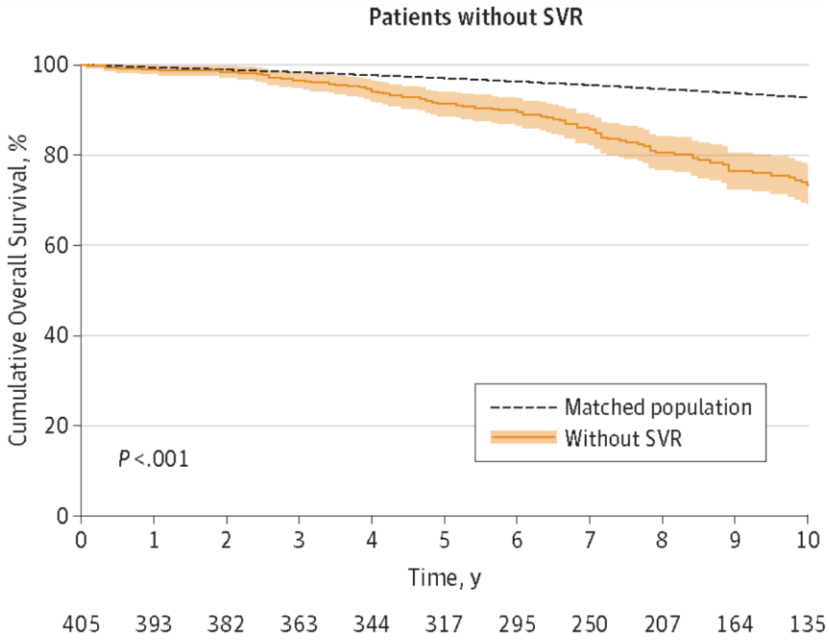
Guadagno di salute (miglioramento della salute) determinato dall’intervento sanitario

ANNI VITA GUADAGNATI

LYG - QALY

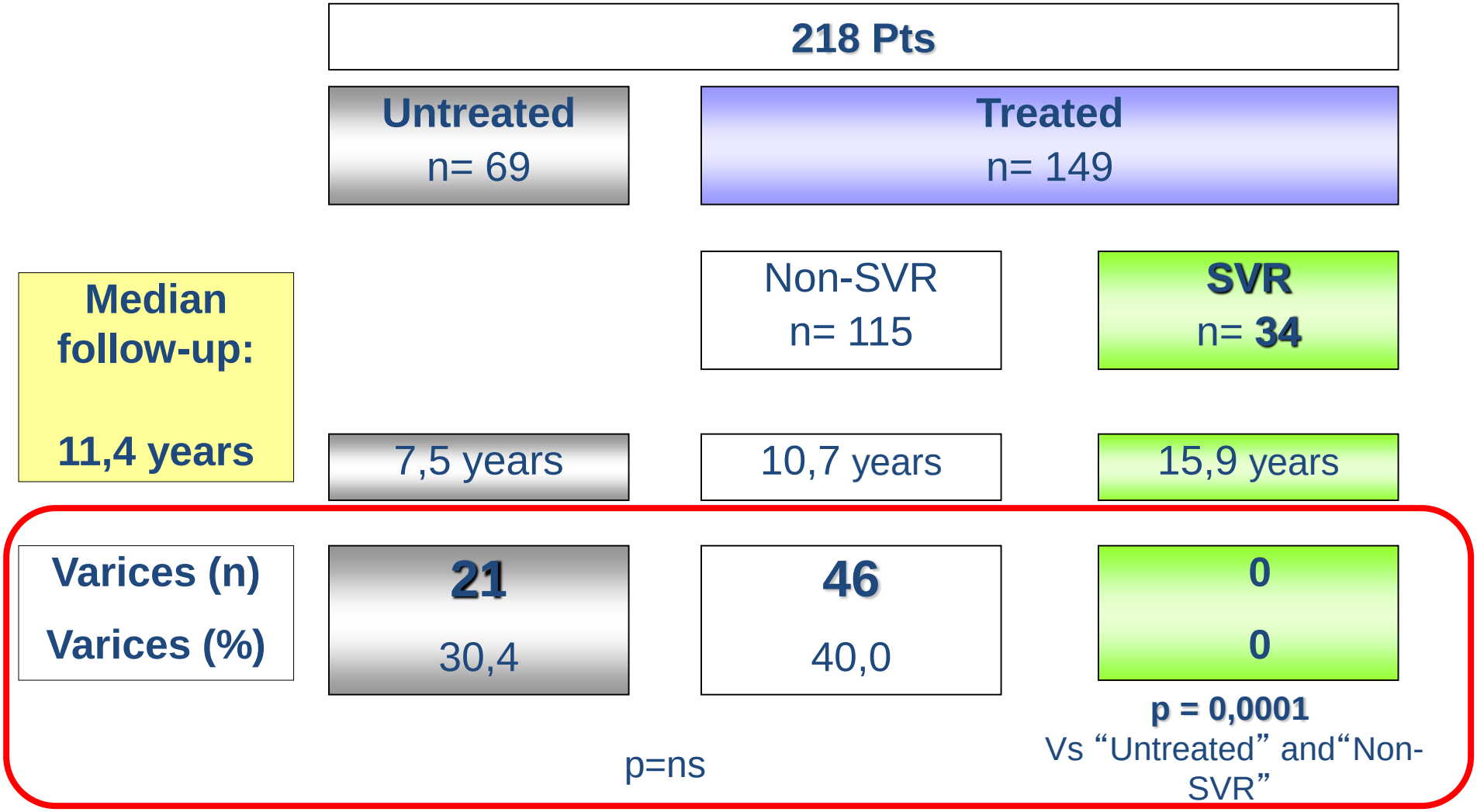
Impact of sustained virologic response in patients with advanced fibrosis





Van der Meer et al., JAMA 2014

SVR prevents de-novo development of esophageal varices in compensated HCV cirrhosis



Bruno et al., Hepatology 2010

BAVENO VI

Changing scenarios: Impact of etiological therapy for cirrhosis (including antiviral treatment for HBV and HCV infections) and of anti-fibrotic therapy on portal hypertension

DRAFT CONSENSUS STATEMENTS

Etiological treatment of underlying liver disease may reduce portal hypertension and prevents complications in patients with established cirrhosis (A1).

A case of HCV-related cirrhosis

2006
A.Z, male, age 65
Diagnosed with compensated HCV-related cirrhosis
Starts IFN/Ribavirin → SVR

2010
Persistently normal liver panel. Discharged from active follow-up

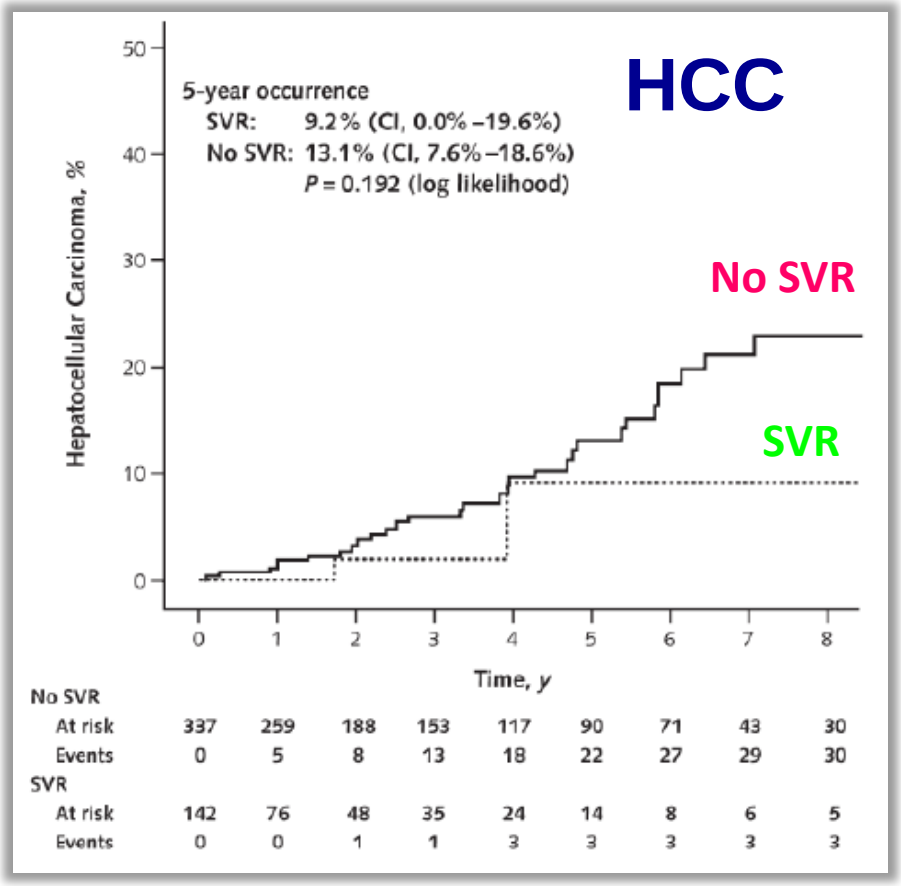
2014
Admitted to the ER for RUQ pain → HCC nodule of S4, 5 cm
CPS A5. Undergoes resective surgery

2015
Early HCC relapse. Starts sorafenib
Deceased after 2 months on sorafenib

Annals of Internal Medicine | ARTICLE

Sustained Virologic Response and Clinical Outcomes in Patients with Chronic Hepatitis C and Advanced Fibrosis

Bart J. Veldt, MD; E. Jenny Heathcote, MD; Heiner Wedemeyer, MD; Juerg Reichen, MD; W. Peter Hofmann, MD; Stefan Zeuzem, MD; Michael P. Manns, MD; Bettina E. Hansen, MSc; Solko W. Schalm, MD, PhD; and Harry L.A. Janssen, MD, PhD



Surveillance should be continued

DAA (commercial name), dose	Category	Dose adjustment in liver or renal impairment	Antiviral activity
Sofosbuvir (Sovaldi®), tablet 400 mg, once daily	NUC NS5B polymerase inhibitor	No change in hepatic impairment Contraindicatedin patients with GFR < 30 mL/min	Genotypes 1-6, High genetic barrier
Simeprevir (Olysio®), tablet 150 mg, once daily with food	NS3/4A protease inhibitor	Contraindicated in Child class C No change in renal impairment	Genotypes 1, 4, Low genetic barrier
Daclatasvir (Daklinza®), tablet 60 mg, once daily	NS5A inhibitor	No change in liver or renal impairment	Genotypes 1,3,4, Low genetic barrier
Ledipasvir/Sofosbuvir/ (Harvoni®), tablet 90/400 mg, once daily	NUC NS5B polymerase inhibitor + NS5A Inhibitor	No change in hepatic impairment Contraindicated in patients with GFR < 30 mL/min	Genotypes 1,3,4, High genetic barrier
Paritaprevir/Ritonavir/ Ombitasvir (Viekirax®), tablet 75/50/12.5 mg, x 2 once daily with food	Ritonavir boosted NS3/4A protease inhibitor/NS5A inhibitor	No safety and efficacy data in Child class B, Contraindicated in Child class C No change in renal dysfunction	Genotypes 1, 4, Genetic barrier depending on HCV genotype
Dasabuvir (Exviera®), tablet 250 mg, every 12 h	Non-NUC NS5B polymerase inhibitor		Genotype 1, Low genetic barrier

NUC: Nucleos(t)ide analogue; CNI: Calcineurin inhibitor.

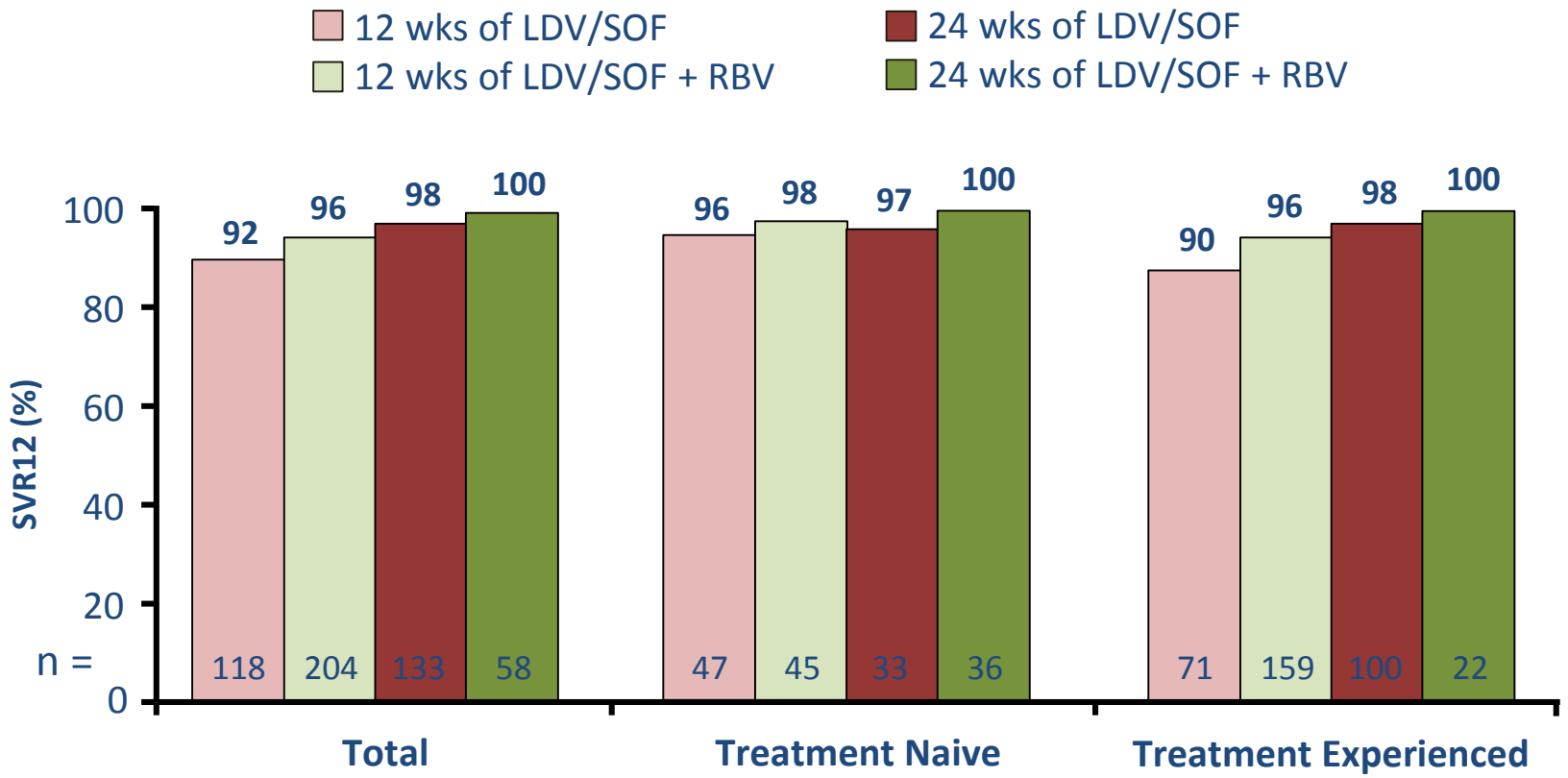
Cholongitas et al., World J Gastroenterol 2015

Treatment of HCV in cirrhosis

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

EASL guidelines, 2015

Ledipasvir/sofosbuvir in compensated Gt1 cirrhosis



Treatment of patients with decompensated cirrhosis with and without an indication for OLT

	GT-1	GT-2	GT-3	GT-4	GT-5	GT-6
SOF + RBV 12 weeks	-	✓	-	-	-	-
SOF/LDV (FDC) + RBV 12 weeks	✓	-	-	✓	✓	✓
DCV + SOF + RBV 12 weeks	✓	✓	✓	✓	✓	✓

EASL guidelines 2015

SVR in patients with compensated and decompensated Gt 1 cirrhosis

	Duration (weeks)	SVR (Compensated)	SVR (Decompensated)
SOF + PEG-IFN + RBV	12–24	81%	43%
SOF + RBV	24–48	36–78%	68% (CTP B)
SOF + SMV	12–24	86–100%	7/7 (CTP B) 79%
SOF + DCV ± RBV	12- 24	94-100%	60-86%
PTV/RTV OMV + DSV ± RBV	12–24	89–100%	No data
SOF LDV ±RBV	12–24	86–100%	60–90%

A case of HBV-related cirrhosis

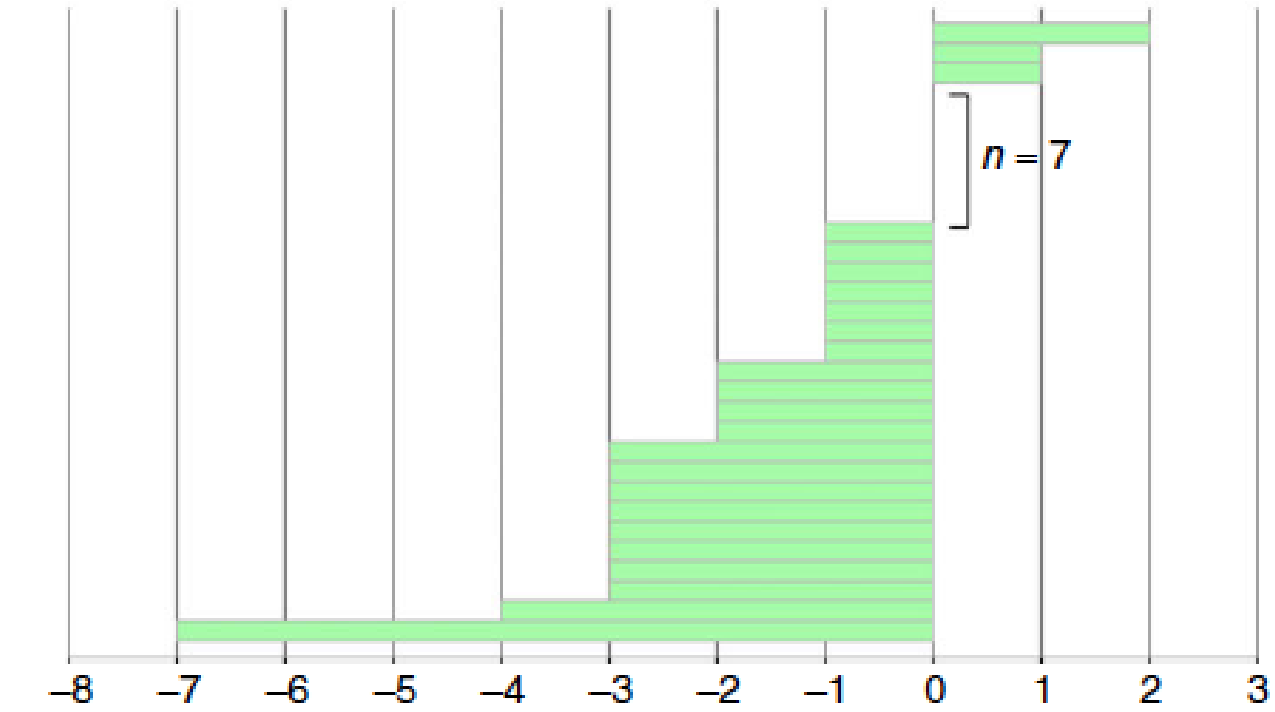
2002
G.S., female, age 51
Admitted for hepatic decompensation, CPS C11, MELD18
Evaluated for OLT at Padova → enlisted for transplantation
Starts lamivudine administration

2005
CPS A5, MELD10
Withdrawn from the OLT waiting list

2015
Still on lamivudine
Compensated cirrhosis
Continues with HCC surveillance at 6-month intervals

MELD changes after DAA treatment

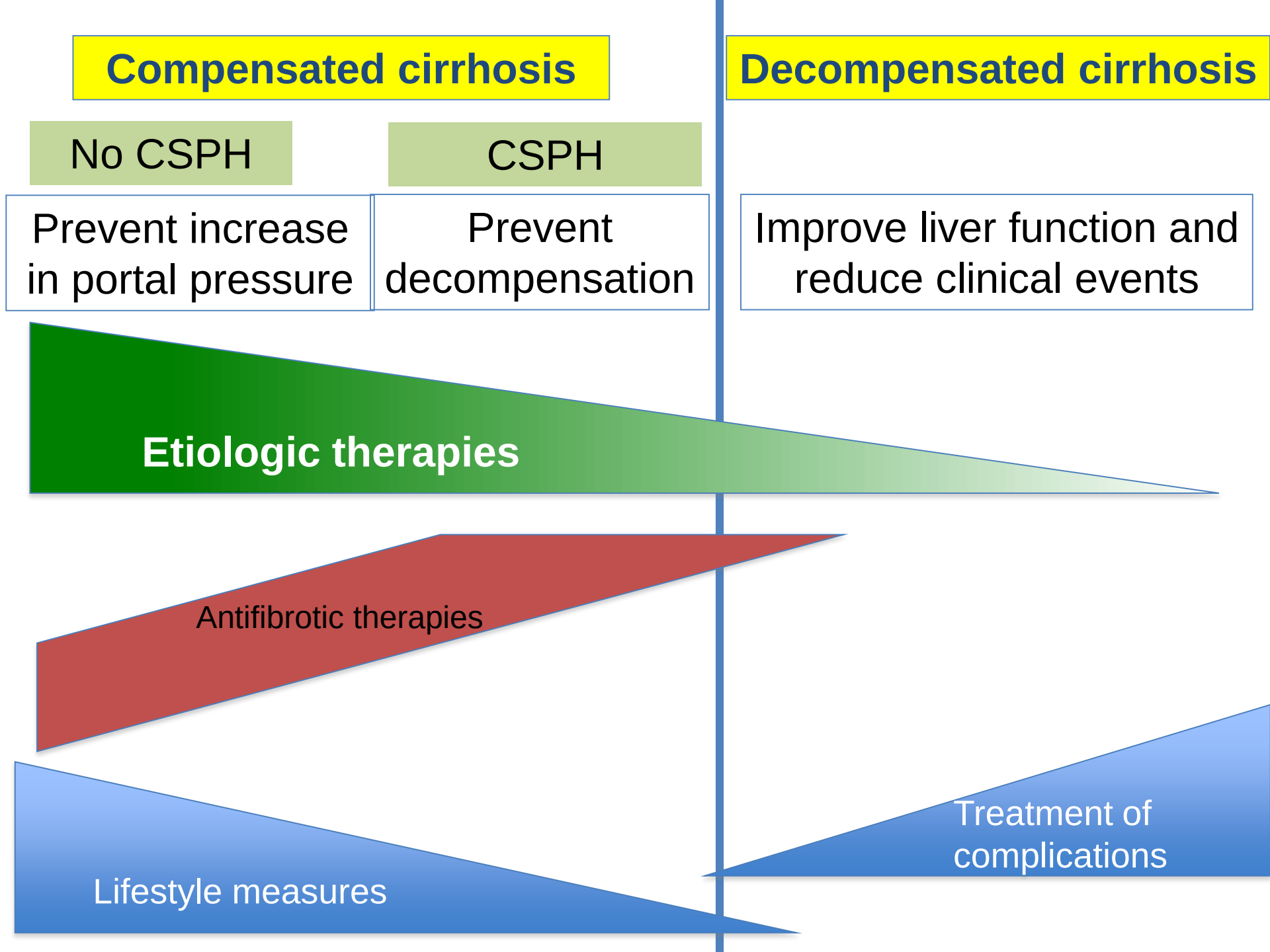
Patients with Child B/C (n = 31)
MELD Score was not available for 3 Child B patients at FU12



* including relapse patients documented at the timepoint of relapse

HCV RNA relapse led to moderate ALT increases but was not associated with hepatic decompensations.

Dieterding et al., APT 2015


Compensated cirrhosis
Decompensated cirrhosis
No CSPH
CSPH
Prevent increase in portal pressure
Prevent decompensation
Improve liver function and reduce clinical events
Etiologic therapies
Antifibrotic therapies
Lifestyle measures
Treatment of complications

Concluding remarks

• Cirrhosis includes several stages and is associated with different clinical pictures

• Patients with compensated or decompensated cirrhosis can be successfully treated with interferon/(ribavirin) - free regimens. However, viral eradication does not mean cure of cirrhosis

• Viral eradication can be achieved in most patients in the waiting list for liver transplantation, but the timing of antiviral therapy in cirrhosis Child-Pugh stage C is a matter of debate

• The impact of novel treatment in patients with advanced or decompensated cirrhosis needs to be assessed

Obituary

EASL JOURNAL OF HEPATOLOGY

Professor Paolo Gentilini, MD (1930–2015)

Paolo Gentilini
(1930–2015)

Professor Paolo Gentilini, Emeritus Professor of Medicine at the University of Florence, Italy, passed away on June 28 2015 at age 85. He was one of the key founders of Italian and International Hepatology and Gastroenterology. Professor Gentilini's scientific activity was focused on the complications of cirrhosis and particularly on the derangement of renal function. In 1990, he founded the International Ascites Club, an informal organisation that has provided key advancements and treatment guidelines. In 1991 he was nominated adjunct Professor of Medicine at Tufts University, Boston, MA, USA. Professor Gentilini allowed us to understand how honesty, sharing and team-work are the key elements to achieve success in research and in clinical medicine. Upon his retirement in 2005, his group had developed internationally renowned excellence in almost all the key areas of Hepatology. He has trained a generation of Italian hepatologists and gastroenterologists who now hold leadership positions worldwide. We are very grateful about his mentorship and career guidance. Announcing his death makes us very sad but also proud to be able to continue our work following his spirit.

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Fabio Cominelli
Division of Gastroenterology, Case Western Reserve University, Cleveland, OH, USA

On behalf of Professor Gentilini's fellows.