

9th LIVER INTEREST GROUP Annual Meeting

Best of EASL : Johannesburg

Saturday 24 November 2018

Radisson Blue Gautrain Hotel



Portal Hypertension: From Early Cirrhosis to Decompensated Liver Disease

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Causes of Portal Hypertension

Pre-hepatic

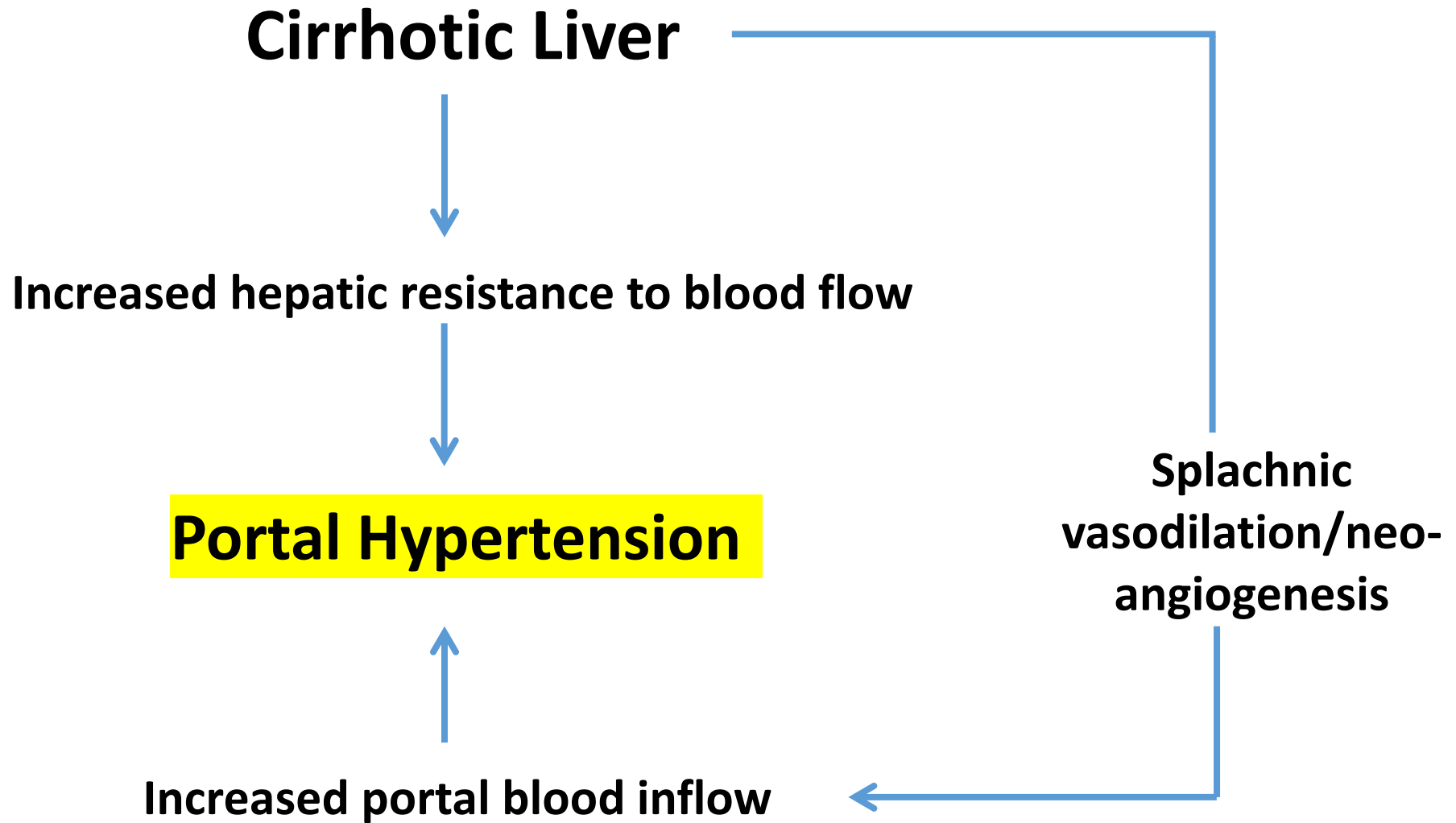
- ⌚ Portal vein thrombosis
- ⌚ Splenic vein thrombosis
- ⌚ Massive splenomegaly

Hepatic

- ⌚ Pre-sinusoidal
 - Schistosomiasis
 - Congenital hepatic fibrosis
- ⌚ Sinusoidal
 - Cirrhosis
 - Alcoholic hepatitis
- ⌚ Post-sinusoidal
 - Hepatic sinusoidal obstruction

Post-hepatic

- ⌚ Budd-Chiari syndrome
- ⌚ Inferior vena caval webs
- ⌚ Cardiac causes
 - Restrictive cardiomyopathy
 - Constrictive pericarditis
 - Severe congestive heart failure



Increased Intrahepatic Resistance in Cirrhosis

Architectural disturbances

Distortion of vascular architecture by fibrosis, scarring, regenerative nodules.
Thrombosis

Mechanical Component
("fixed")

~70 %

Functional alterations

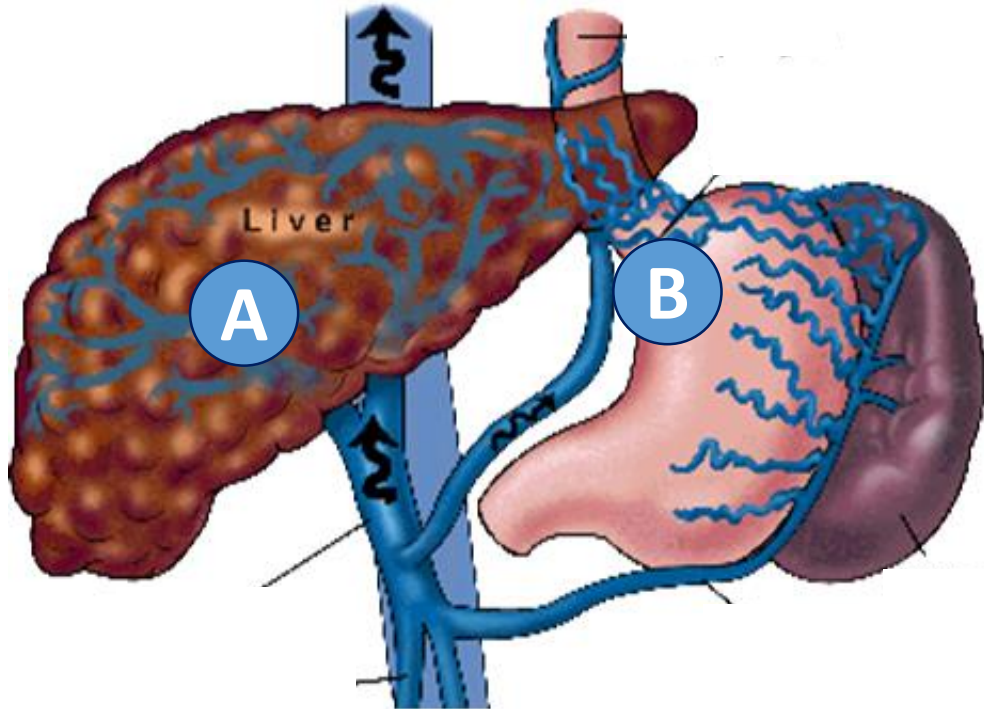
Active contraction of hepatic stellate cells, vascular smooth cells in the portal venules, and myofibroblasts

Dynamic Component
(modifiable by drugs)

~30 %

Vascular Network in Cirrhosis & Portal Hypertension

Portal Venous System



A

Increased intrahepatic resistance

- Sinusoidal vasoconstriction
- Mechanical compression: fibrosis
- Impaired sinusoidal flow, microthrombosis

B

Collateral Circulation

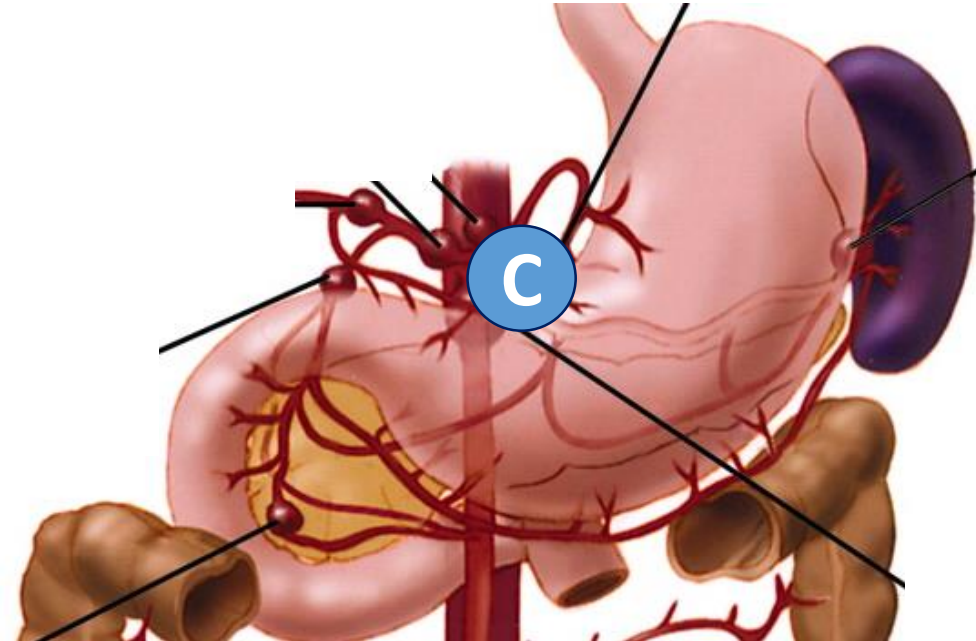
- PHT GI Bleeding
- Portosystemic Shunting

C

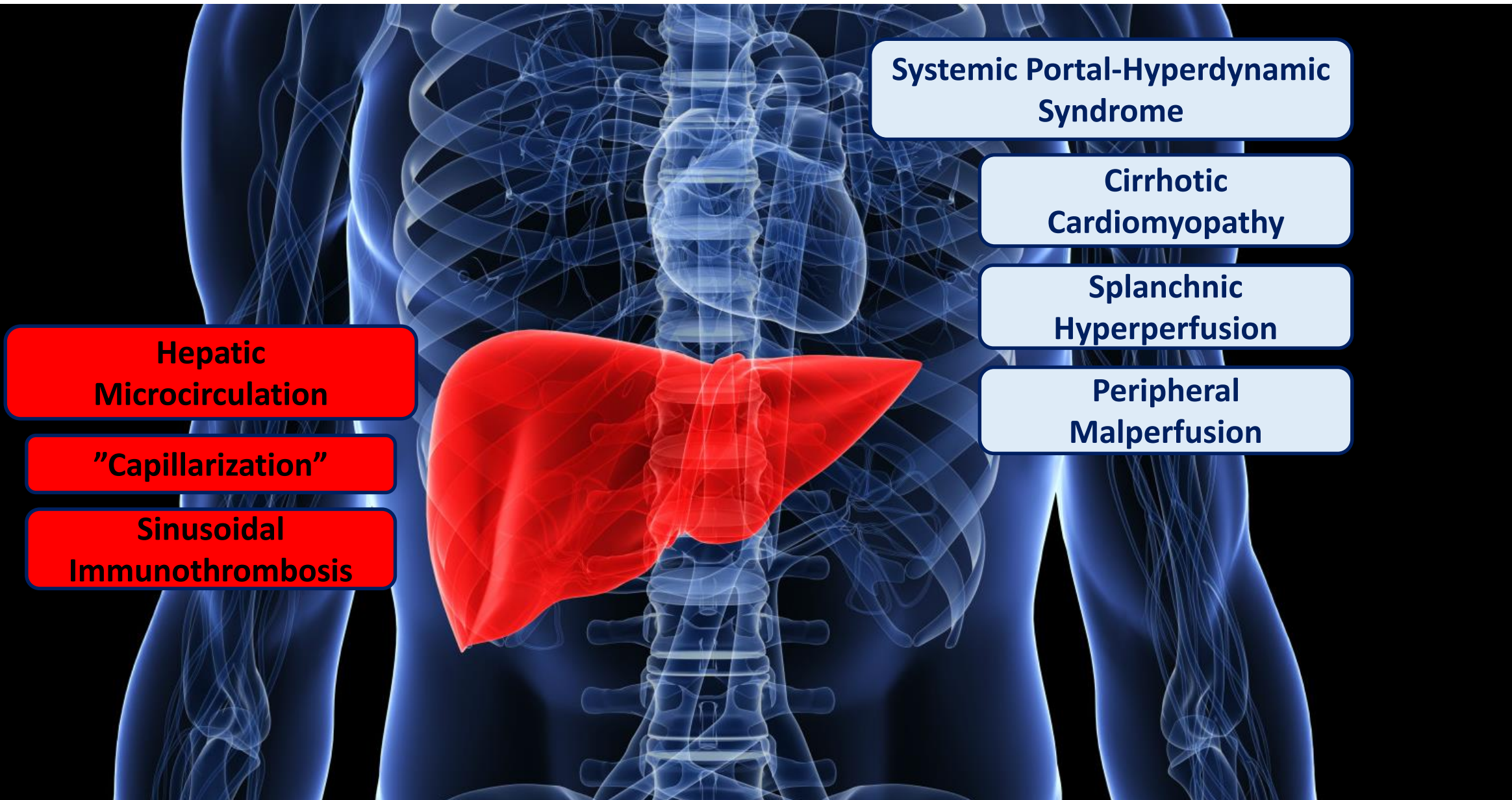
Increased Splanchnic Inflow

- Mesenteric vasodilation

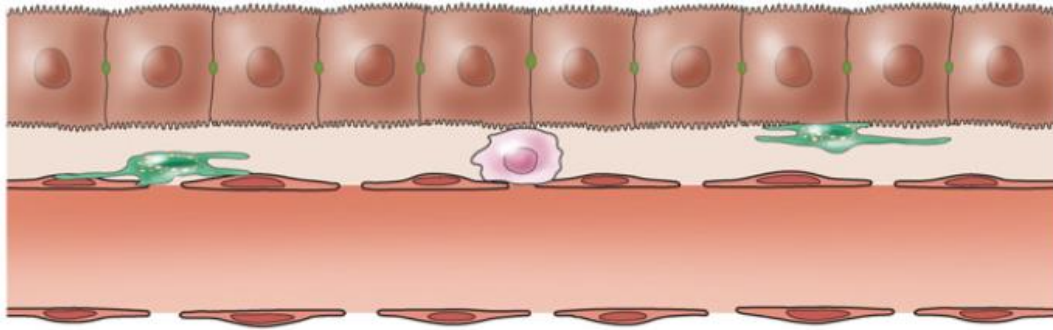
Splanchnic (Arterial) Vasculature



Vascular Implications of Liver Cirrhosis



Sinusoidal remodeling: the abnormal vascular niche in cirrhosis



Healthy Liver



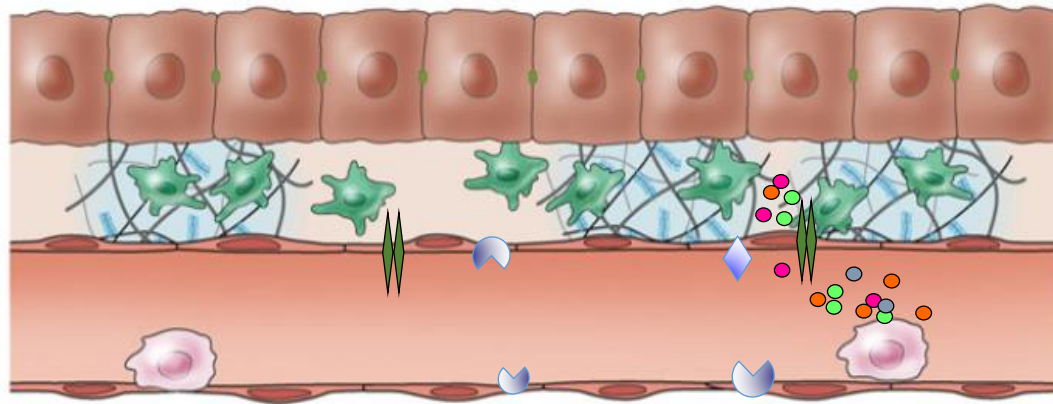
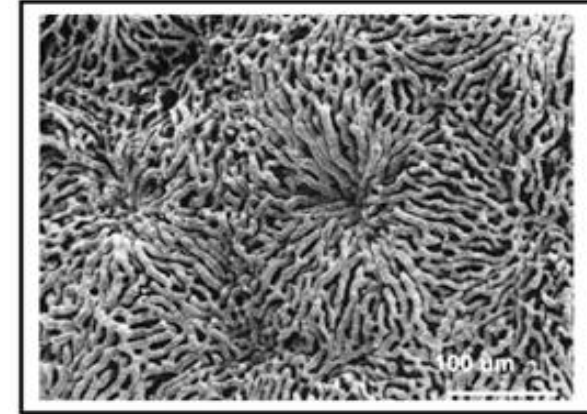
Kupffer Cells



Quiescent Hepatic Stellate Cell (HSC)



Fenestrated / discontinuous LSECs



Liver Cirrhosis



Activated HSCs → Myofibroblasts
Extracellular Matrix Deposition

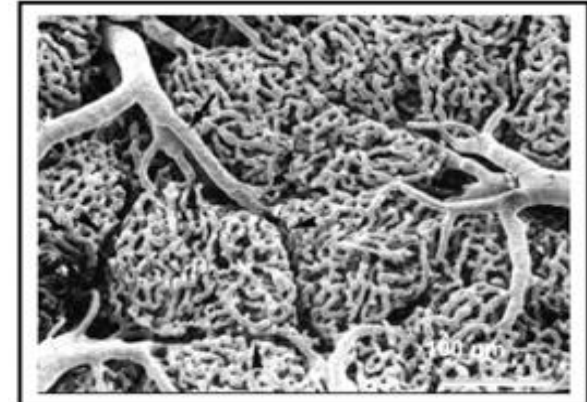


Inflammatory Cells / Kupffer Cells



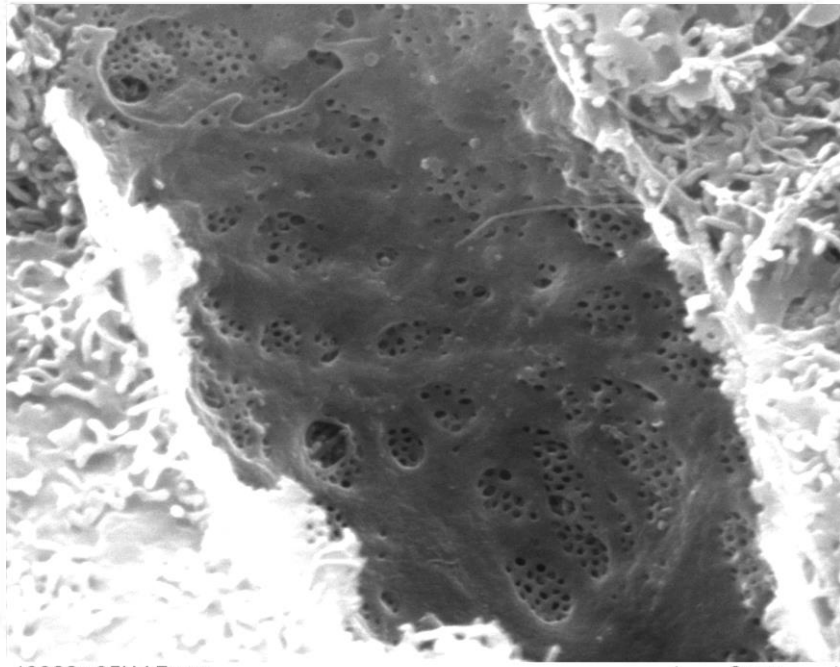
Tyrosine Kinases, Angiocrine

Nonfenestrated, continuous LSECs



Sinusoidal remodeling: the abnormal vascular niche in cirrhosis

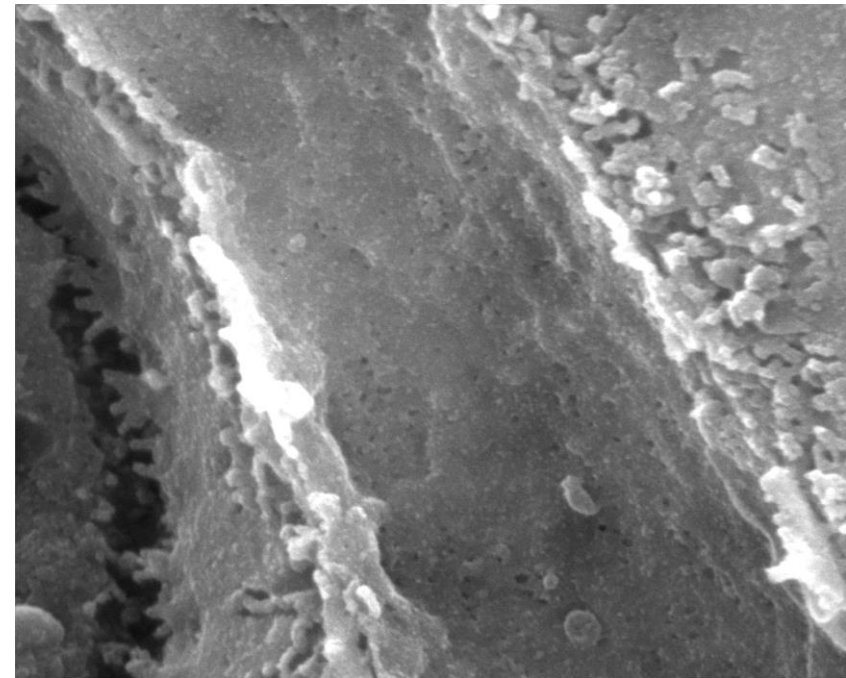
Normal liver



12300x 25kV 7mm

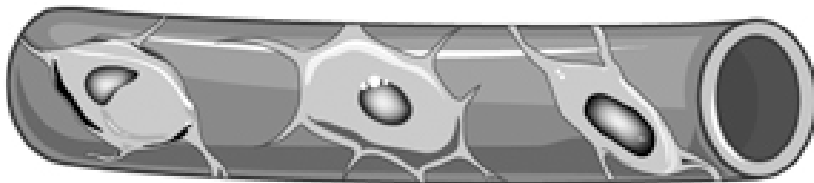
2 µm

Cirrhotic liver



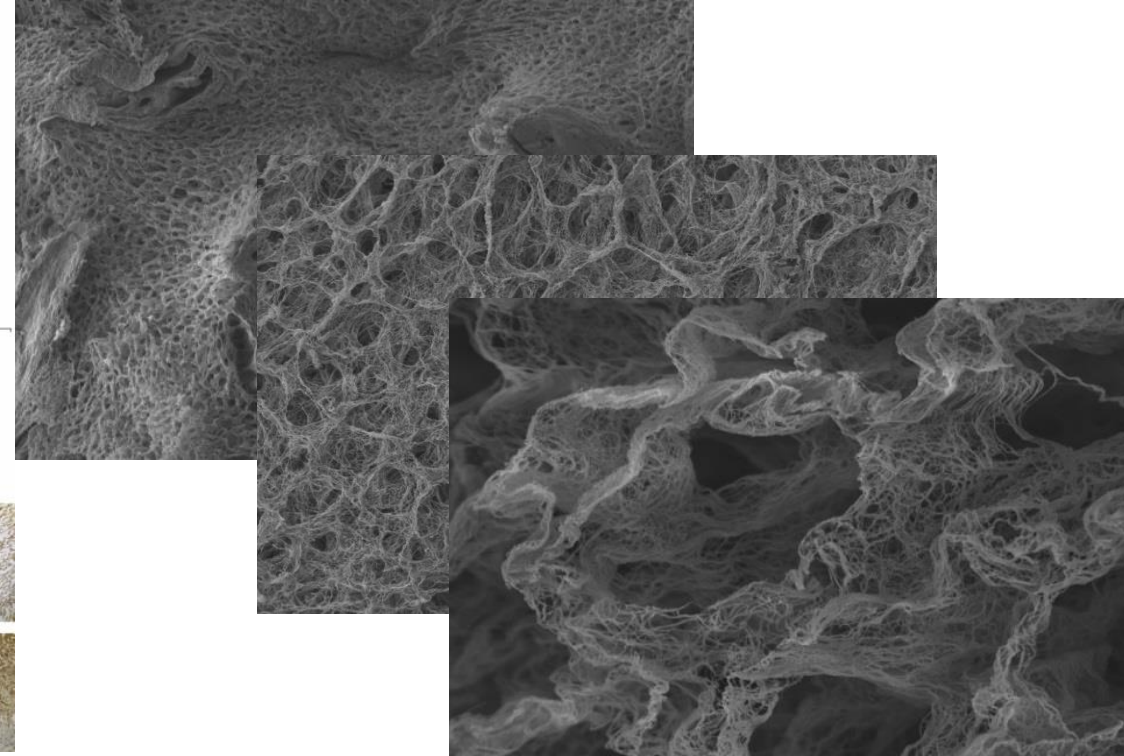
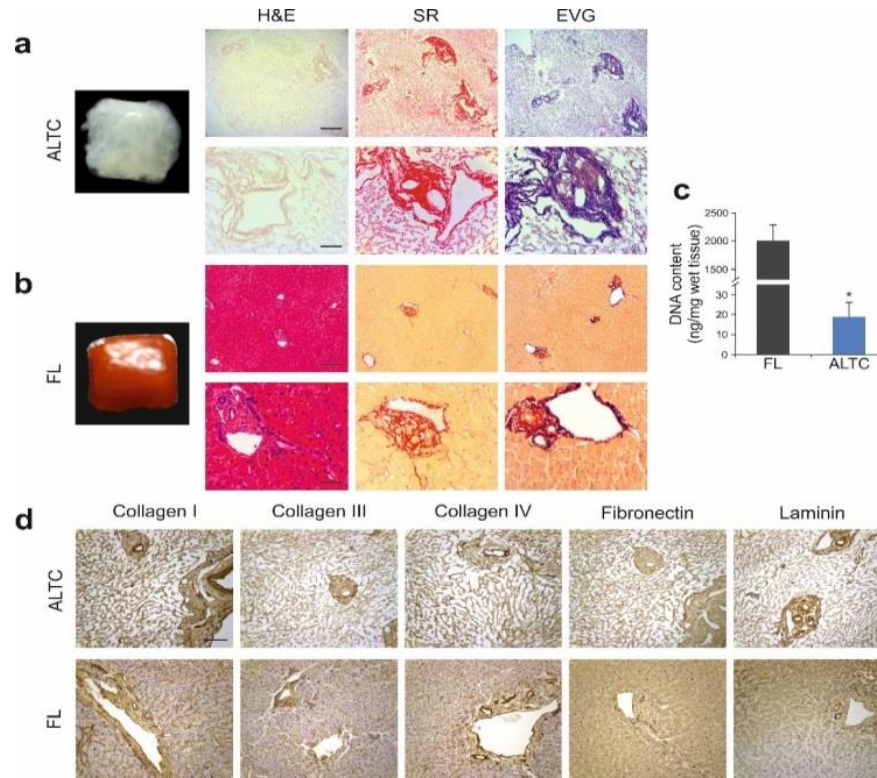
14700x 25kV 5mm

2 µm

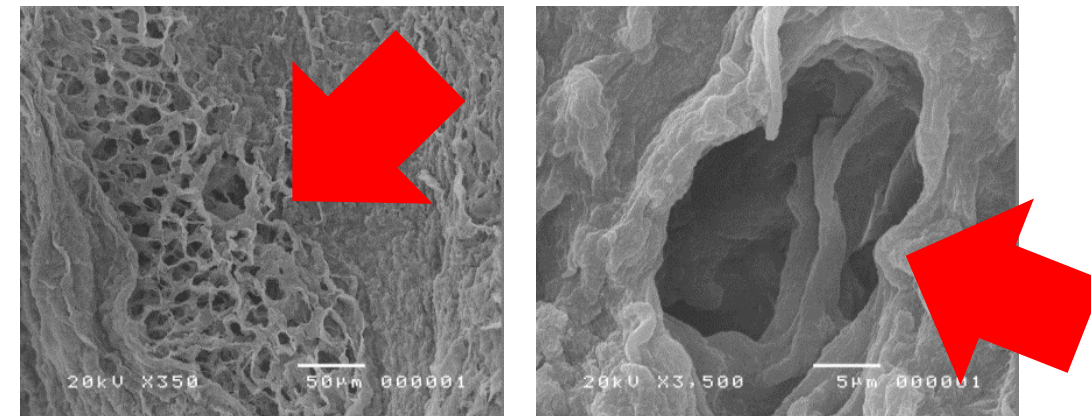
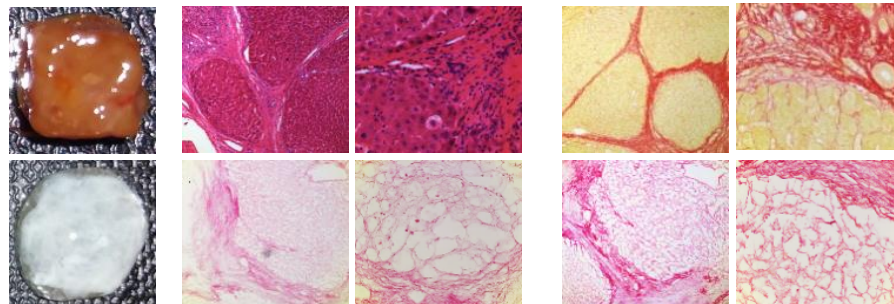


3D Human Healthy and Fibrotic Liver ECM

Donor healthy human liver



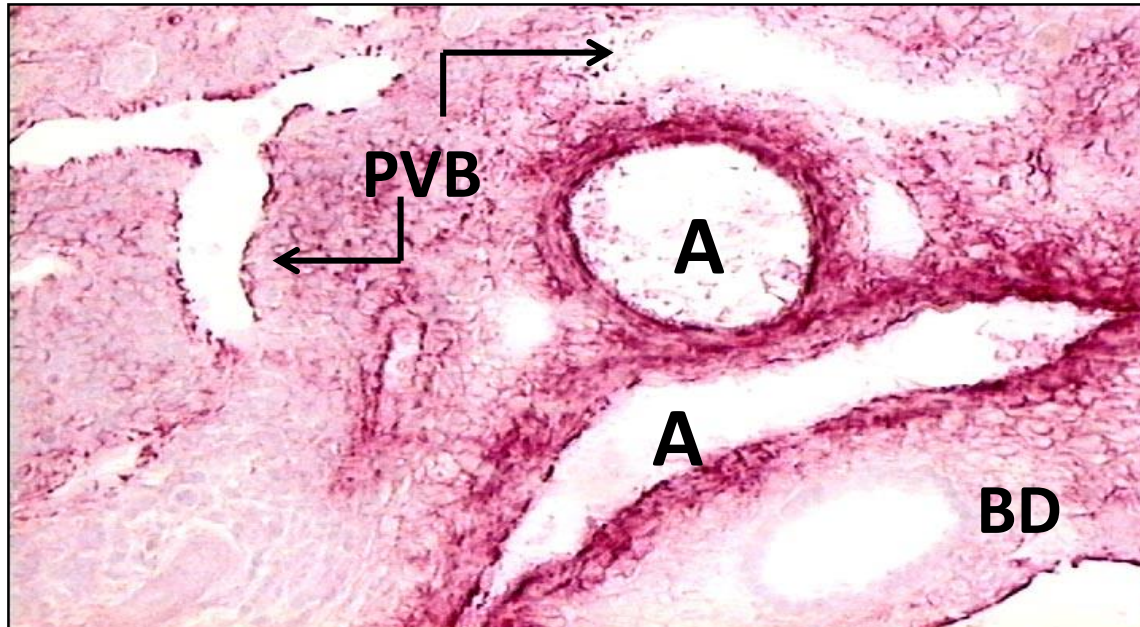
Explanted cirrhotic liver



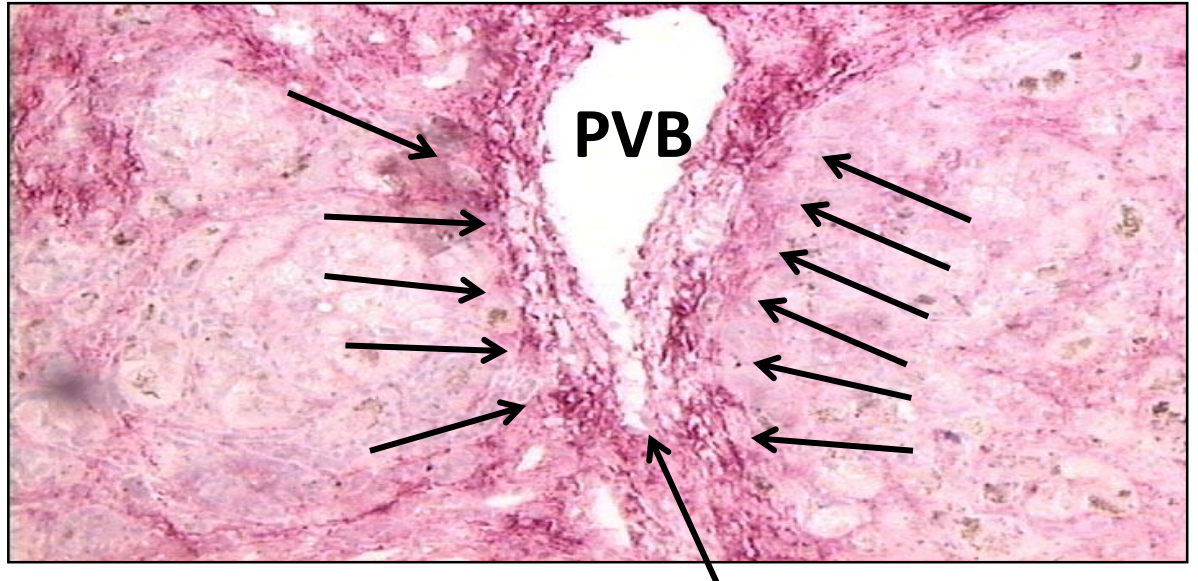
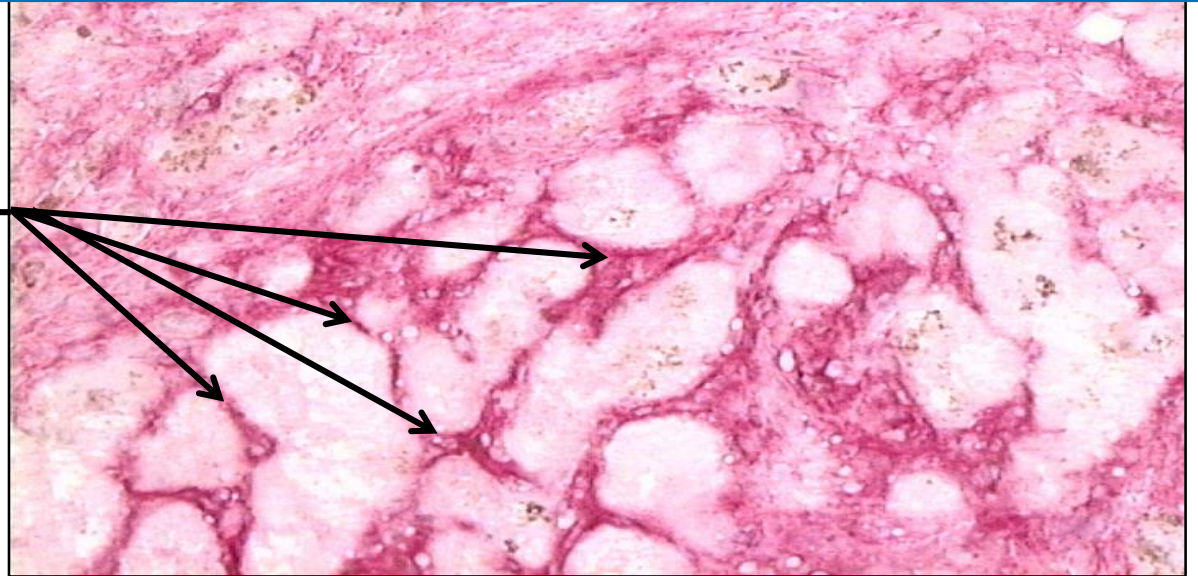
Contractile Cells in Cirrhotic Angio-architecture

IHC: α -SMA

Sinusoids

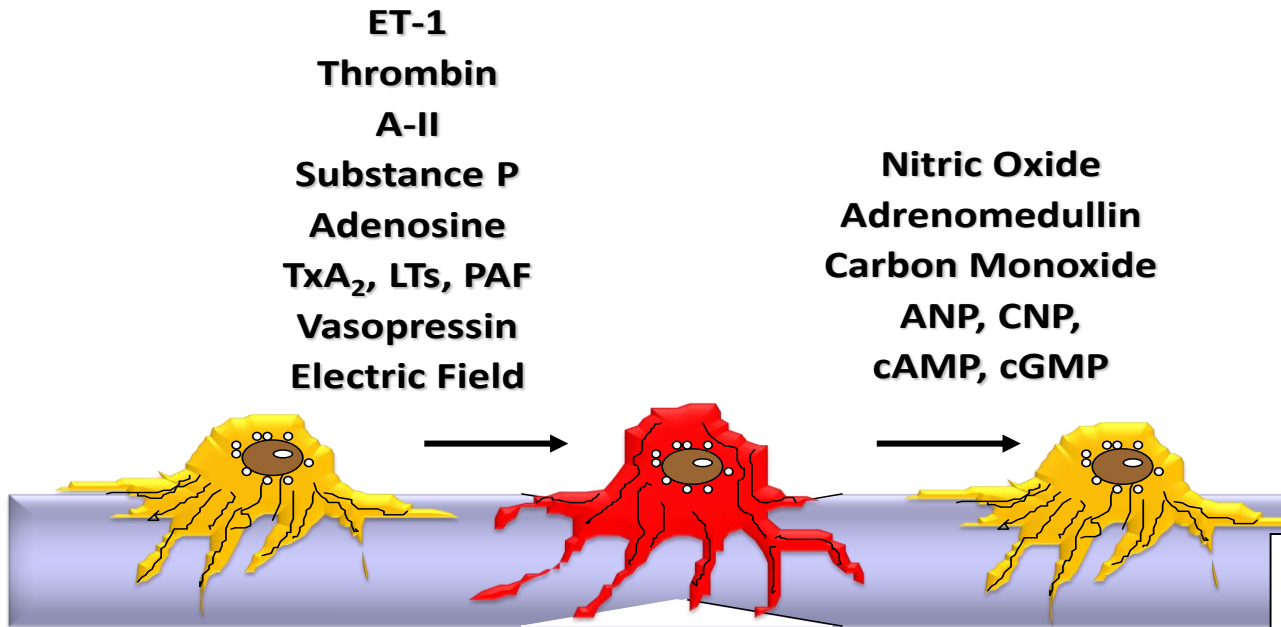


Fibrous Septum



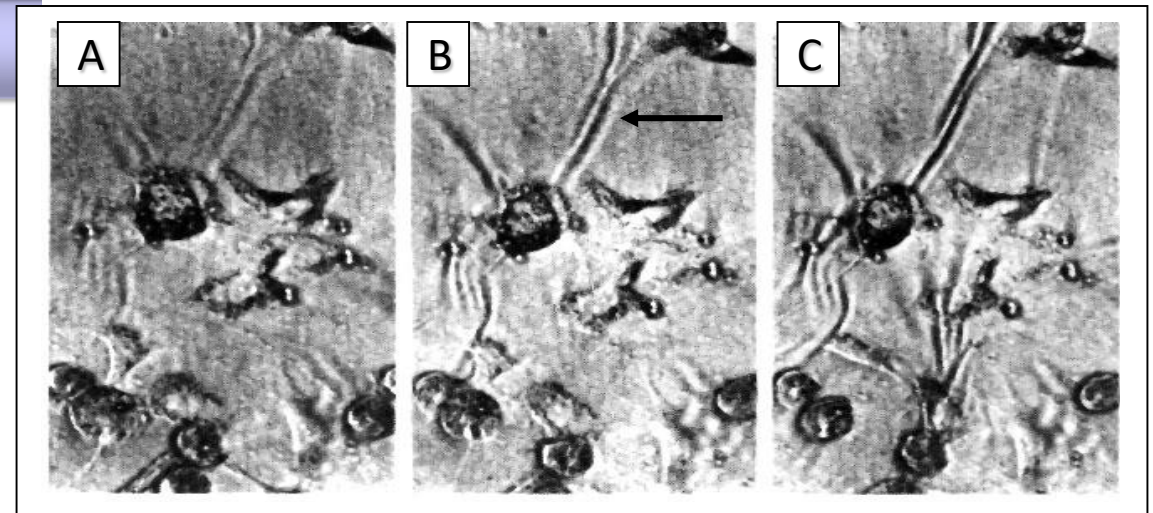
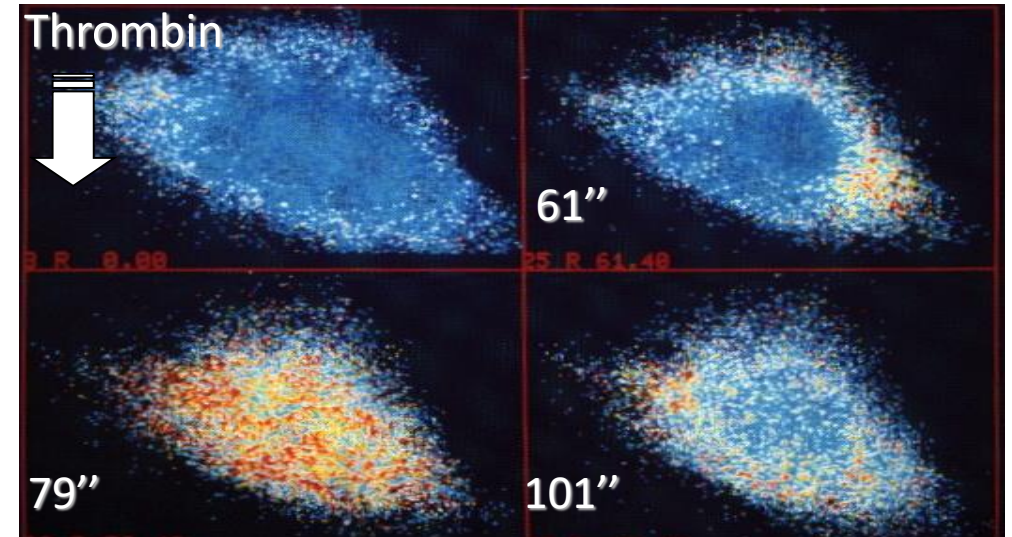
Contractile Features of Activated HSC

Actions of Vasoactive Agonists on HSC



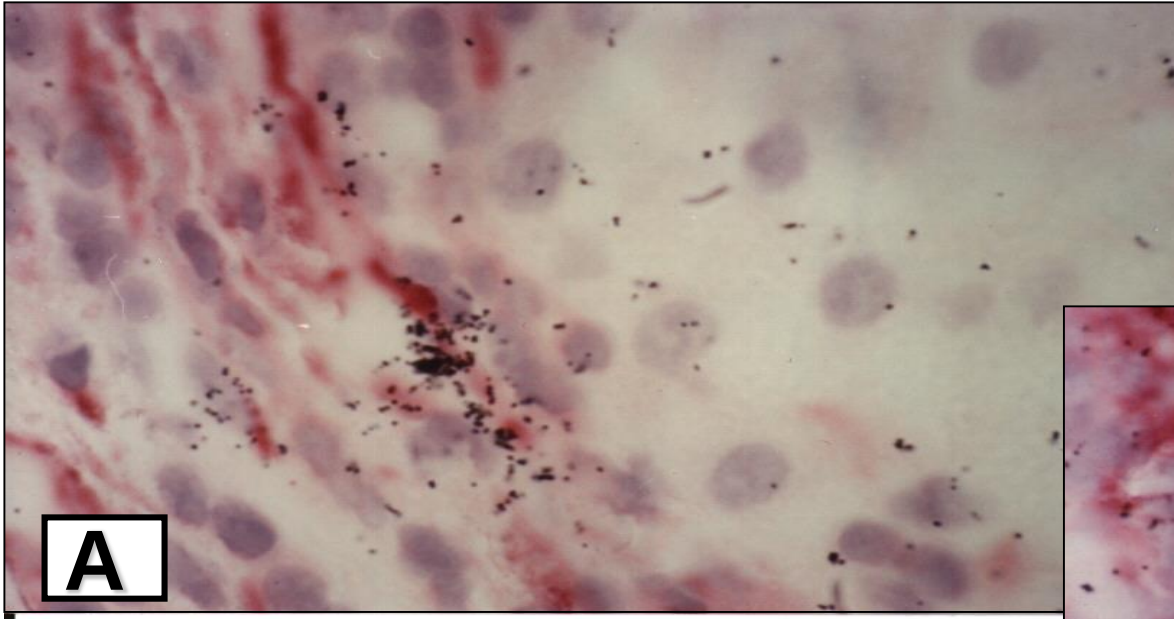
Kawada et al., Biochem J. 1992; 285:367-371

Pinzani M. et al. J.Clin.Invest. 1992;90:642-646

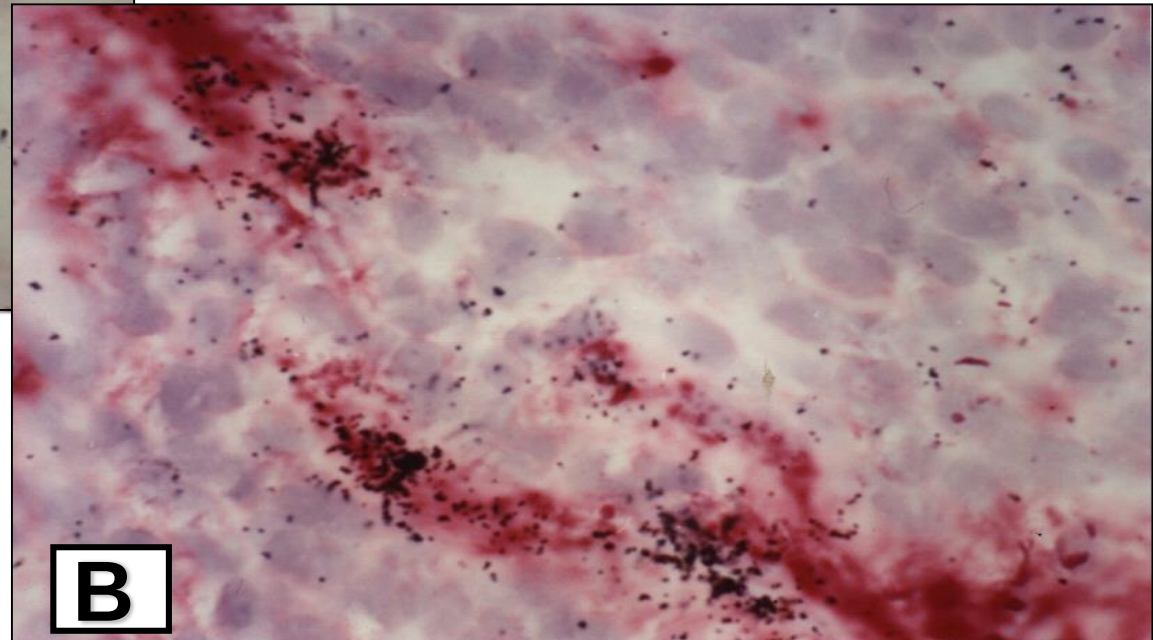


Expression and Distribution of Pre-pro ET-1 mRNA in Human Cirrhotic Liver

Pinzani M. et al., Gastroenterology 1996; 110:534-548

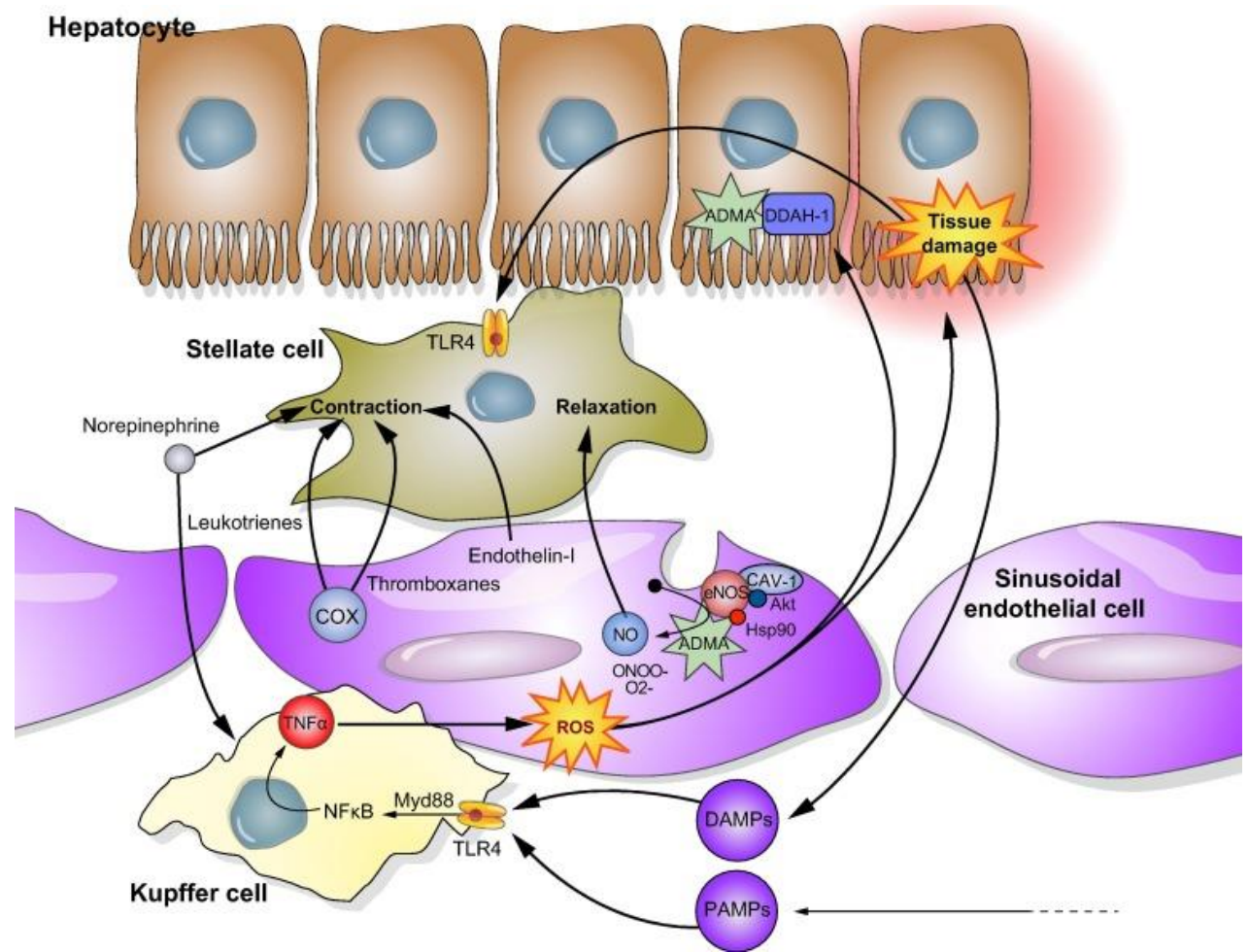
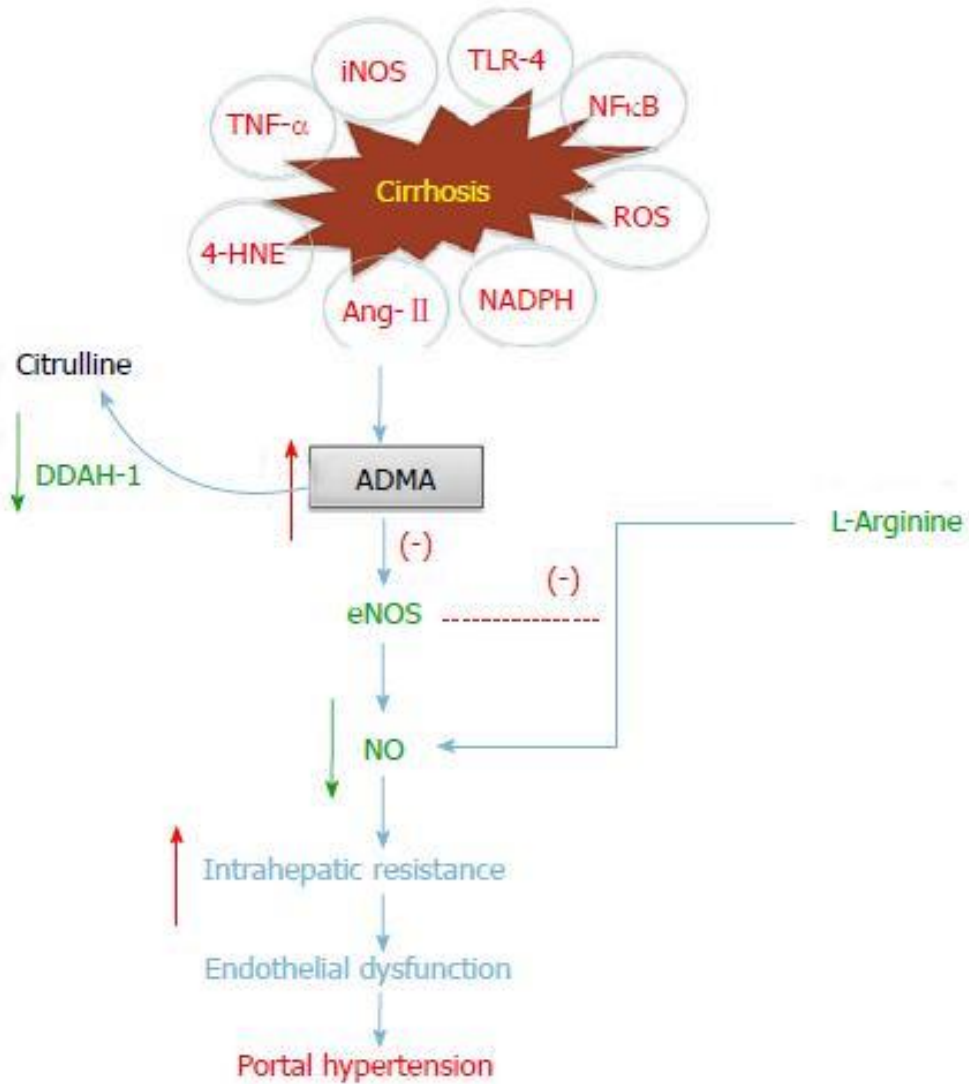


Co-distribution with **FVIII-positive** cells: **activated sinusoidal endothelial cells**



↑ Co-distribution with **α -SMA-positive** cells: **activated hepatic stellate cells**

Endothelial Dysfunction in Cirrhosis



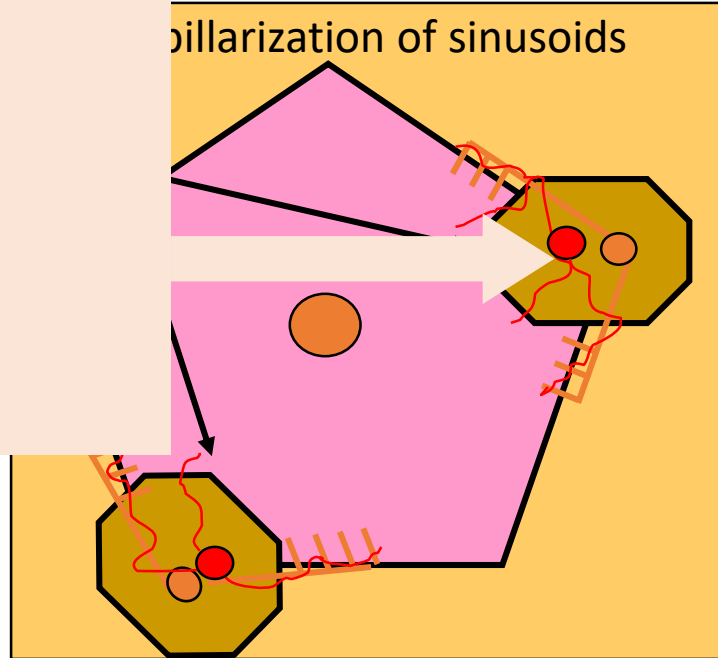
Fibrogenesis and Portal Hypertension

PORTAL TRACT

- 1.- Thickening of portal vein branches
- 2.- Increased diameter of hepatic artery branches
- 3.- **ARTERIALIZATION**

Portal tract expansion and fibrosis

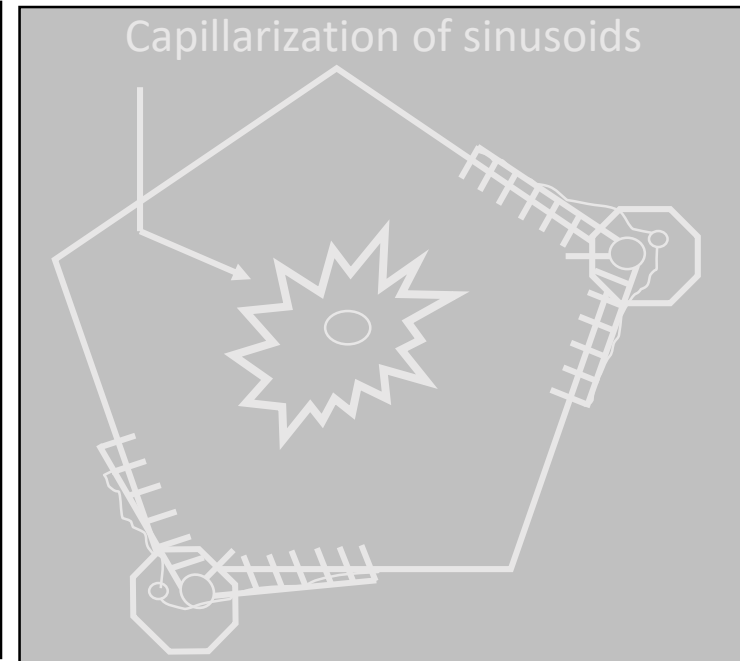
Capillarization of sinusoids



e.g. : chronic viral hepatitis, autoimmune, PBC, PSC

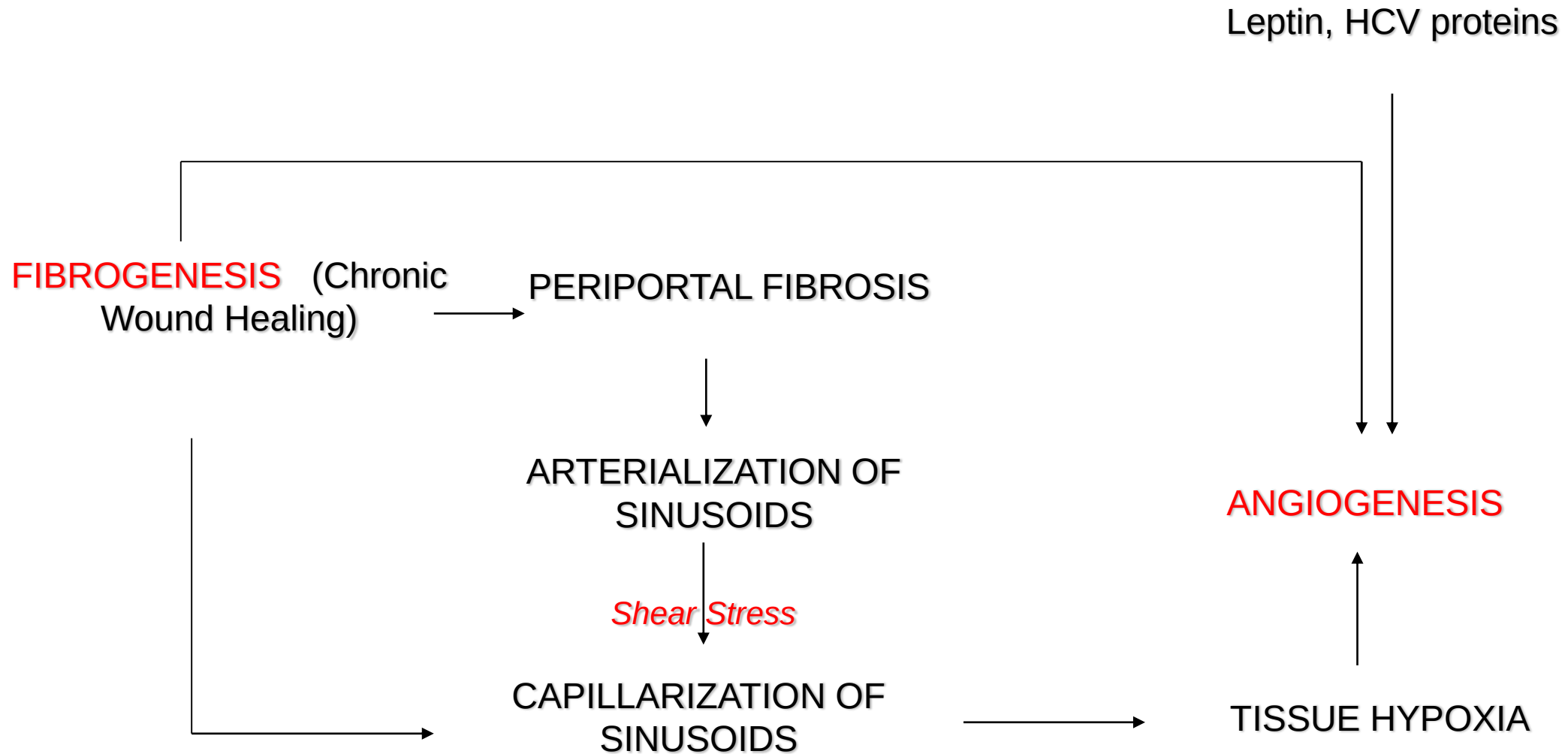
Pericentral fibrosis

Capillarization of sinusoids



e.g. : chronic alcoholic hepatitis, steatohepatitis

Fibrogenesis and Angiogenesis in CLDs



Why progressive liver fibrosis is associate with tissue hypoxia?

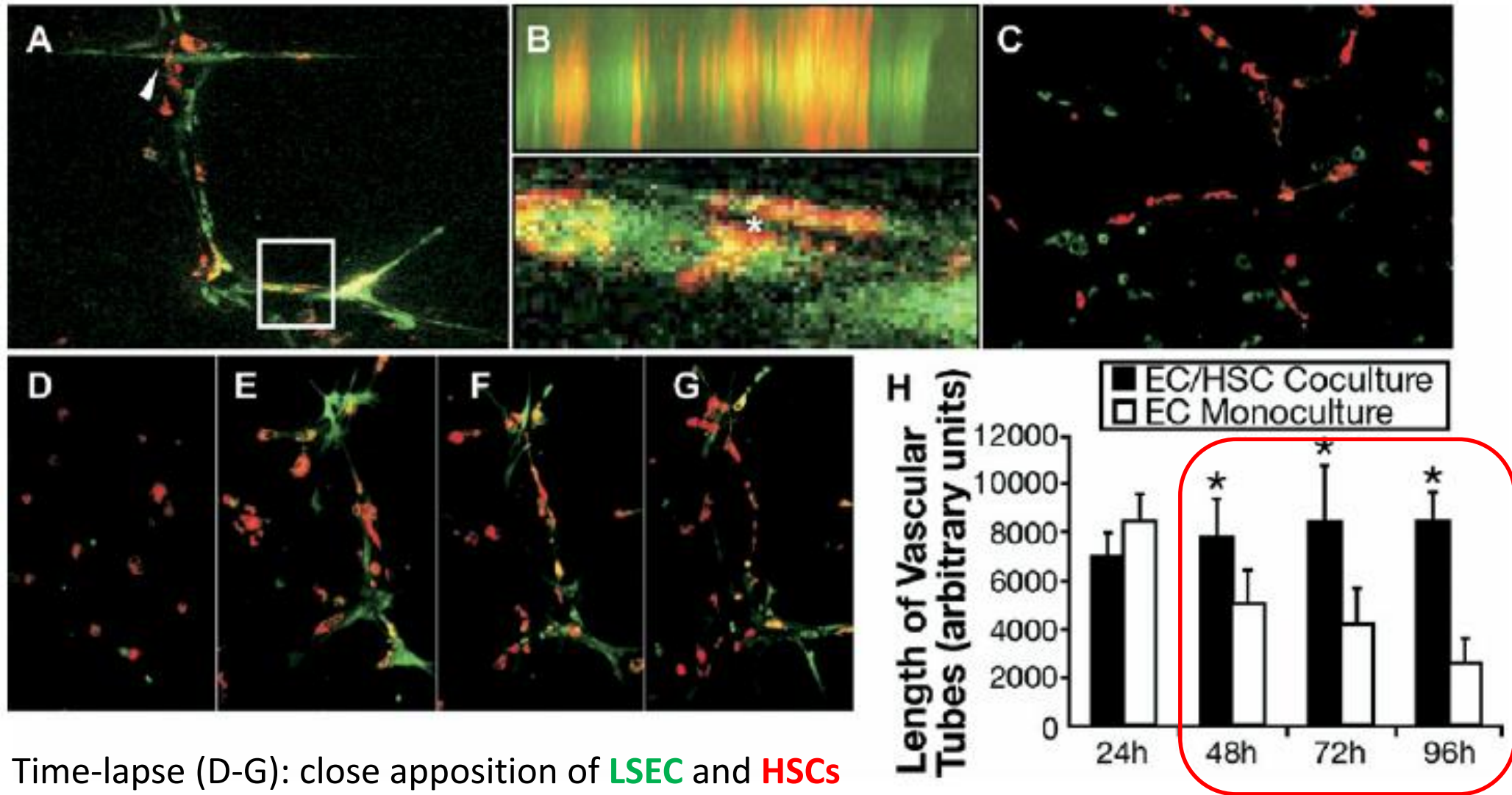


1.- Sinusoidal blood flow becomes more and more “arterialized”

2.- Liver tissue progressively adapts to a higher PO_2

3.- Capillarization of sinusoids impairs O_2 diffusion

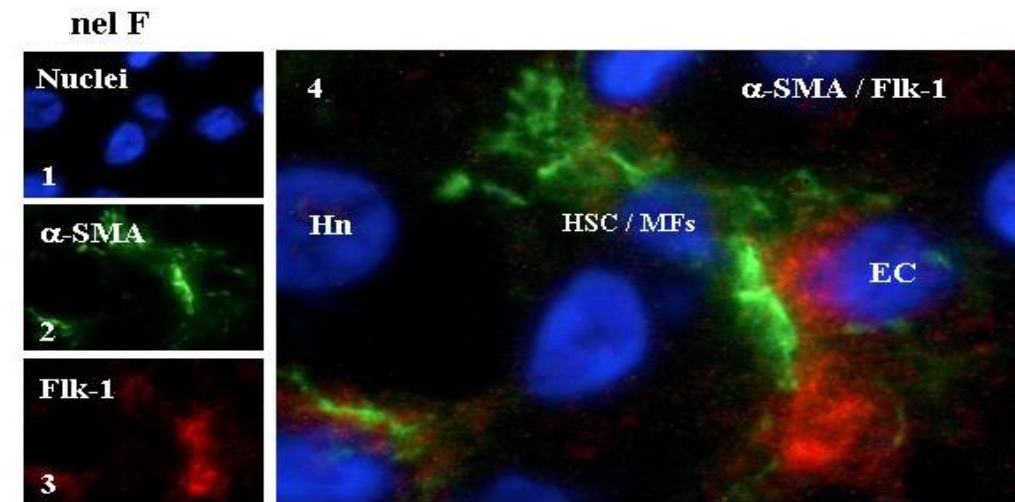
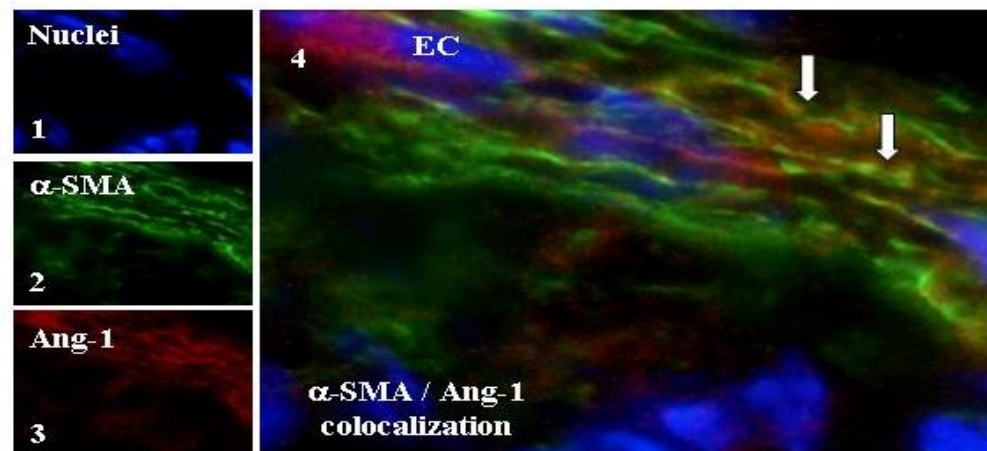
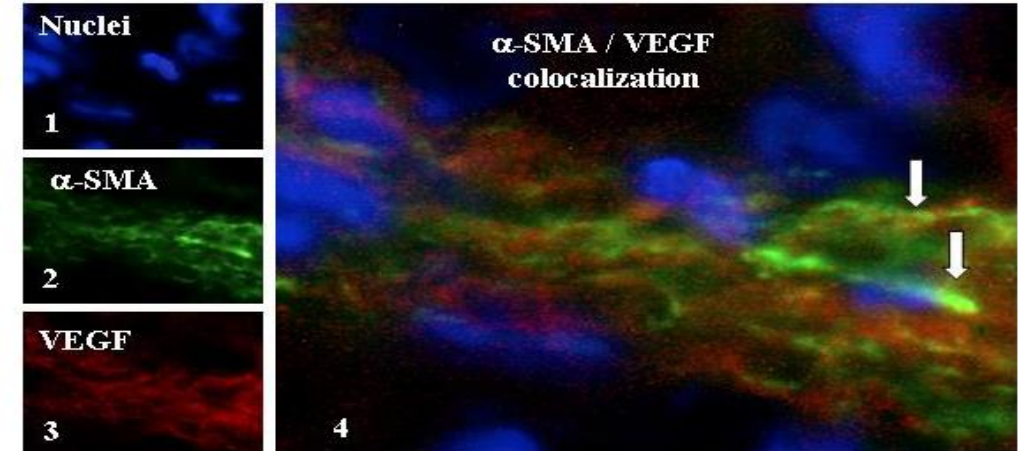
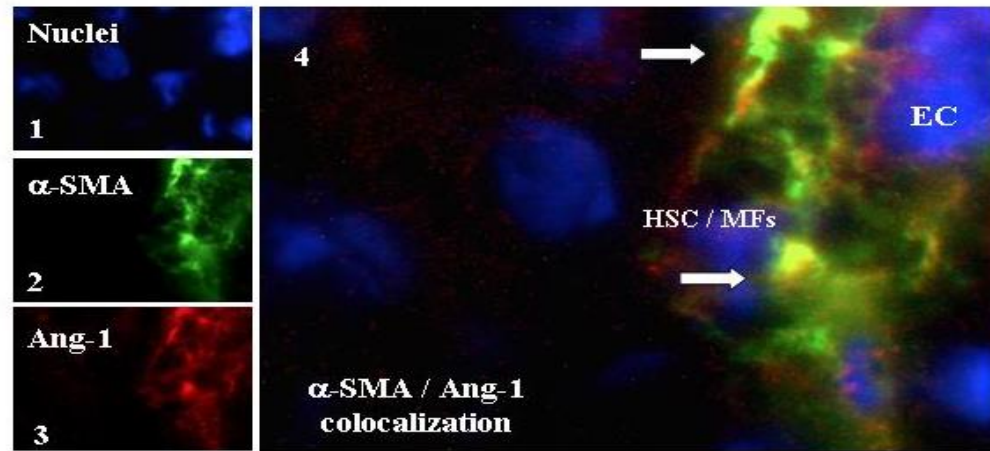
Vascular tube formation by LSECs and HSC co-culture



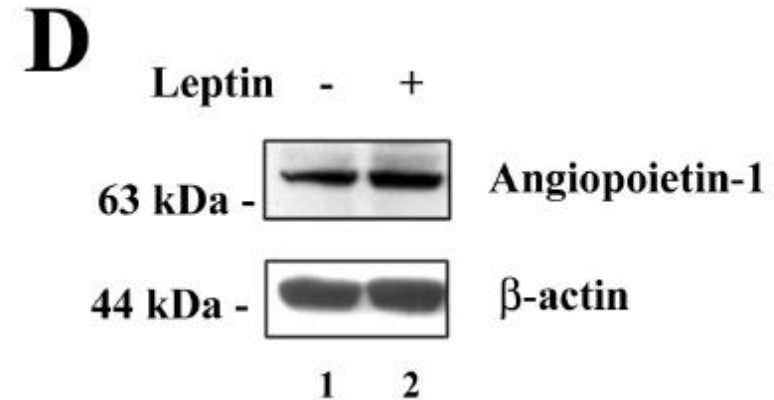
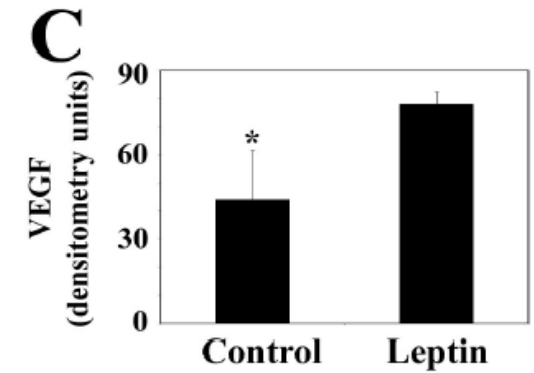
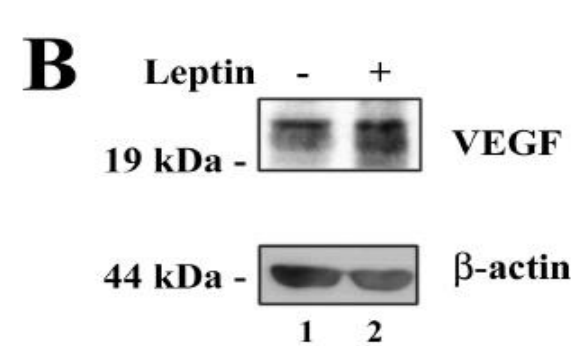
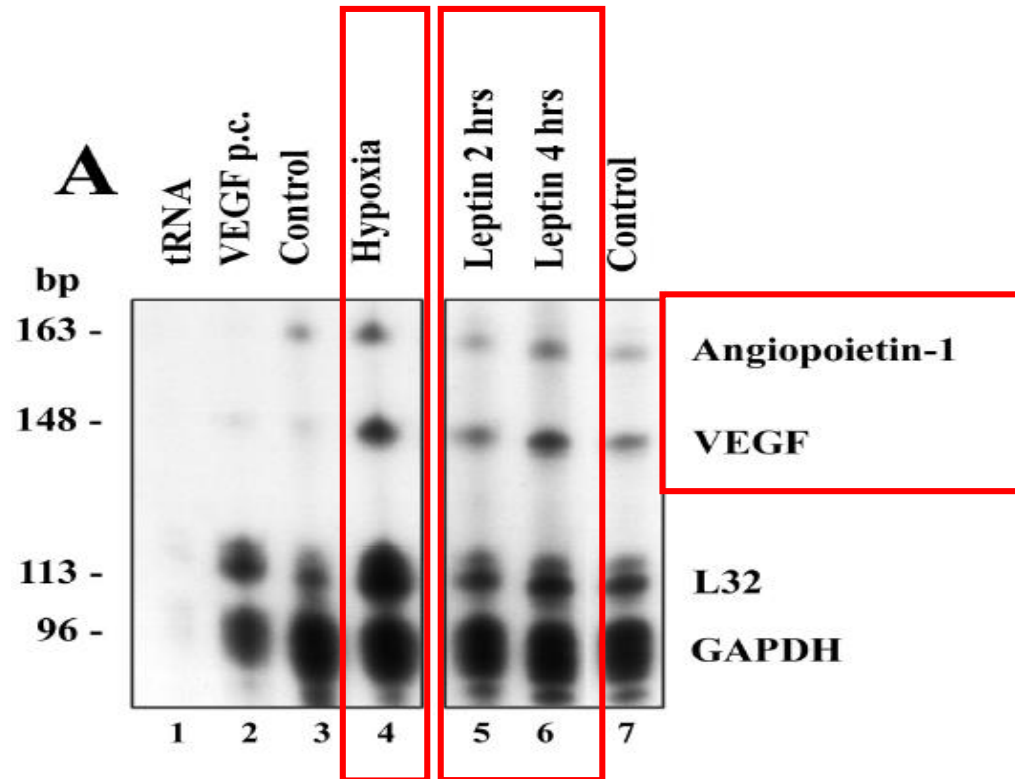
Time-lapse (D-G): close apposition of **LSEC** and **HSCs**

Coculture with HSC leads to **stabilization of LSEC-vascular tube formation**

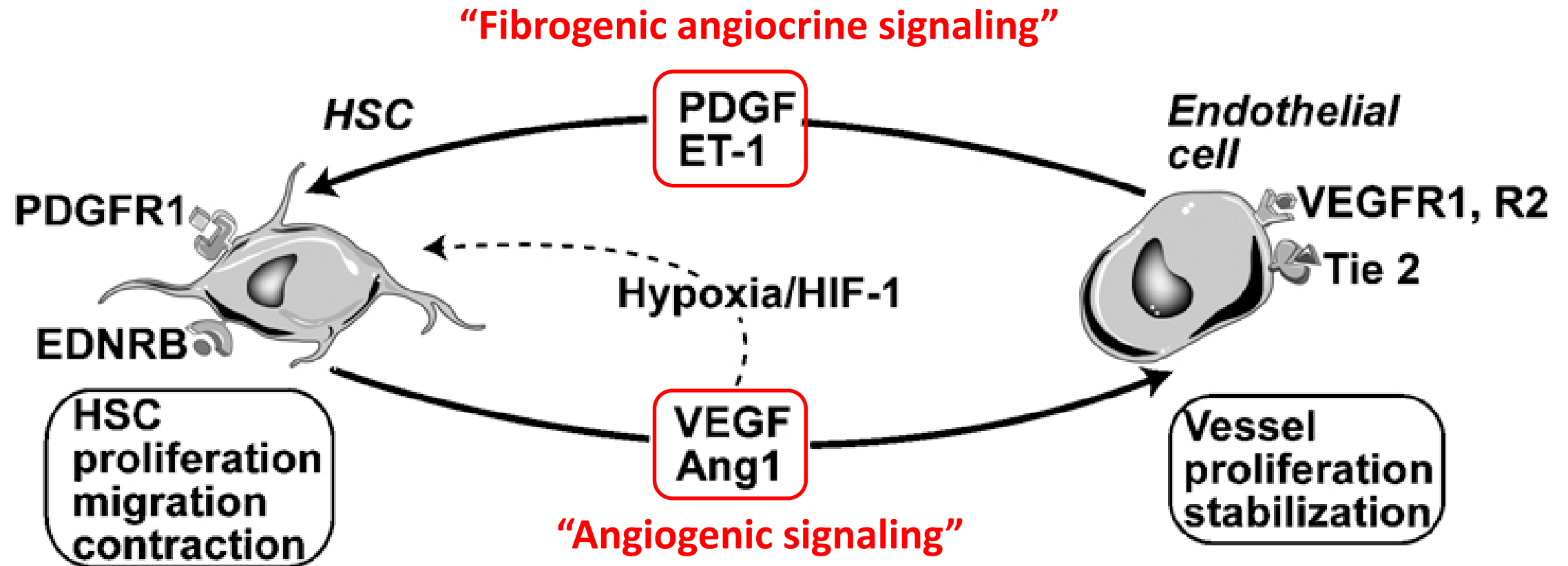
Activated Stellate Cells Release Pro-angiogenic Cytokines in Human Cirrhotic Liver



Leptin Promotes the Pro-angiogenic Role of Human HSC



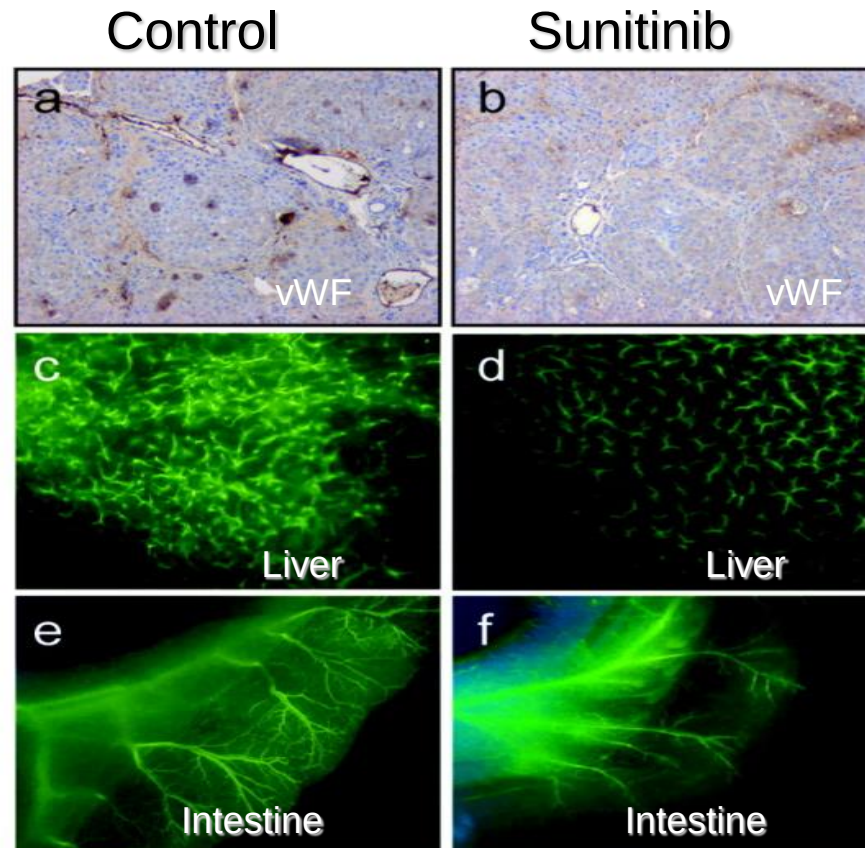
Sinusoidal remodeling: the abnormal vascular niche in cirrhosis



Antiangiogenic Treatment with Sunitinib Ameliorates Inflammatory Infiltrate, Fibrosis, and Portal Pressure in Cirrhotic Rats

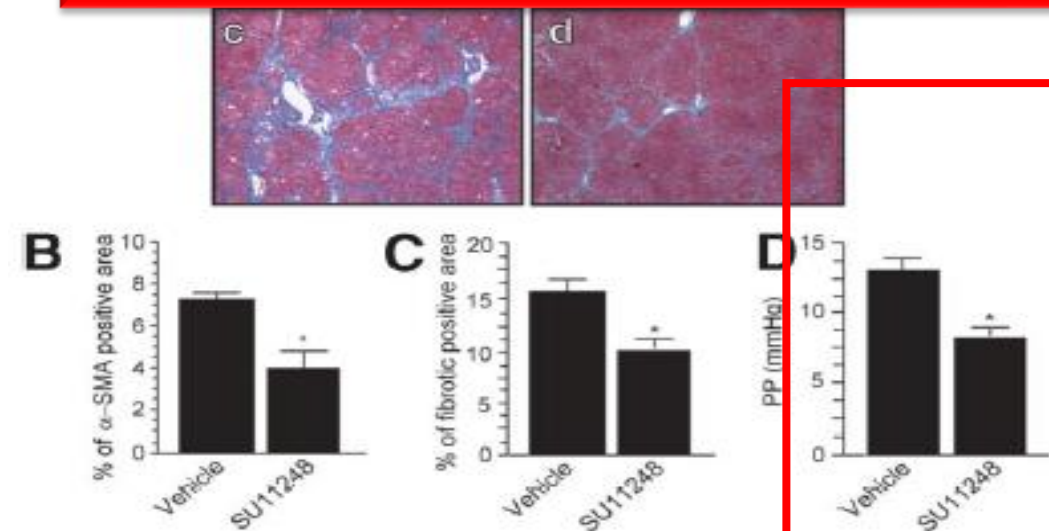
(HEPATOLOGY 2007;46:1919-1926.)

Sònia Tugues,¹ Guillermo Fernandez-Varo,¹ Javier Muñoz-Luque,¹ Josefa Ros,¹ Vicente Arroyo,² Juan Rodés,² Scott L. Friedman,³ Peter Carmeliet,^{4,5} Wladimiro Jiménez,¹ and Manuel Morales-Ruiz¹



FITC-dextran angiography

ANTI-ANGIOGENIC IS
ALSO
ANTI-FIBROGENIC



Targeting multiple angiogenic pathways: Tyrosin Kinase Inhibitors

Beneficial Effects of Sorafenib on Splanchnic, Intrahepatic, and Portocollateral Circulations in Portal Hypertensive and Cirrhotic Rats

Marc Mejias,¹ Ester Garcia-Pras,¹ Carolina Tiani,¹ Rosa Miquel,² Jaime Bosch,¹ and Mercedes Fernandez¹

Sorafenib attenuates the portal hypertensive syndrome in partial portal vein ligated rats[☆]

Thomas Reiberger¹, Bernhard Angermayr¹, Philipp Schwabl¹, Natascha Rohr-Udilova¹, Markus Mitterhauser², Alfred Gangl¹, Markus Peck-Radosavljevic^{1,*}

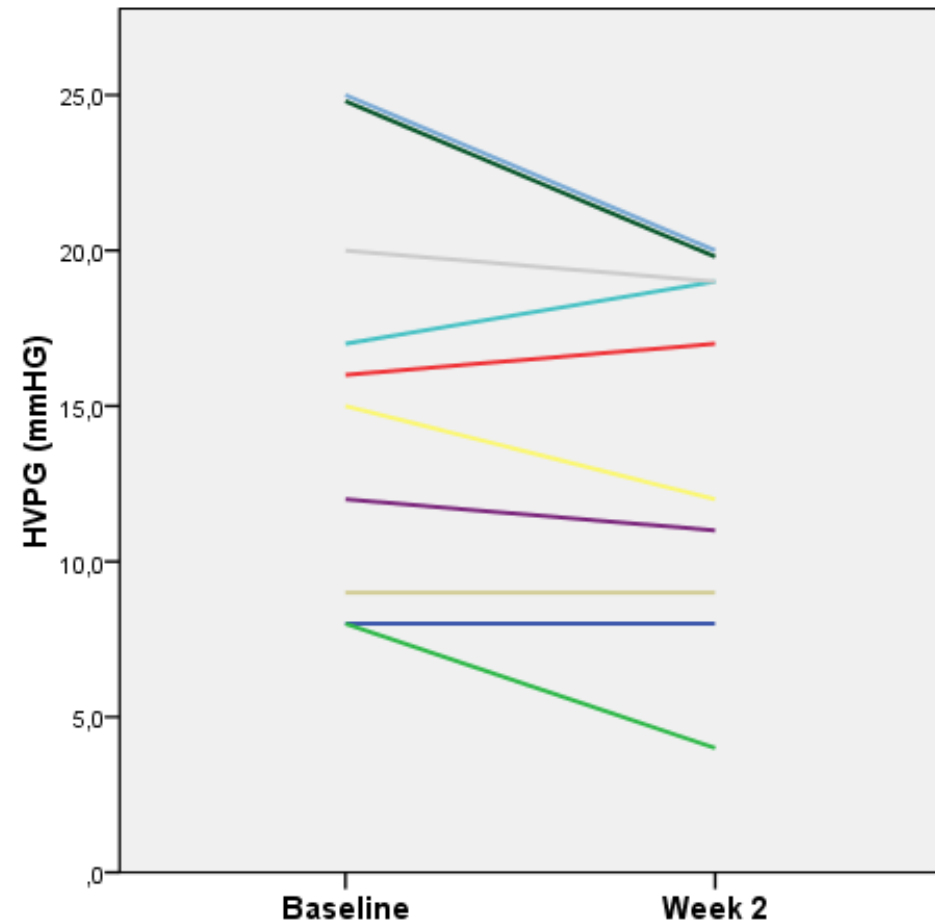
Sorafenib targets dysregulated Rho kinase expression and portal hypertension in rats with secondary biliary cirrhosis

M Hennenberg, J Trebicka, C Stark, AZ Kohistani, J Heller and T Sauerbruch

Antiangiogenic Treatment with Sunitinib Ameliorates Inflammatory Infiltrate, Fibrosis, and Portal Pressure in Cirrhotic Rats

Sònia Tugues,¹ Guillermo Fernandez-Varo,¹ Javier Muñoz-Luque,¹ Josefa Ros,¹ Vicente Arroyo,² Juan Rodés,² Scott L. Friedman,³ Peter Carmeliet,^{4,5} Wladimiro Jiménez,¹ and Manuel Morales-Ruiz¹

Sorafenib and Portal Hypertension: First in human study

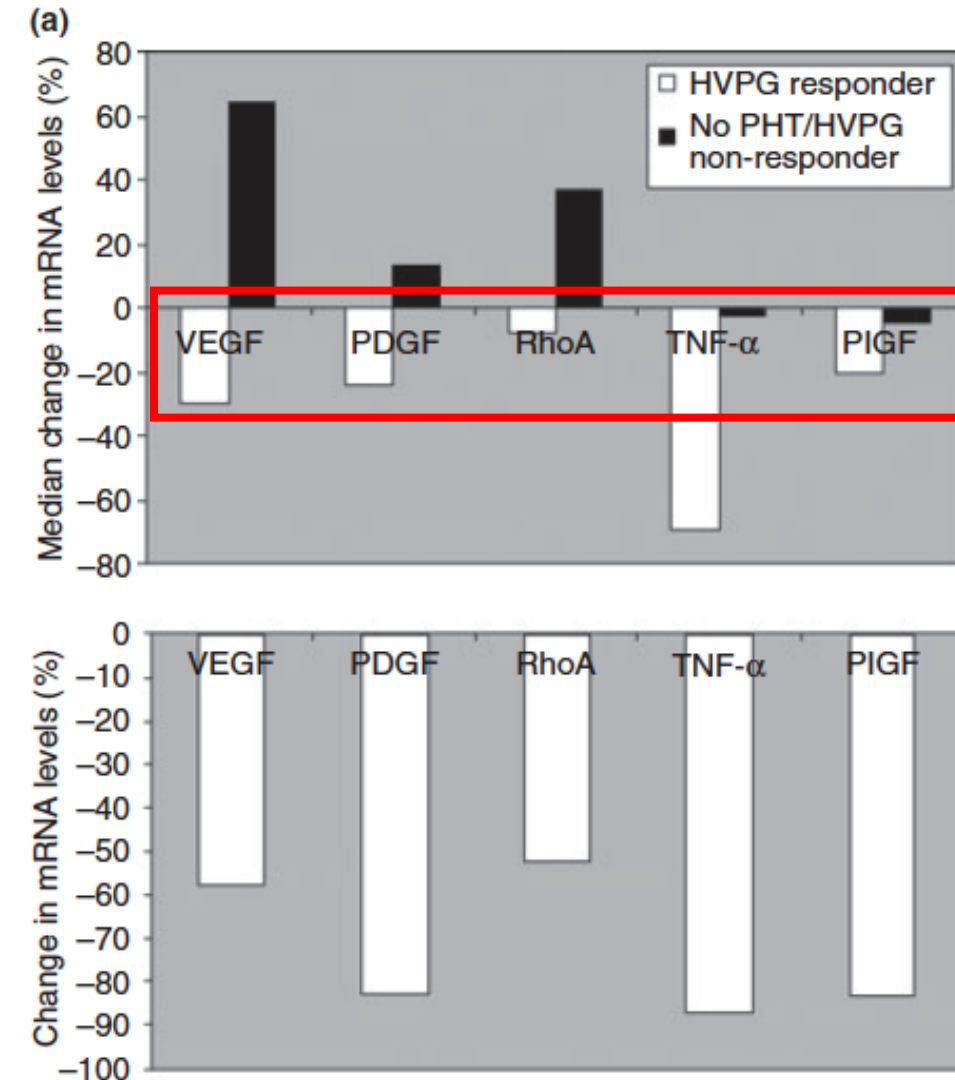


SORATACE:

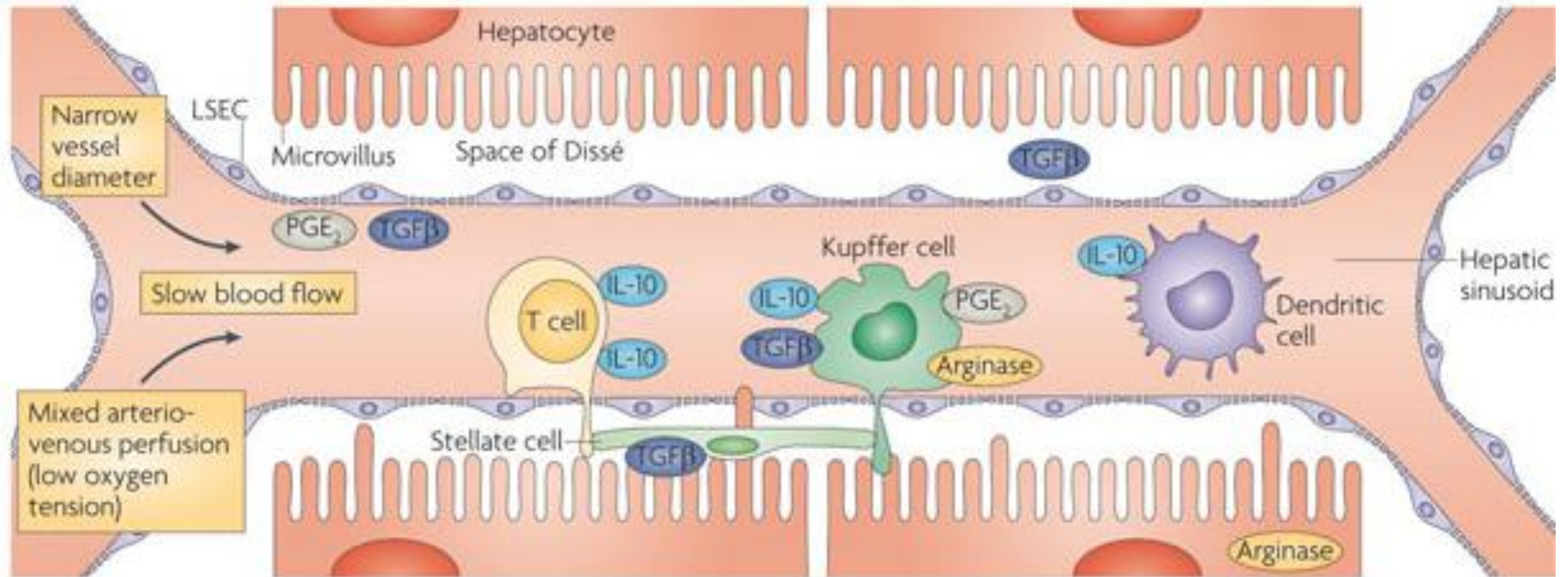
Sorafenib+TACE for HCC
2 week lead-in phase with
sorafenib without TACE

Change in HVPG: -9%

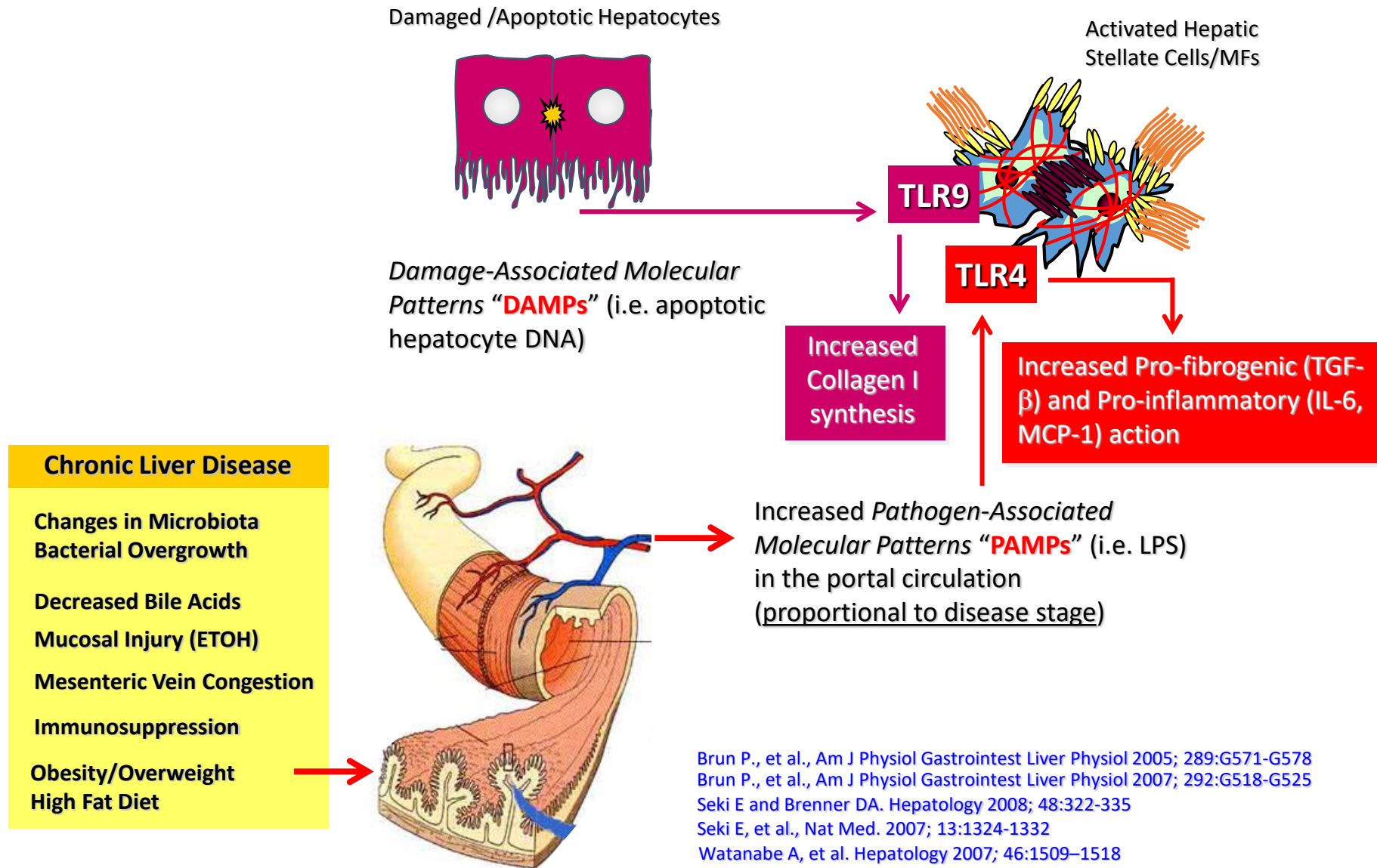
Hemodynamic Response:
4/10 patients (40%)
(>20% decrease in HVPG)



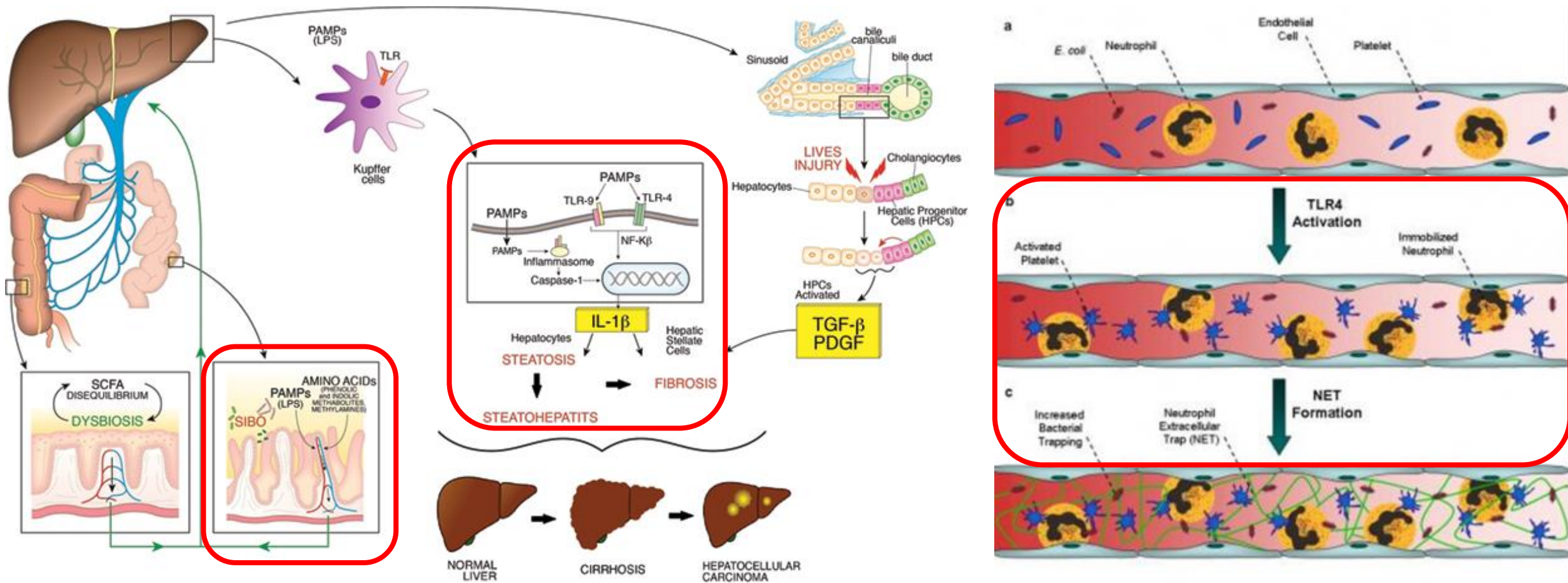
Sinusoidal Immunology



Intestinal Permeability and the Activation of the Gut-Liver Innate Immunity



Intestinal integrity and sinusoidal immunothrombosis



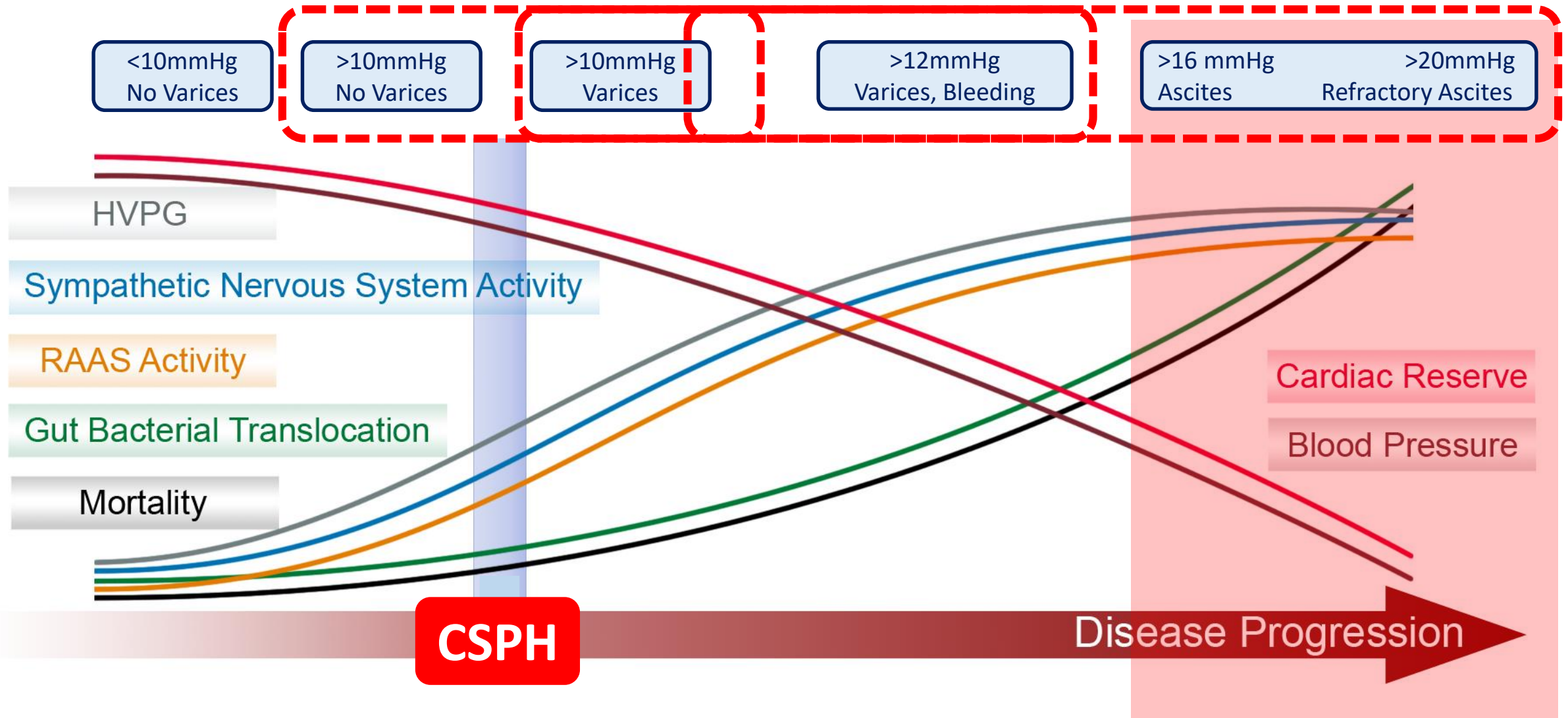
Pilsczek (J Immunol 2010): A novel mechanism of rapid nuclear neutrophil extracellular trap formation in response to *Staphylococcus aureus*.

Clark (Nat Med 2007): Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood.

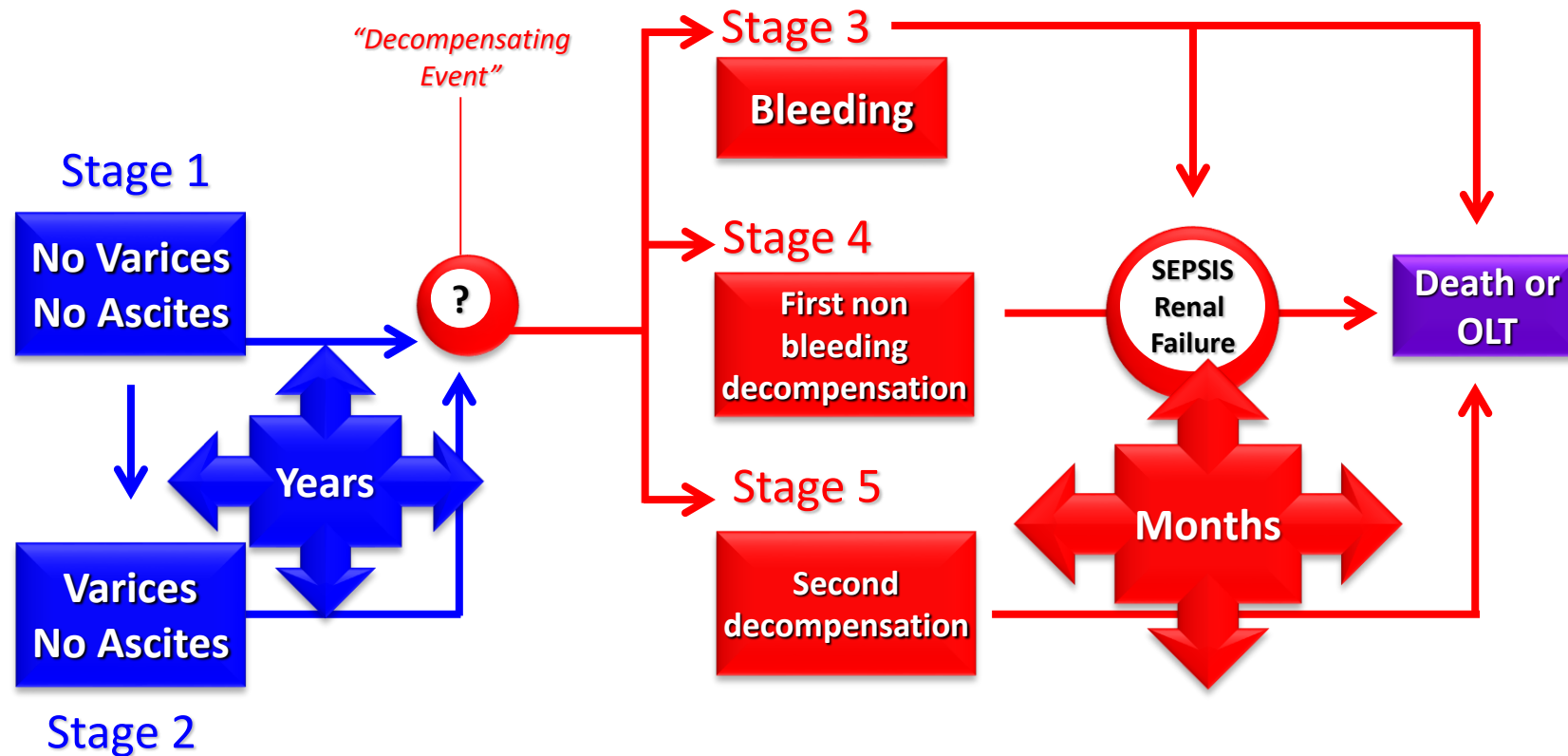
Ma (J Thromb Haemost 2008): Platelets and neutrophils interact to create bacterial traps in sepsis.

Lee (Nat Immunol 2010): An intravascular immune response to *Borrelia burgdorferi* involves Kupffer cells and iNKT cells.

Portal Hypertension in the Natural History of Chronic Liver Disease



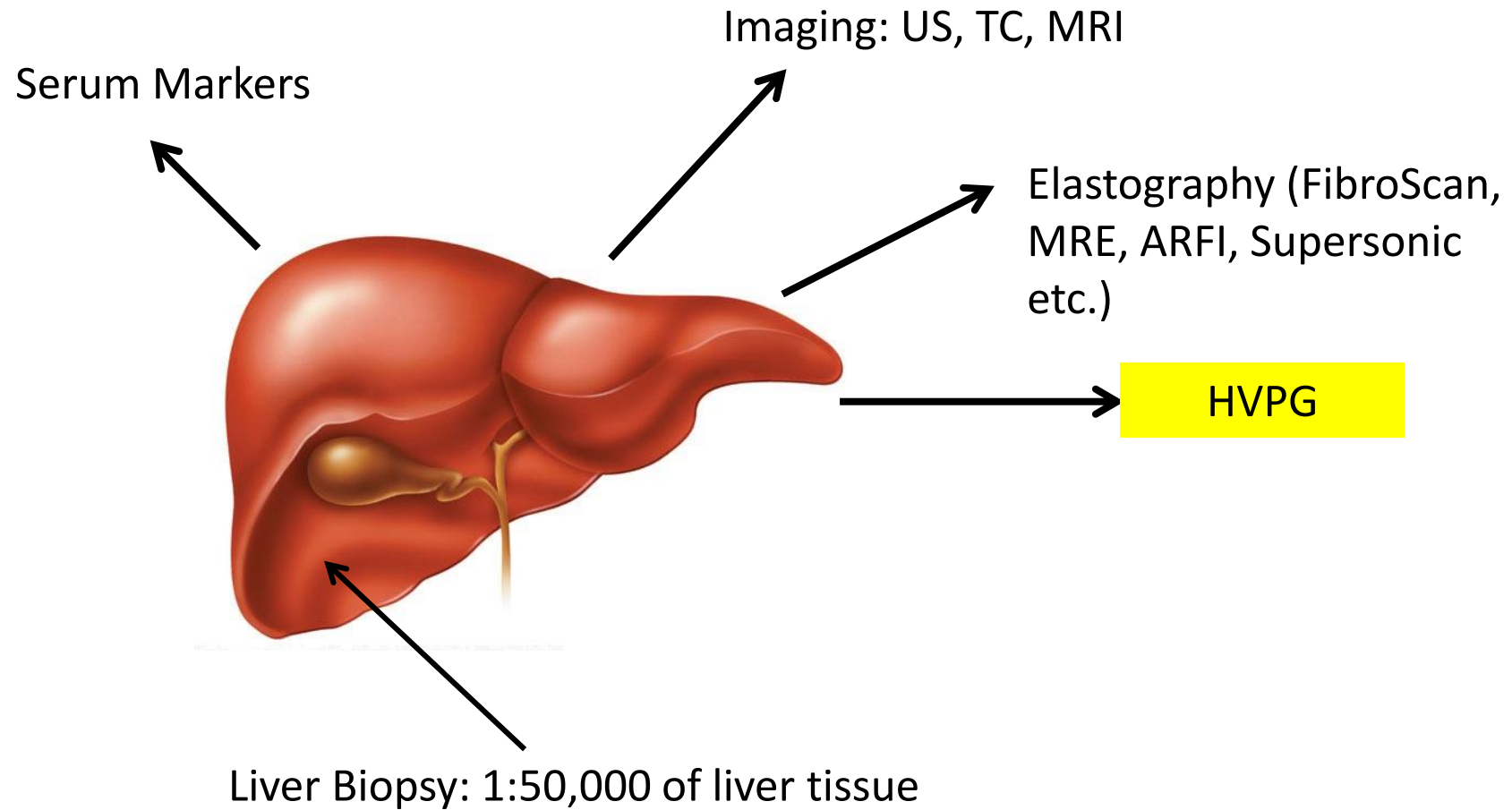
Compensated Cirrhosis a Clinical Stage with Very Limited Diagnostic Resources



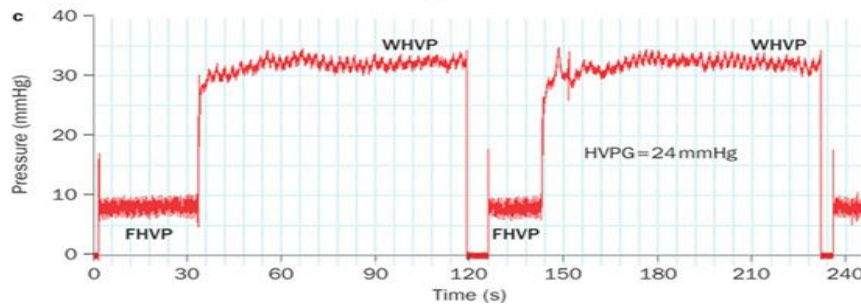
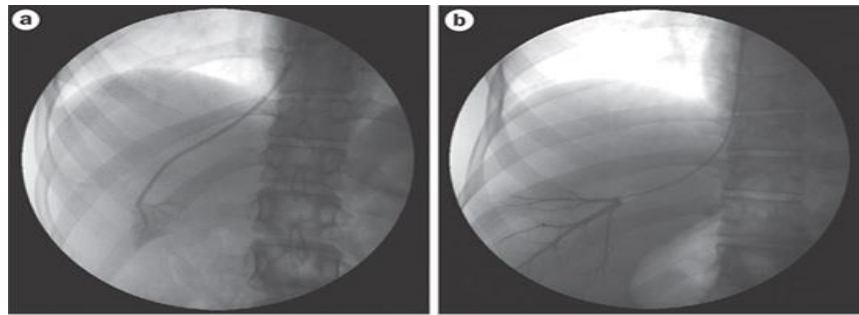
Detection of Clinically Significant Portal Hypertension (CSPH) in compensated cirrhosis

Decompensated Cirrhosis

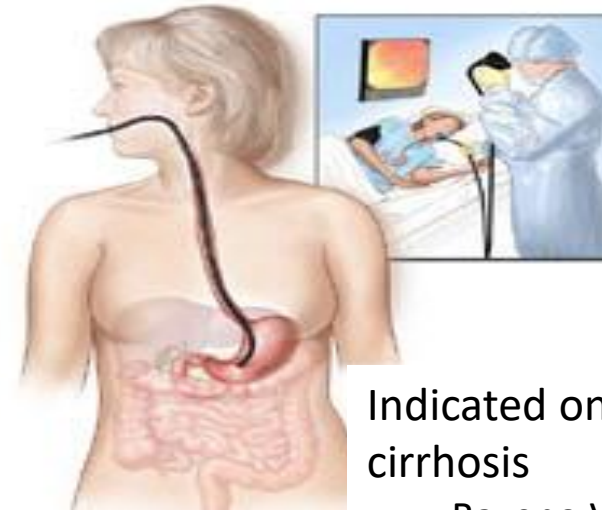
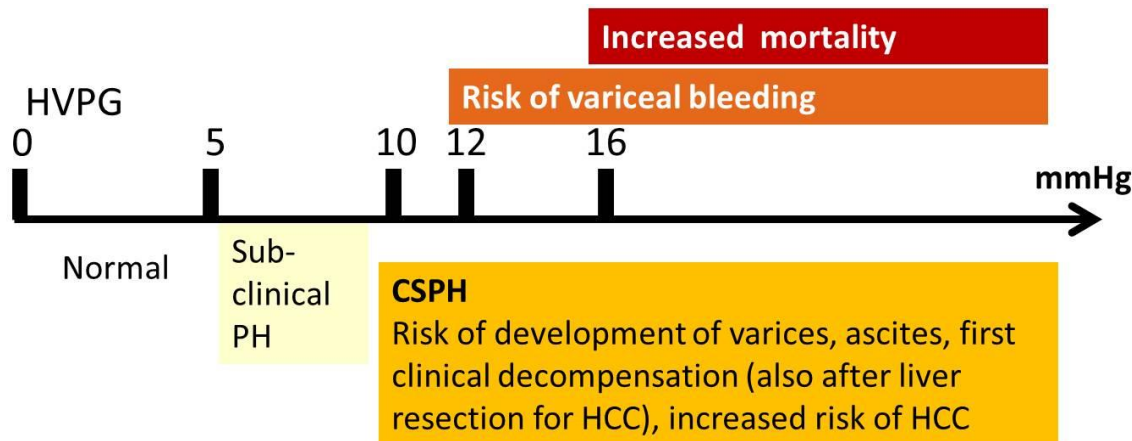
Non Invasive Evaluation of Liver Tissue Fibrosis (Staging)



Assessment of Portal Hypertension: Reference Standards



HVPG



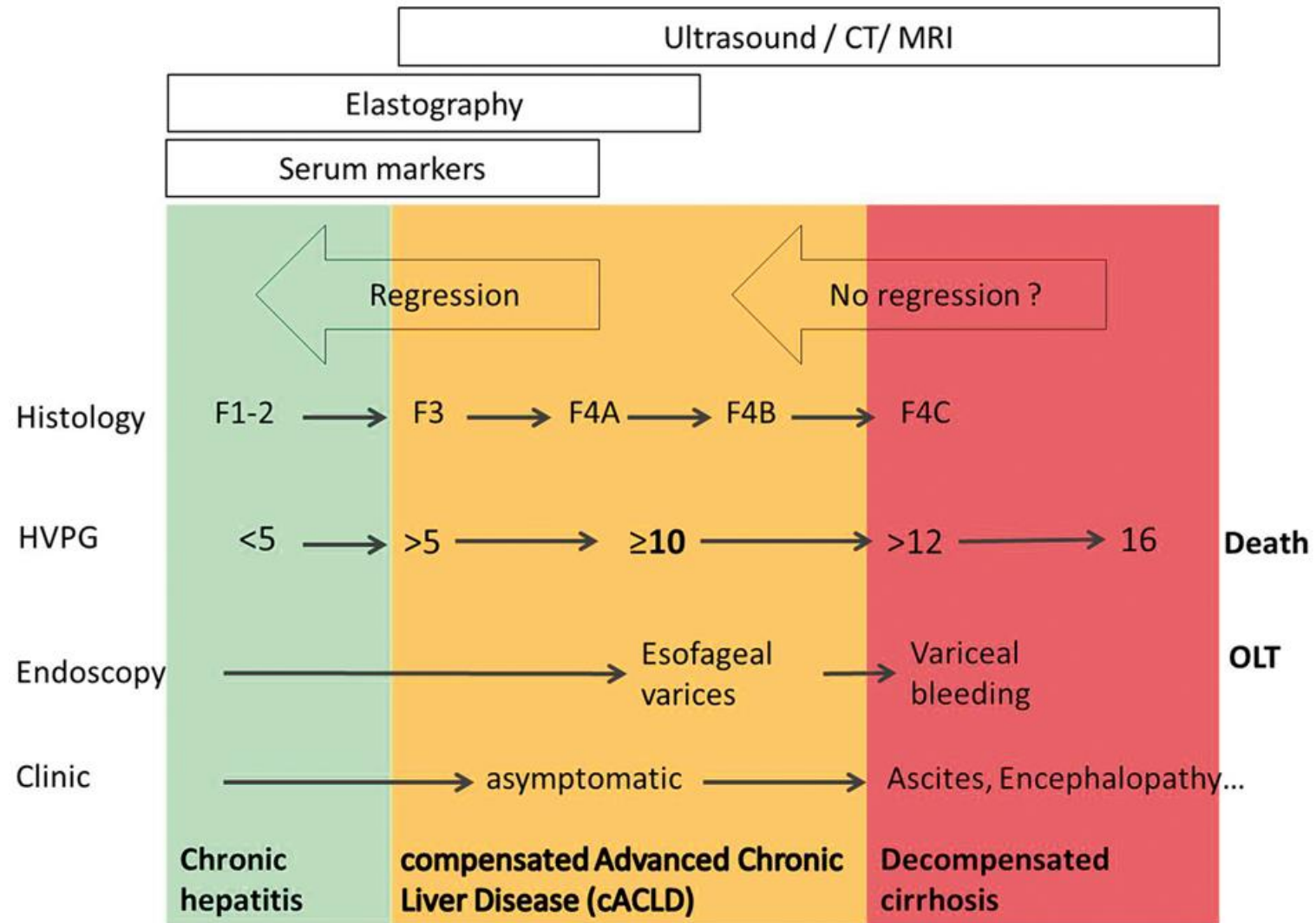
Indicated on first diagnosis of cirrhosis

Baveno V consensus conference

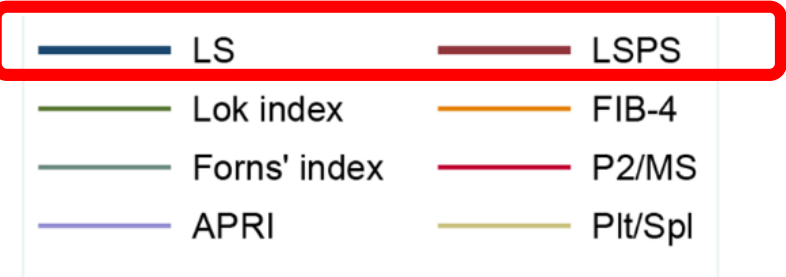
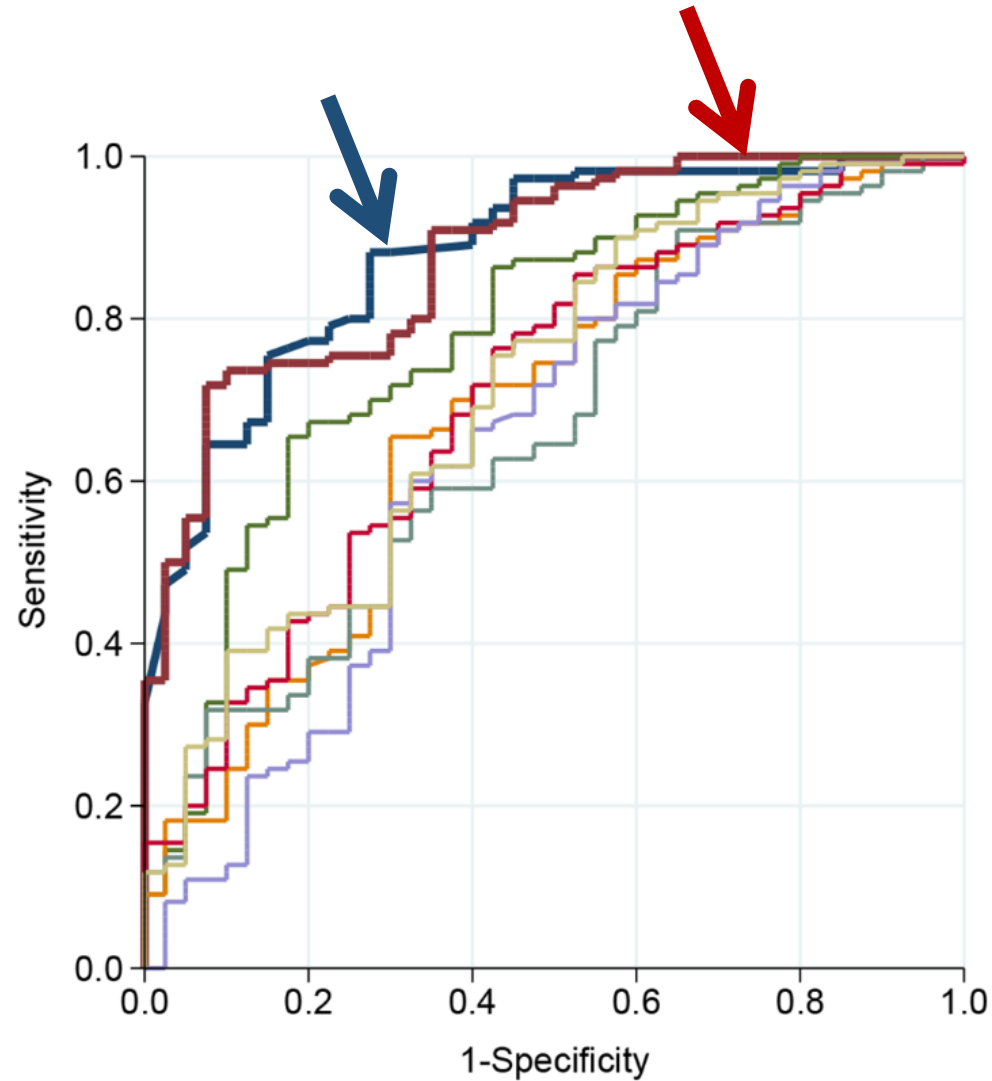
Upper GI endoscopy

Best technique to identify gastroesophageal varices (consequences of PH)

Diagnosis of Cirrhosis and Portal Hypertension



Non-invasive Liver Fibrosis Tests for the Detection of CSPH in Compensated Cirrhosis



Cho EJ, Kim MY, Lee J-H, Lee IY, Lim YL, Choi DH, et al. (2015) Diagnostic and Prognostic Values of Noninvasive Predictors of Portal Hypertension in Patients with Alcoholic Cirrhosis. PLoS ONE 10(7): e0133935. doi:10.1371/journal.pone.0133935

Transient Elastography for the Detection of CSPH

Authors	Patients (n)	Etiologies	Study design	Prevalence of Clinically Significant Portal hypertension	Cut-offs HVPG ≥ 10 mm Hg (kPa)	AUC	Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	-LR
Carrion et al. (35)	124	HCV-LT	Prospective monocentric	21%	8.7*	0.92	90	81	81	90	4.7	0.12
Vizzutti et al. (36)	61	HCV	Prospective monocentric	77%	13.6 17.6**	0.99 0.92	97 94	92 81	97 86	92 91	13.7 4.9	0.02 0.08
Sanchez-Condé et al. (39)	38	HIV-HCV	Prospective monocentric	74%	14.0 23.0**	0.80 0.80	93 83	50 67	84 79	71 71	3.5 2.5	0.62 0.49
Lemoine et al. (38)	44	HCV	Retrospective monocentric	77%	20.5	0.76	63	70	88	35	2.1	0.53
Bureau et al. (37)	48	Alcohol	Prospective monocentric	83%	34.9	0.94	90	88	97	64	7.5	0.13
	150	CLD	Prospective monocentric	51%	21.0	0.94	90	93	93	91	12.8	0.10

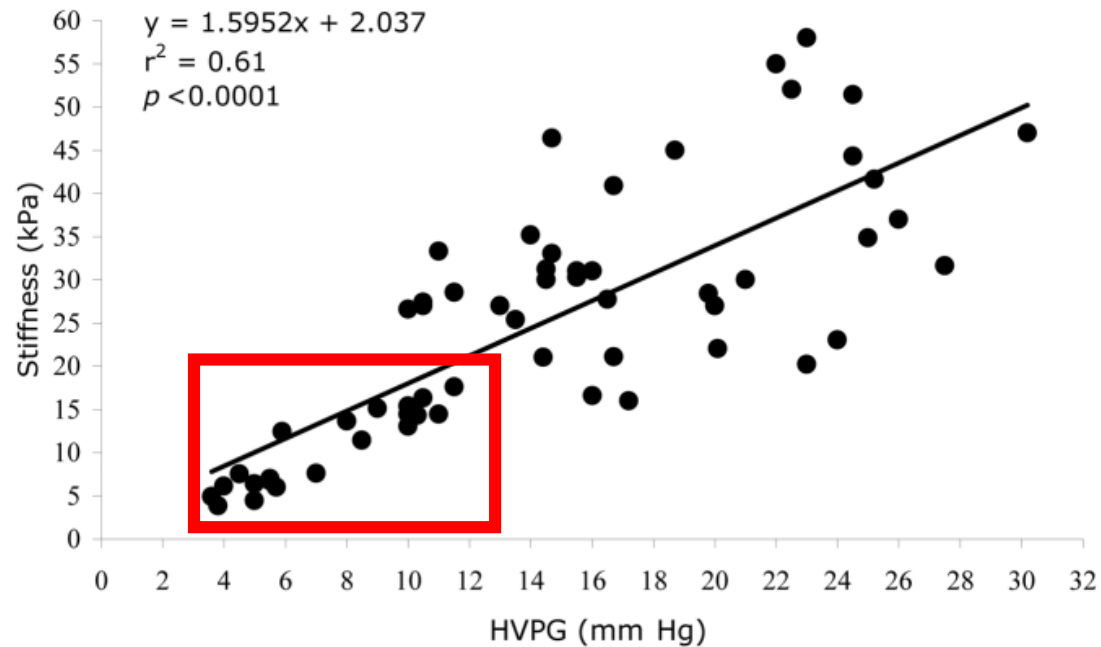
* Hepatic Venous Pressure Gradient (HVPG) ≥ 6 mm Hg; ** severe portal hypertension HVPG ≥ 12 mm Hg

AUC: area under ROC curve; Se sensitivity; Sp specificity; +LR positive likelihood ratio; -LR negative likelihood ratio;
HCV chronic hepatitis C; HCV-LT Liver transplant for hepatitis C; CLD chronic liver diseases;

Castera L, Pinzani M, Bosch J, J Hepatology 2012

Liver Stiffness Measurement Predicts Severe Portal Hypertension in Patients with HCV-Related Cirrhosis

Francesco Vizzutti,¹ Umberto Arena,¹ Roberto G. Romanelli,¹ Luigi Rega,² Marco Foschi,¹ Stefano Colagrande,² Antonio Petrarca,¹ Stefania Moscarella,¹ Giacomo Belli,³ Anna Linda Zignego,¹ Fabio Marra,¹ Giacomo Laffi,¹ and Massimo Pinzani¹



HEPATOLOGY, Vol. 45, No. 5, 2007

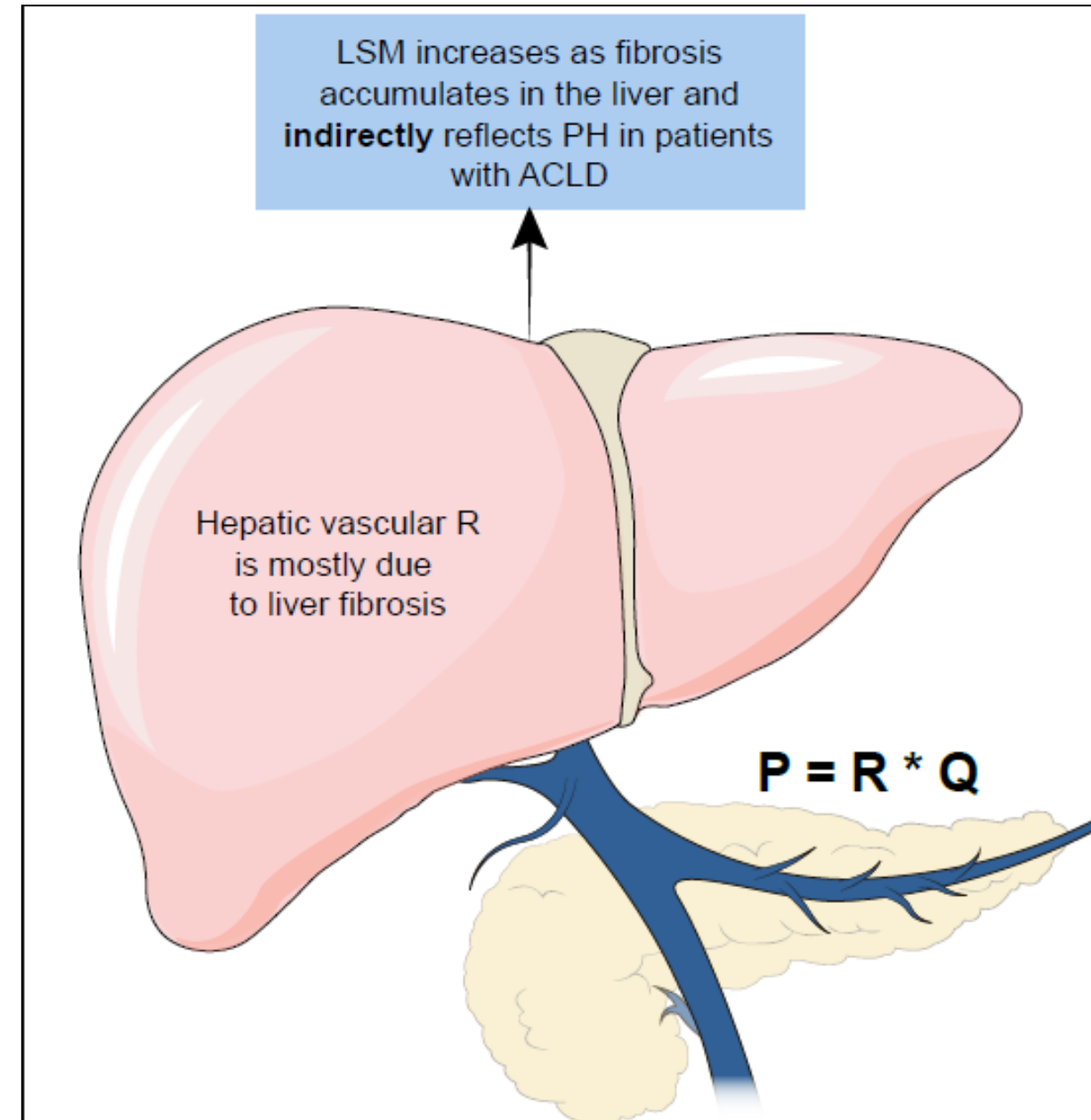
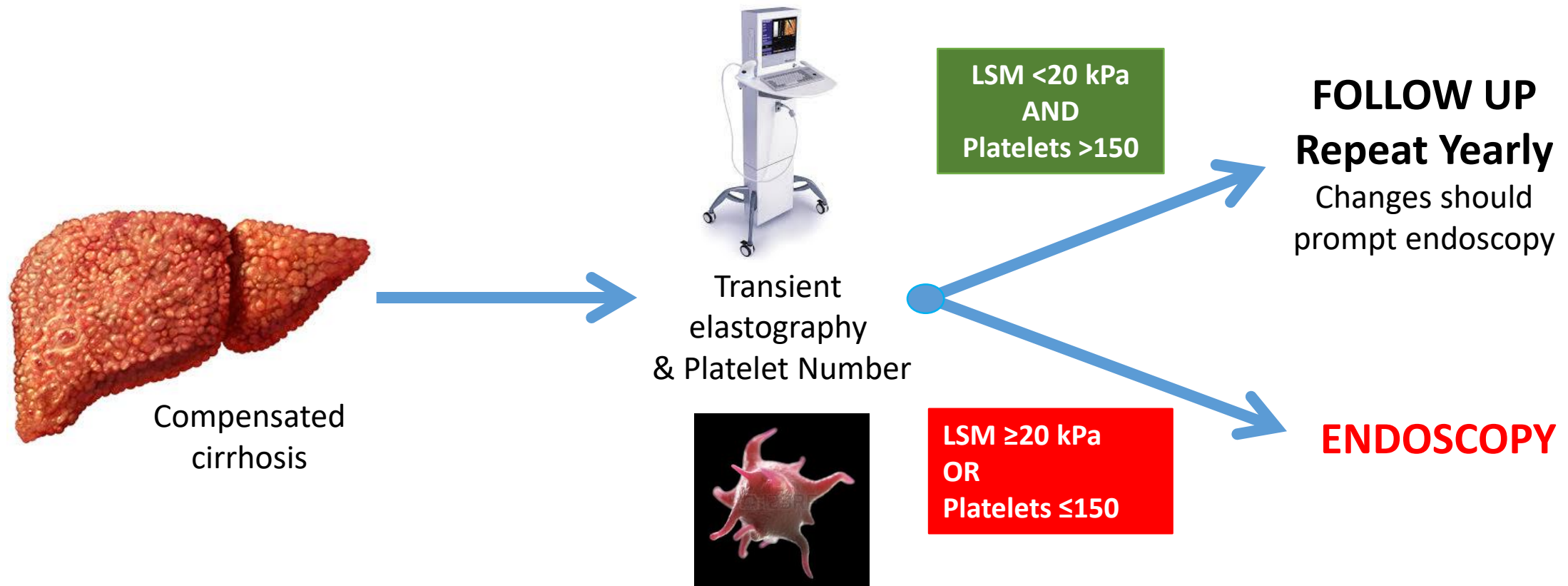


Fig. 5. Receiver operating characteristic curve showing the prediction of esophageal varices with transient elastography in patients with cirrhosis.

Baveno VI: Identification of Low Risk Patients not Immediately Requiring Endoscopic Surveillance



Validation of Baveno VI Criteria for Avoiding Screening Endoscopy

Study	N	Viral %	ALD %	Varices	VNT	Varices missed	VNT missed	OGD spared	OGD unneeded
Perazzo	97	-	-	54%	-	6%	0	22%	29%
Tossetti	146	100	-	45%	8%	6%	0	27%	34%
Chang*	173	55	-	31%	8%	-	1.7%	20%	-
Thabut*	790	100	-	-	-	10%	0	20%	-
Paternostro*	135	47	30	65%	24%	3%	0	7%	30%
Silva*	112	80	7	48%	15%	1.8%	0	11%	43%
Cales*	287	26	64	44%	17%	2%	0	16.5%	41.5%
Ahmed*	478	33	36	-	11%	-	0.5%	23%	-
Maurice	310	55	13	23%	5%	3.5%	0.6%	33%	48%
TOTAL	2528				12%		0.3%	20%	38%

Perazzo, J Hepatol 2015; Tossetti, DLD 2016; *EASL 2016; Maurice, J Hepatol 2016

Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices

James B Maurice^{1,2}, Edgar Brodtkin¹, Frances Arnold¹, Annalan Navaratnam¹, Heidi Paine², Sabrina Khawar¹, Ameet Dhar², David Patch¹, James O’Beirne¹, Raj Mookerjee^{1,3}, Massimo Pinzani^{1,3}, Emmanouil Tsochatzis^{1,3}, Rachel H. Westbrook^{1,*}

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Table 3. Performance of each variable for diagnosing high risk varices. (B)
Sub-analysis of population with OGD within 6 months of LSM.

A

Variable (Cut-off value)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
LSM (20 kPa)	0.67	0.55	0.07	0.97	1.48	0.61
Platelets (150 x10 ³ /µl)	0.60	0.49	0.06	0.96	1.18	0.81
Baveno VI criteria [LSM (20 kPa) and platelets (150 x10 ³ /µl)]	0.87	0.34	0.06	0.98	1.31	0.39

B

Variable (Cut-off value)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
LSM (20 kPa)	0.60	0.52	0.06	0.94	1.24	0.77
Platelets (150 x10 ³ /µl)	0.80	0.47	0.07	0.98	1.52	0.42
Baveno VI criteria [LSM (20 kPa) and platelets (150 x10 ³ /µl)]	0.90	0.31	0.06	0.98	1.31	0.32

OGD, oesophagogastroduodenoscopy; LSM, liver stiffness measurement; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR–, negative likelihood ratio.

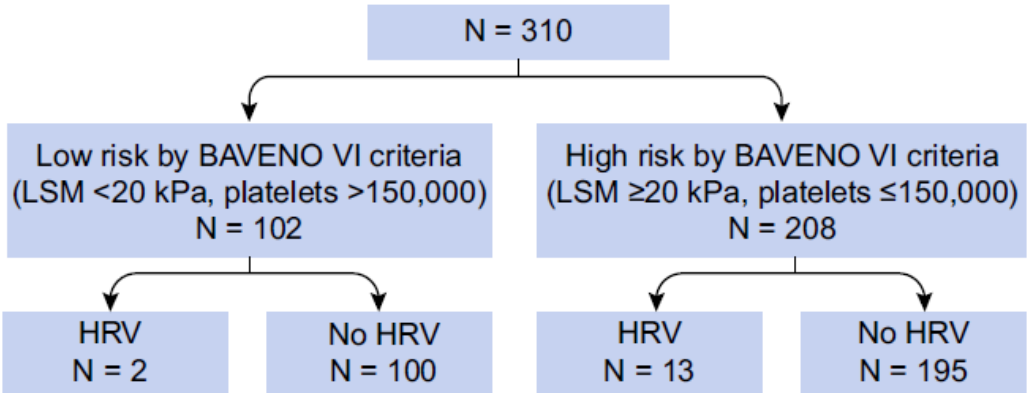
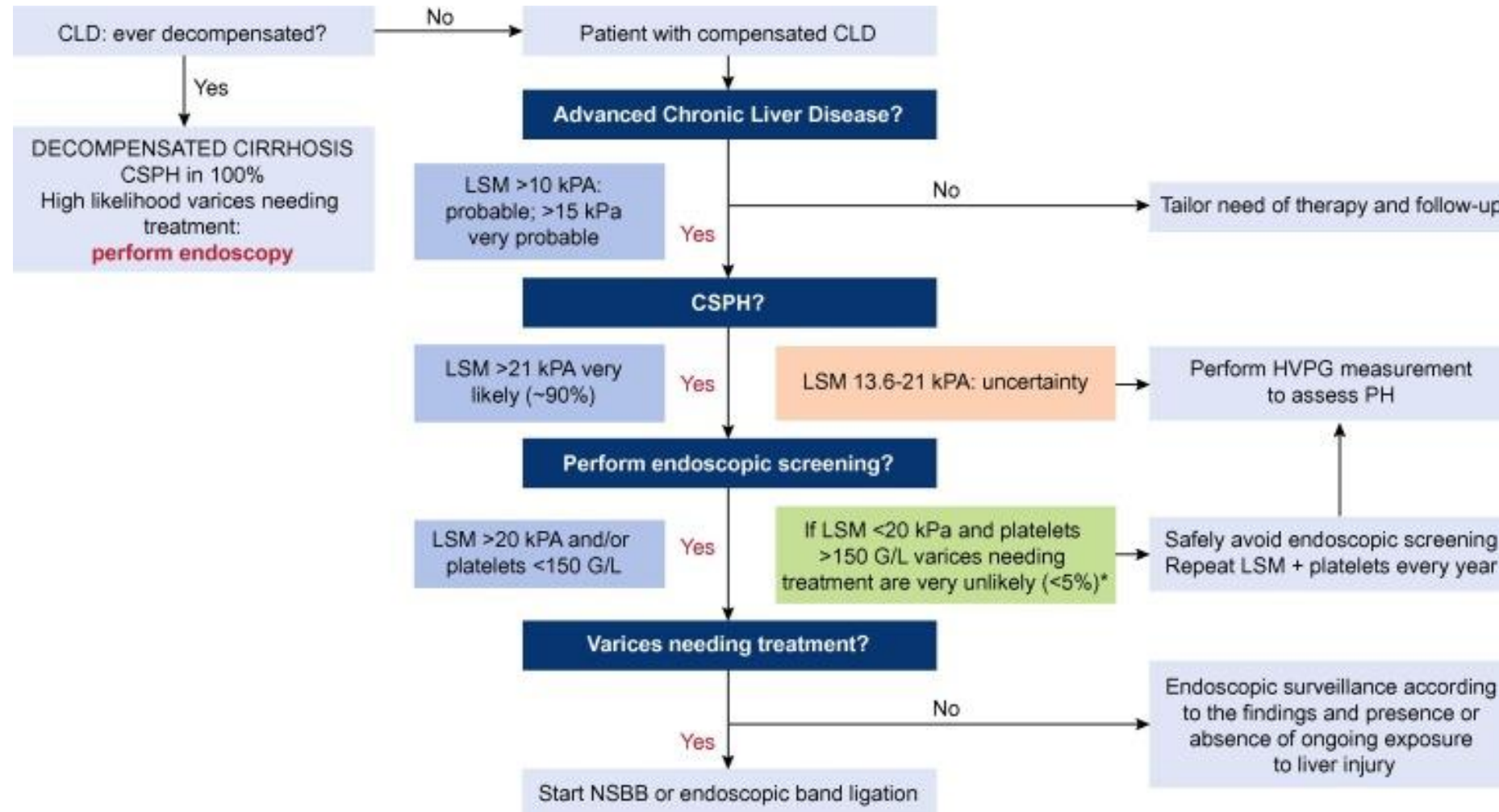


Fig. 2. Summary prevalence of HRV in the study cohort of low risk and high risk patients as defined by the Baveno VI criteria. HRV, high risk varices; LSM, liver stiffness measurement.

Liver Stiffness Measurement for the Management of Compensated Cirrhosis: Baveno VI Recommendations

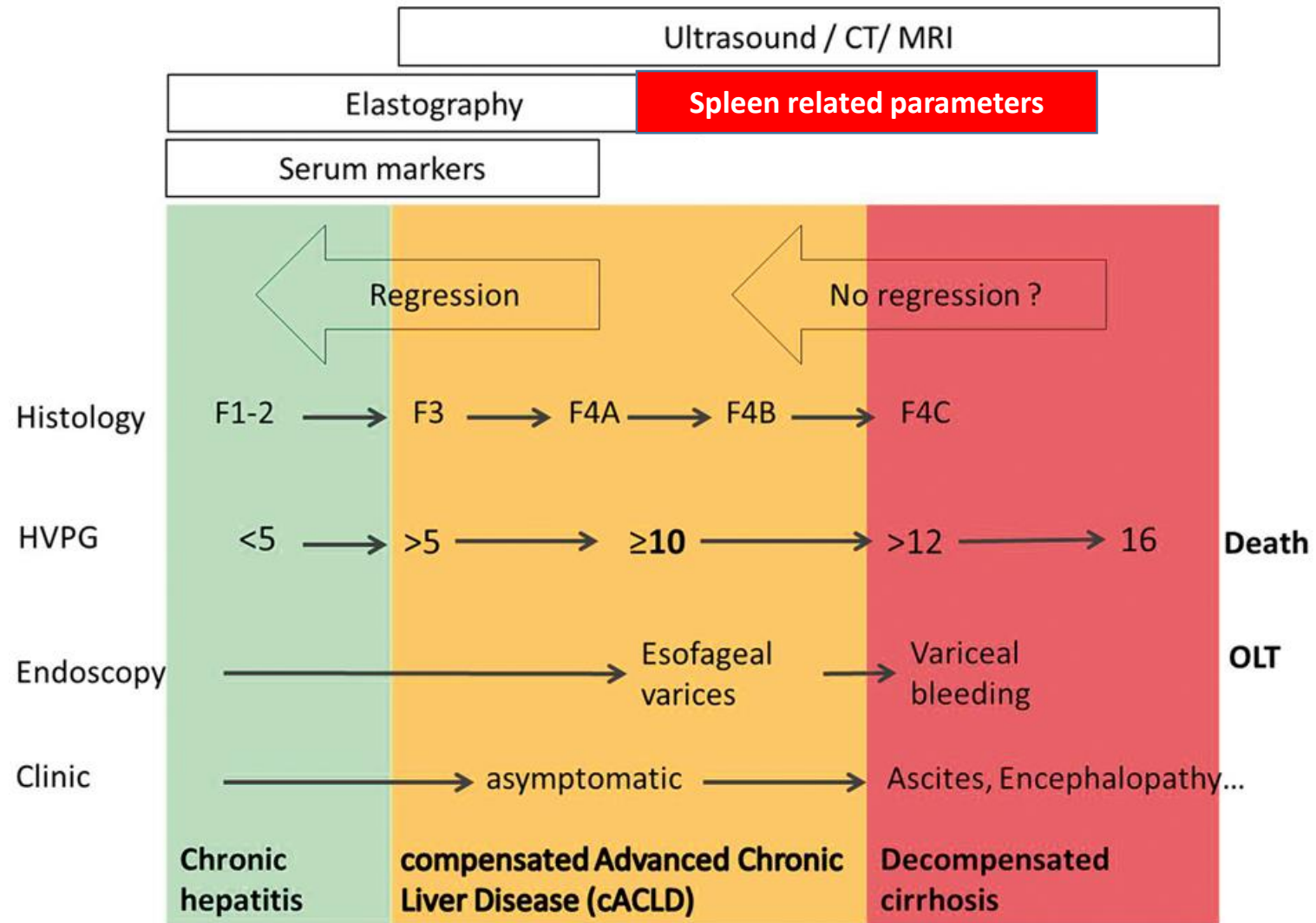


New: Expanded Baveno VI Criteria are Safe and Effective

N=499	Spared endoscopies	VNT missed
Platelets >150 + LSM <20 kPa (Baveno VI)	68 (14%)	2/68 (3%) (0.8-10%) [§]
Platelets >110 + LSM <25 kPa (Expanded-Baveno VI)	158 (32%)	3/158 (1.9%) (0.6-5.4%)

Study cohort	Spared endoscopies	VNT missed/ Expanded-Baveno VI*	VNT missed/ All patients [§]
Anticipate	158/499 (32%)	3/158 (1.9%) (0.6-5.4%) [¥]	3/499 (0.6%) (0.1-1.9%)
London	161/309 (52%)	3/161 (1.9%) (0.6-5.3%)	3/309 (1%) (0.3-2.8%)
Vall d'Hebron	48/117 (41%)	0/48 (0%) (0.7-9.2%)	0/117 (0%) (0-3.1%)
All cohorts	367/925 (40%)	6/367 (1.6%) (0.7-3.5%)	6/925 (0.6%) (0.3-1.4%)

Diagnosis of Cirrhosis and Portal Hypertension

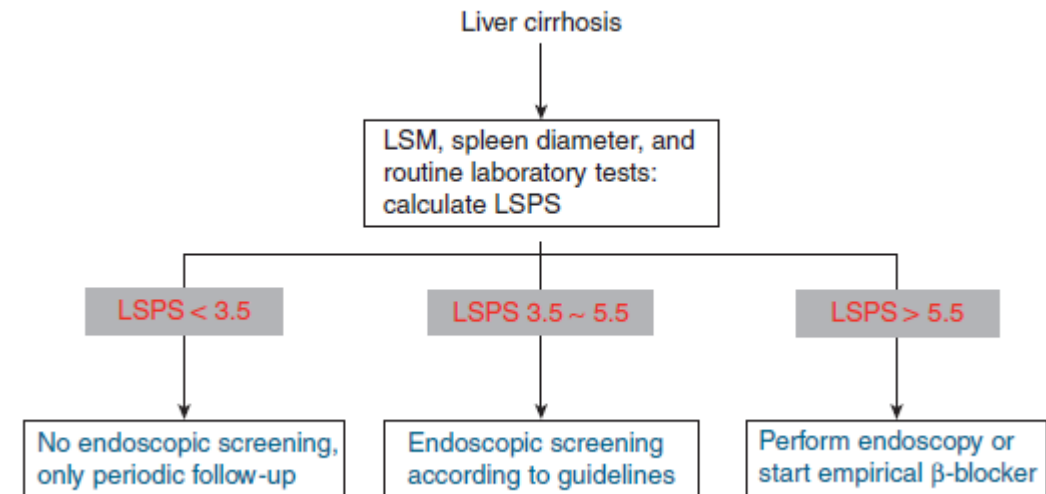
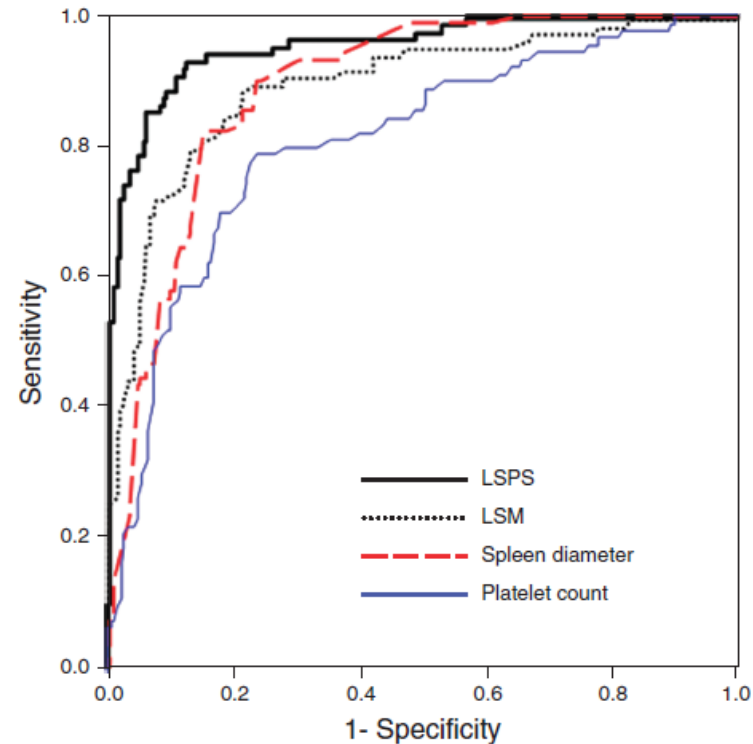


Spleen Parameters for the Detection of Esophageal Varices

A Liver Stiffness Measurement-Based, Noninvasive Prediction Model for High-Risk Esophageal Varices in B-Viral Liver Cirrhosis

Beom Kyung Kim, MD¹, Kwang-Hyub Han, MD¹⁻⁴, Jun Yong Park, MD¹⁻³, Sang Hoon Ahn, MD, PhD¹⁻³, Ja Kyung Kim, MD¹⁻³, Yong Han Paik, MD, PhD¹⁻⁴, Kwan Sik Lee, MD¹⁻³, Chae Yoon Chon, MD¹⁻³ and Do Young Kim, MD¹⁻³

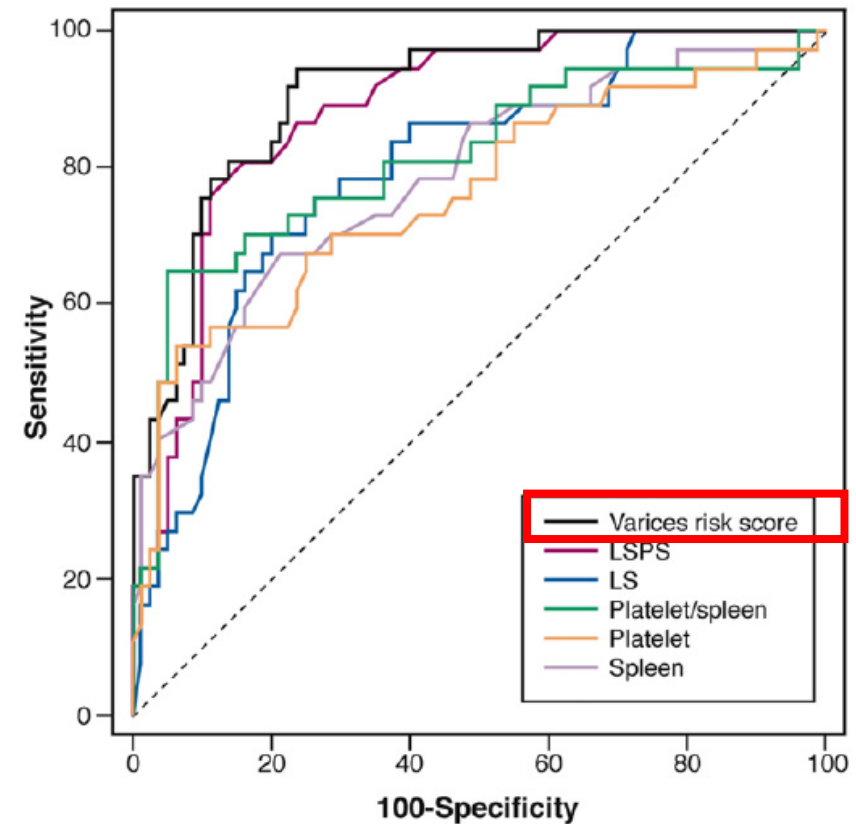
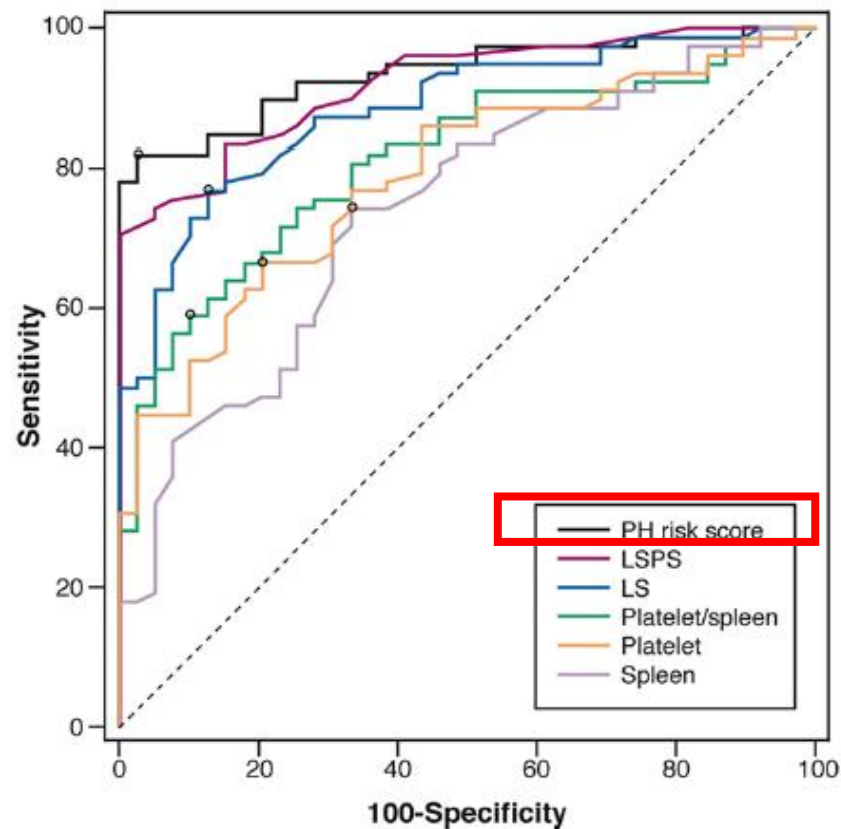
(LSPS): $\text{LSM} \times \text{spleen diameter} / \text{platelet count}$



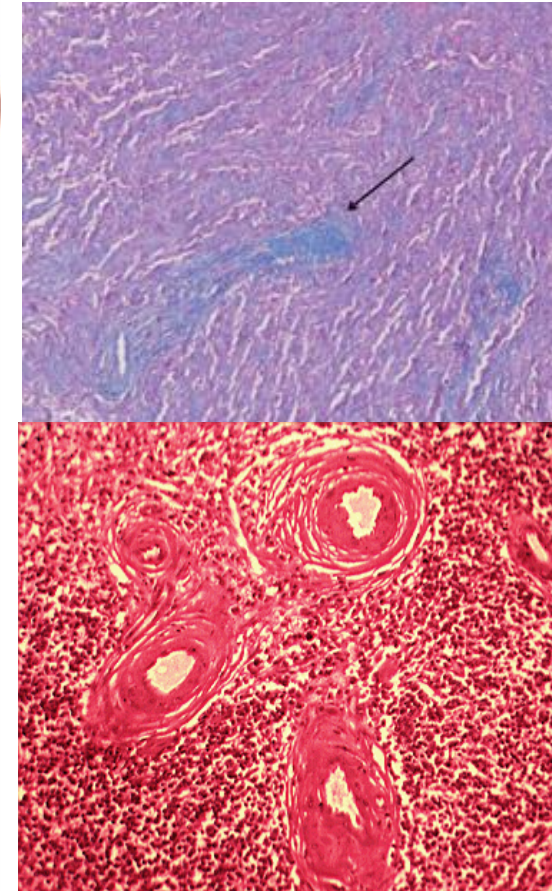
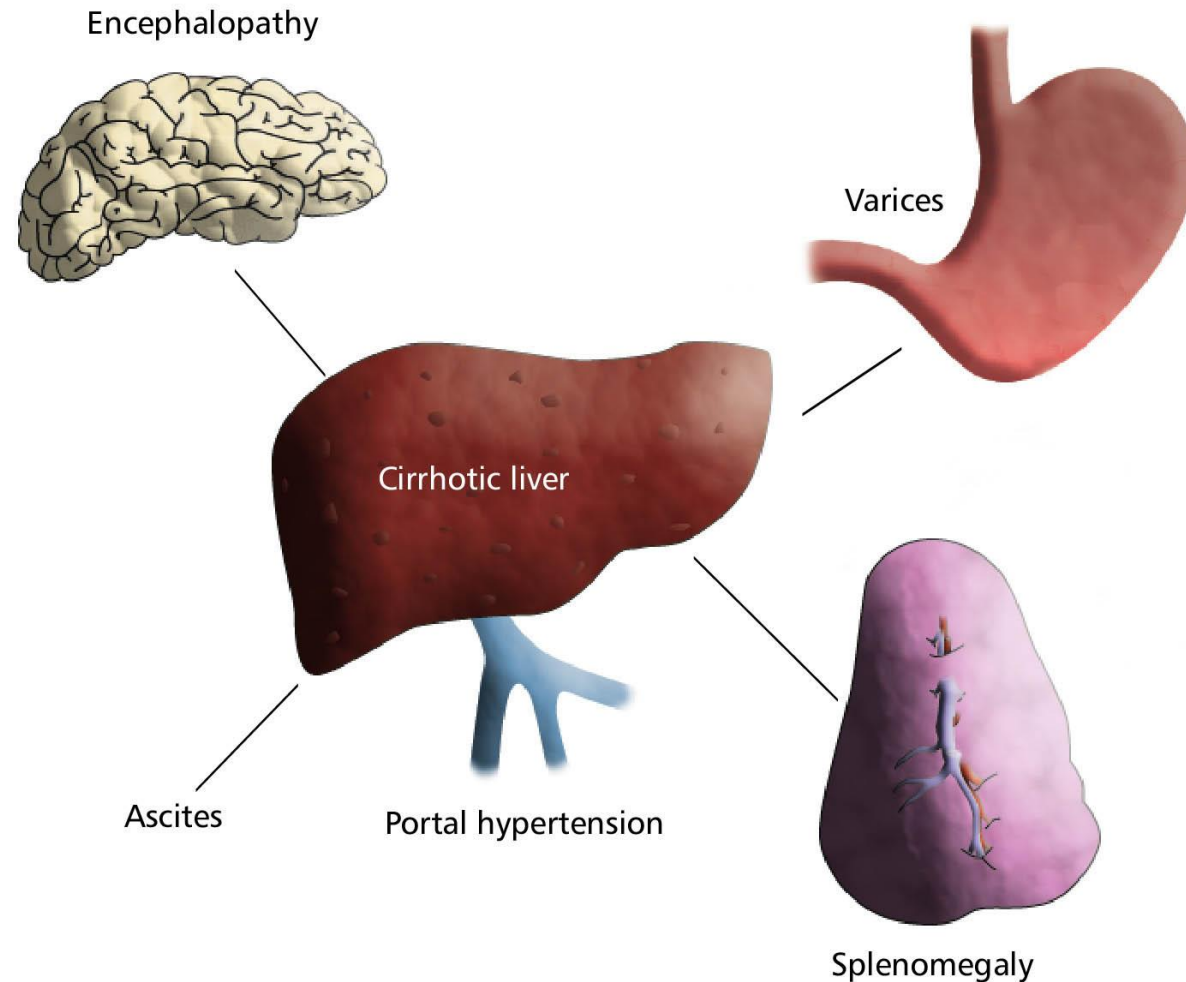
Spleen Parameters for the Detection of Esophageal Varices

Elastography, Spleen Size, and Platelet Count Identify Portal Hypertension in Patients With Compensated Cirrhosis

ANNALISA BERZIGOTTI,^{1,2,3} SUSANA SEJO,^{1,3} UMBERTO ARENA,⁴ JUAN G. ABRALDES,^{1,3} FRANCESCO VIZZUTTI,⁴
JUAN CARLOS GARCÍA-PAGÁN,^{1,3} MASSIMO PINZANI,⁴ and JAIME BOSCH^{1,3}



The Spleen in the Assessment of Advanced Chronic Liver Disease

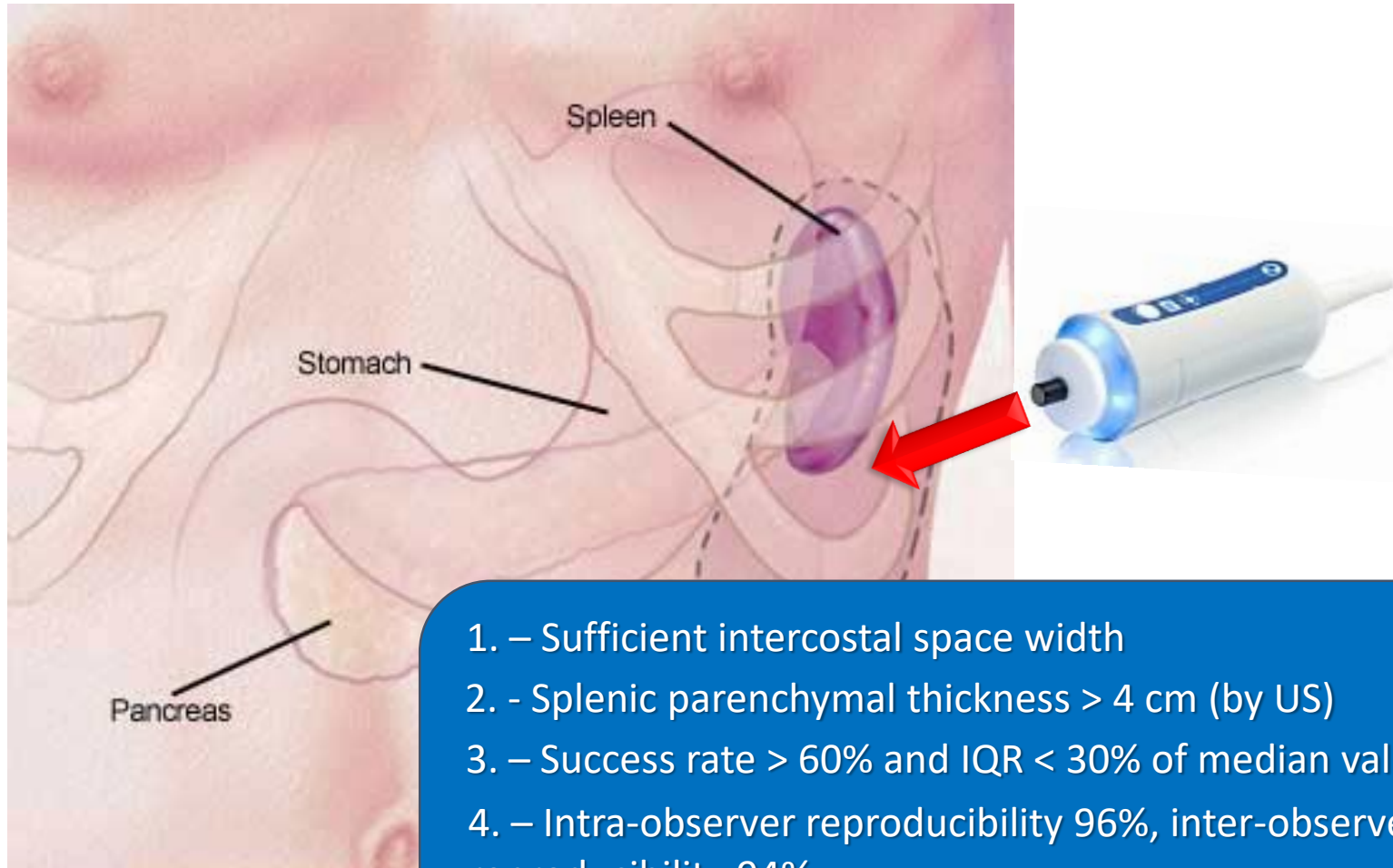


**INCREASE IN
SPLEEN
STIFFNESS ??**



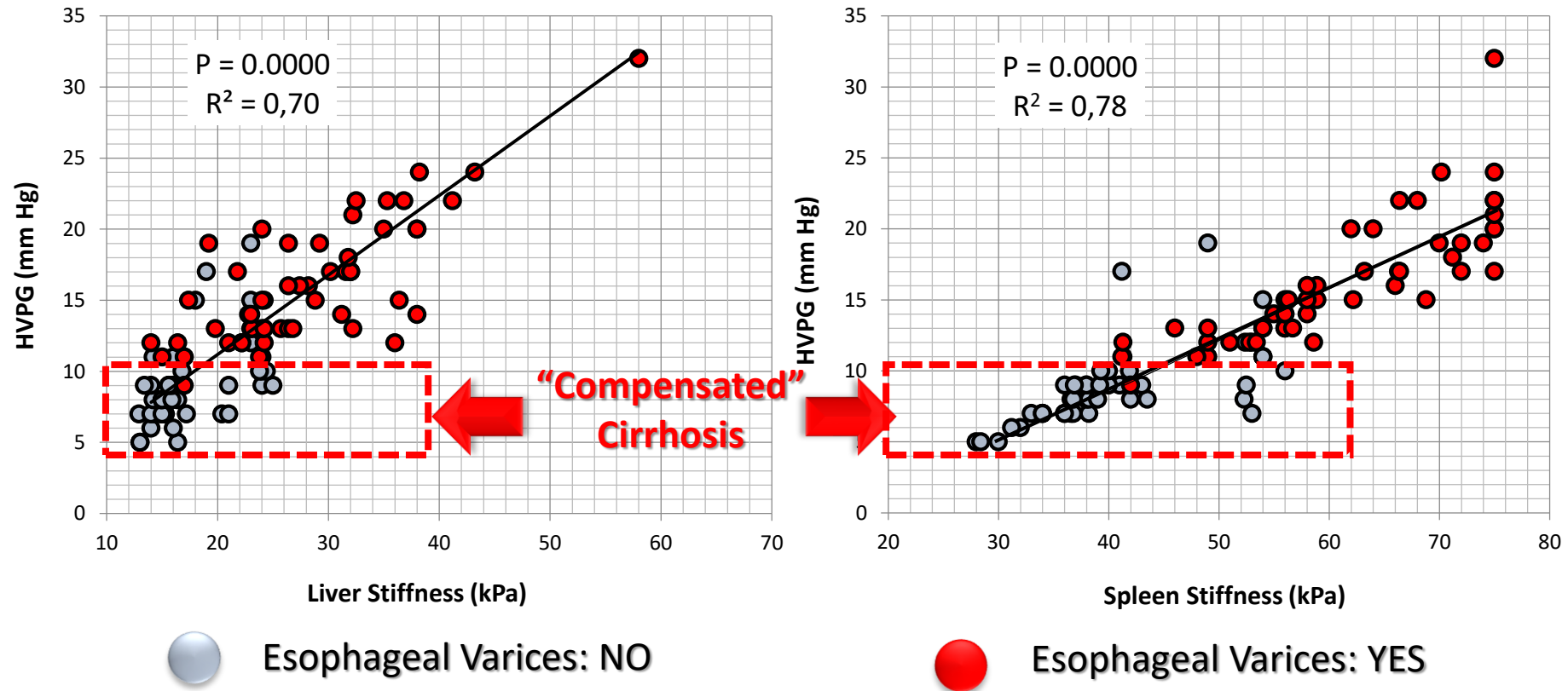
nd

Measurement of Spleen Stiffness by TE

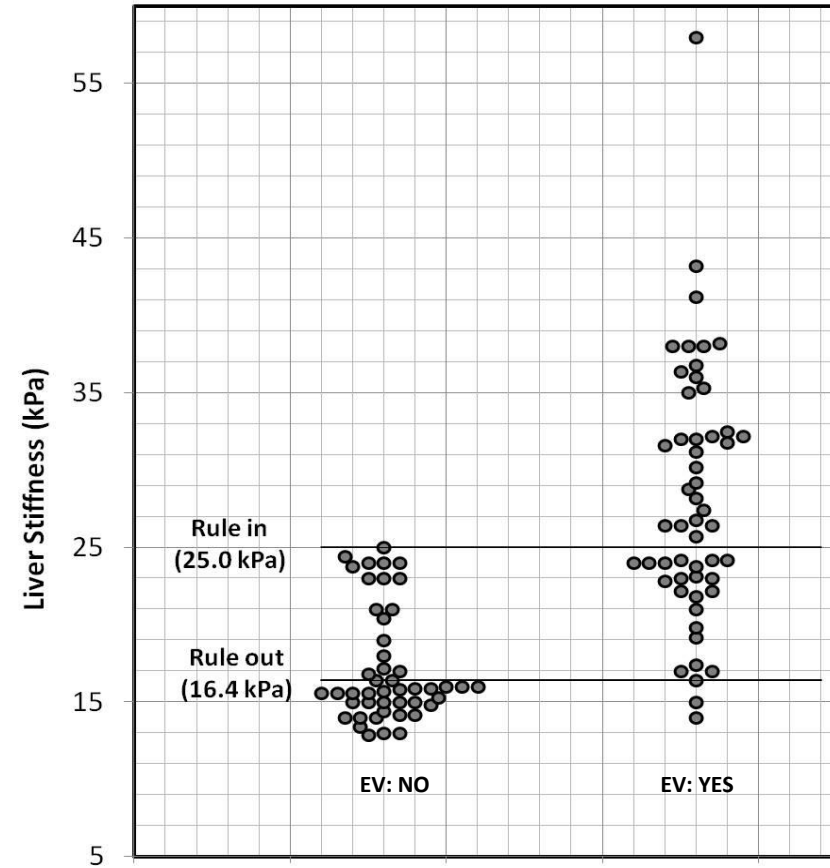
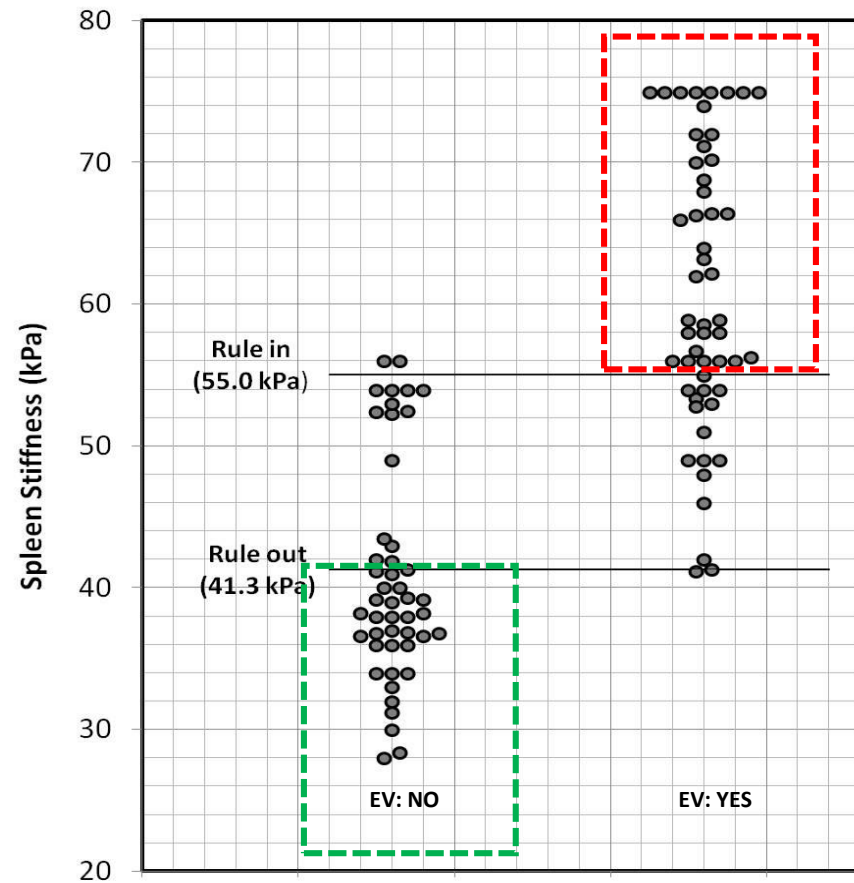


1. – Sufficient intercostal space width
2. – Splenic parenchymal thickness > 4 cm (by US)
3. – Success rate $> 60\%$ and IQR $< 30\%$ of median value
4. – Intra-observer reproducibility 96%, inter-observer reproducibility 94%
5. – Probe upper limit 75 kPa

Spleen Stiffness Vs. Liver Stiffness for the Detection of Esophageal Varices



Spleen Stiffness Vs. Liver Stiffness for the Detection of Esophageal Varices



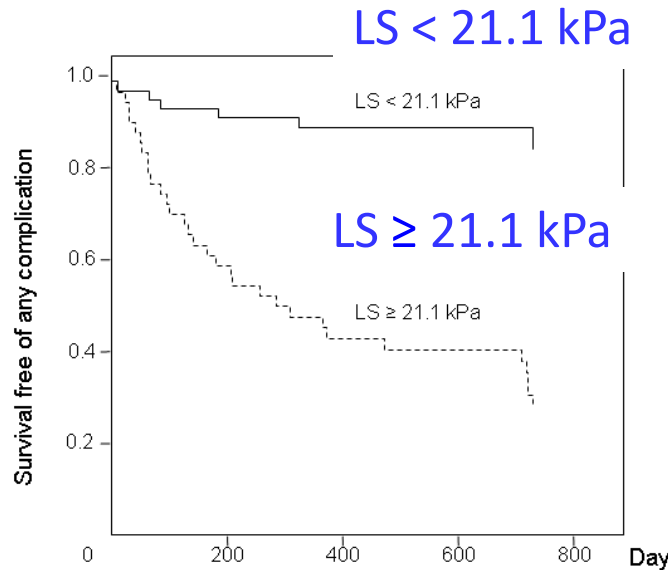
Combination of Spleen Stiffness and Liver Stiffness for the Diagnosis of PH



Site of increased resistance to portal flow		Liver stiffness	Spleen stiffness	HVPG
Pre-hepatic PH (EHPVO)		Normal	Increased	Normal
Intrahepatic PH	Pre-sinusoidal PH (idiopathic PH)	Normal or slightly elevated (<12 kPa)	Increased	Normal or slightly elevated (<10 mmHg) Often veno-venous communications
	Sinusoidal PH (cirrhosis; others)	Increased >13.6 kPa LSM ≥21 kPa: Spec >90% for CSPH	Increased	Increased: HVPG ≥10 mmHg defines CSPH
Post-hepatic PH (Budd-Chiari syndrome)		No published data; likely increased due to venous congestion	No published data; likely increased due to PH	Normal or increased, with high free hepatic venous P

Prognostic Capacity of Liver Stiffness Values

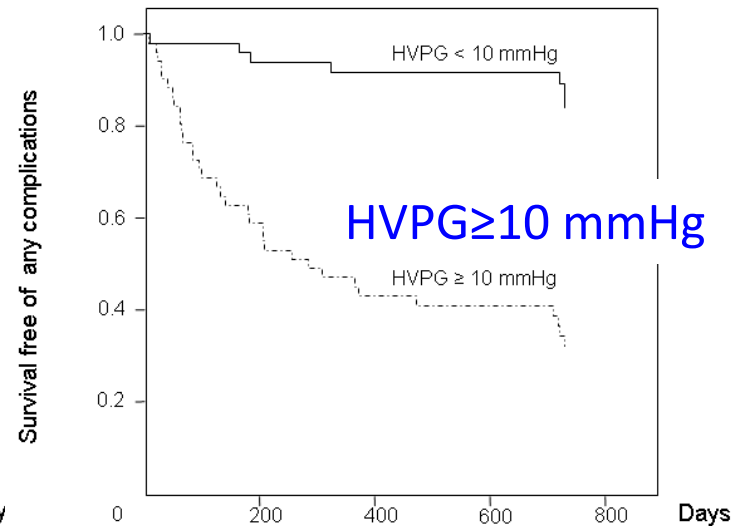
Risk of Decompensation



LS ≥ 21.1 kPa
AUROC 0.845
(0.767-0.923)

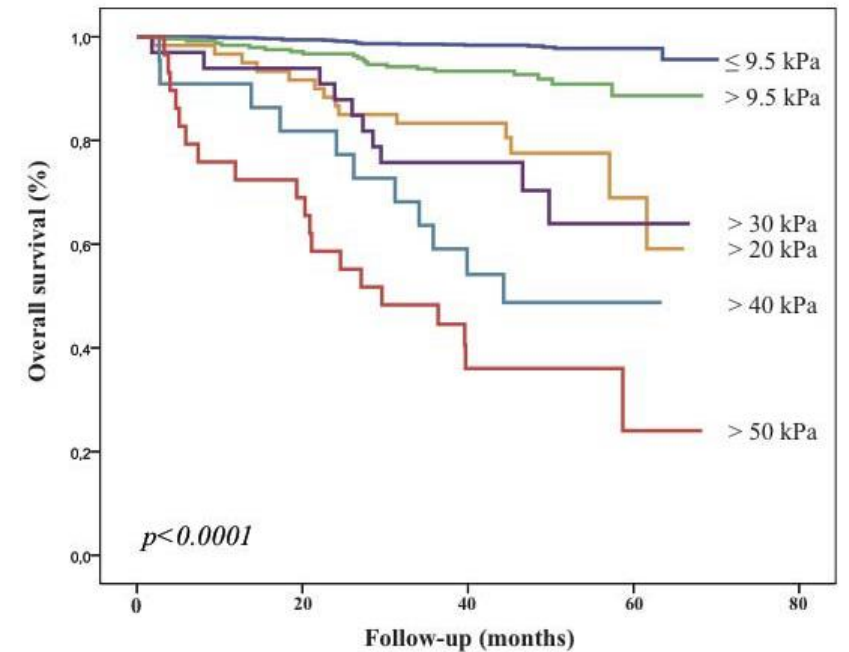
Robic, J Hepatol 2011

HVPG < 10 mmHg



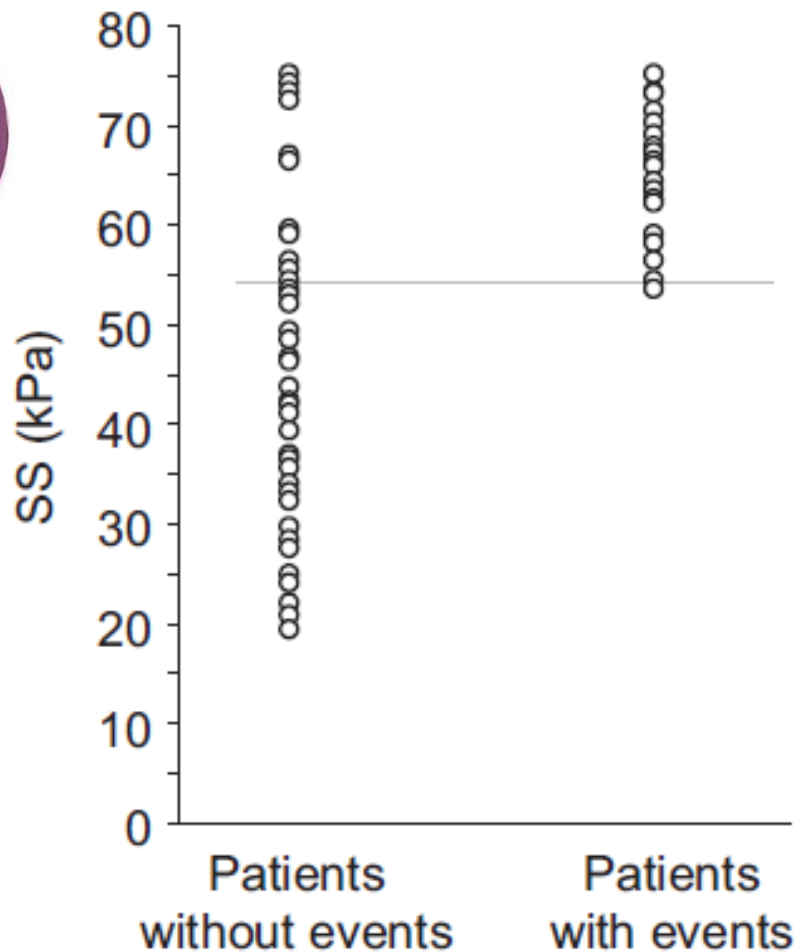
HVPG ≥ 10 mmHg
AUROC 0.830
(0.751-0.910)

Risk of Death



Vergniol, Gastroenterology 2011

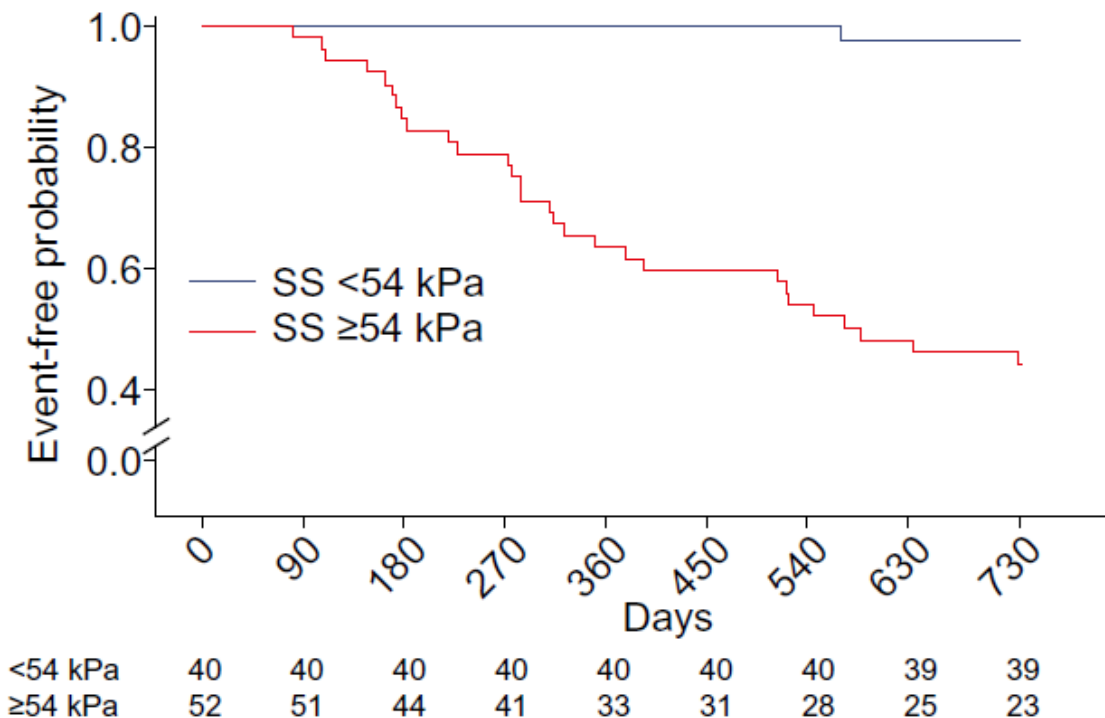
Prognostic Value of Spleen Stiffness in Cirrhosis



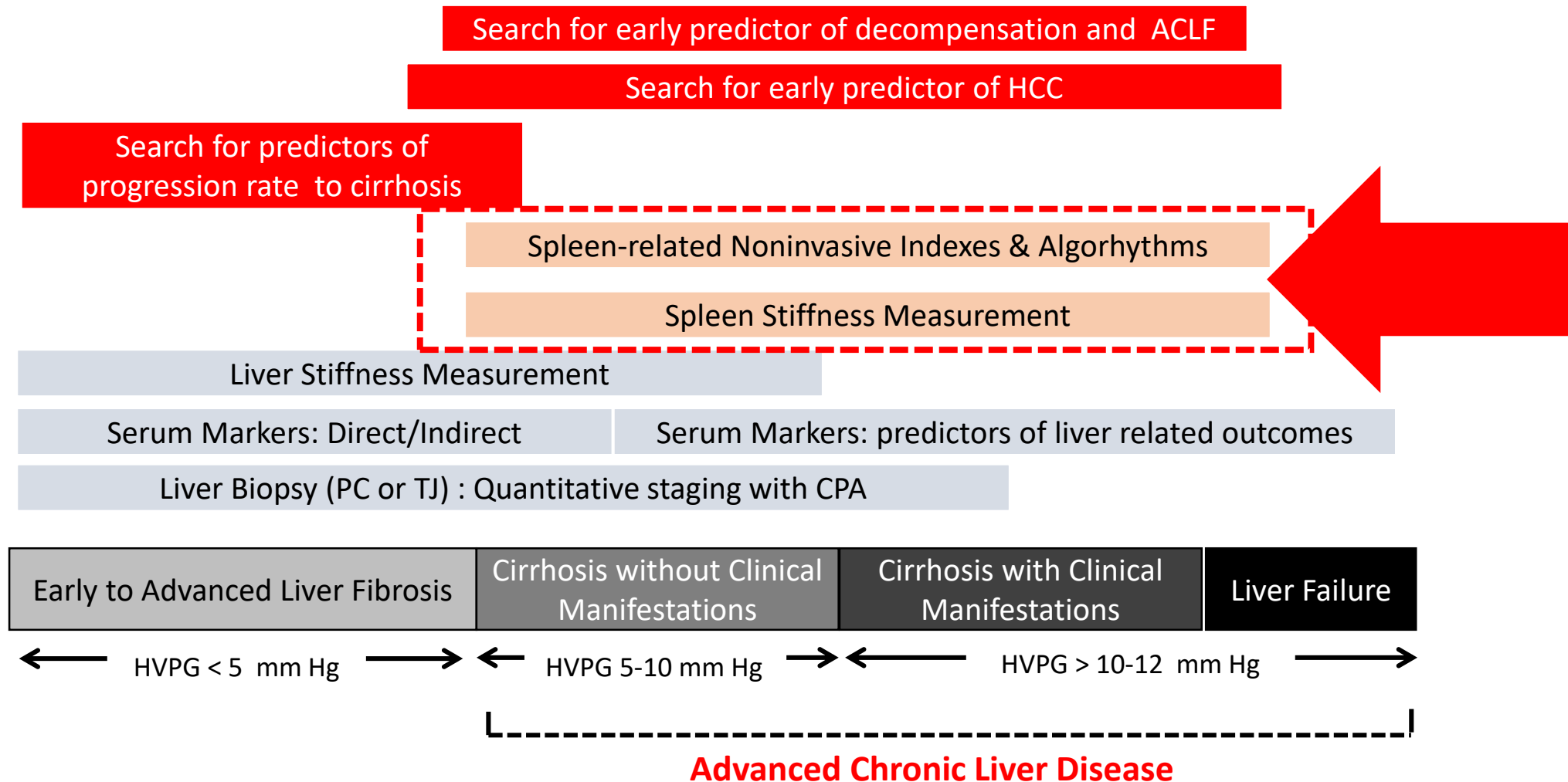
Cut-off = 54.0 kPa

NPV = 0.975, 95% CI: 0.868-0.999

LR- = 0.061, 95% CI: 0.009-0.424



Invasive and Non Invasive Methods for the Assessment of Liver Fibrosis



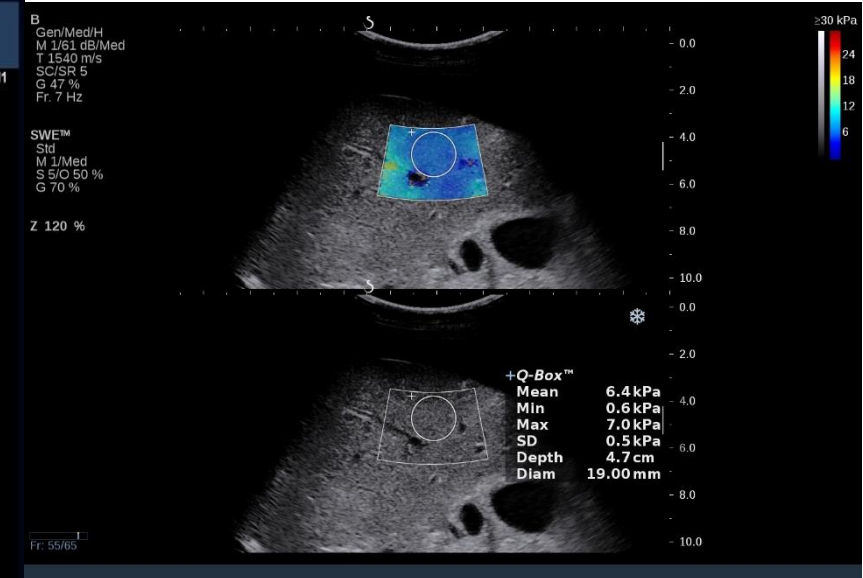
Newer US Elastography: Visual Control of Stiffness Measurement



Acoustic Radiation Force Impulse Im.
Virtual touch imaging (Siemens)



PQ Shearwave elastography
(Philips)

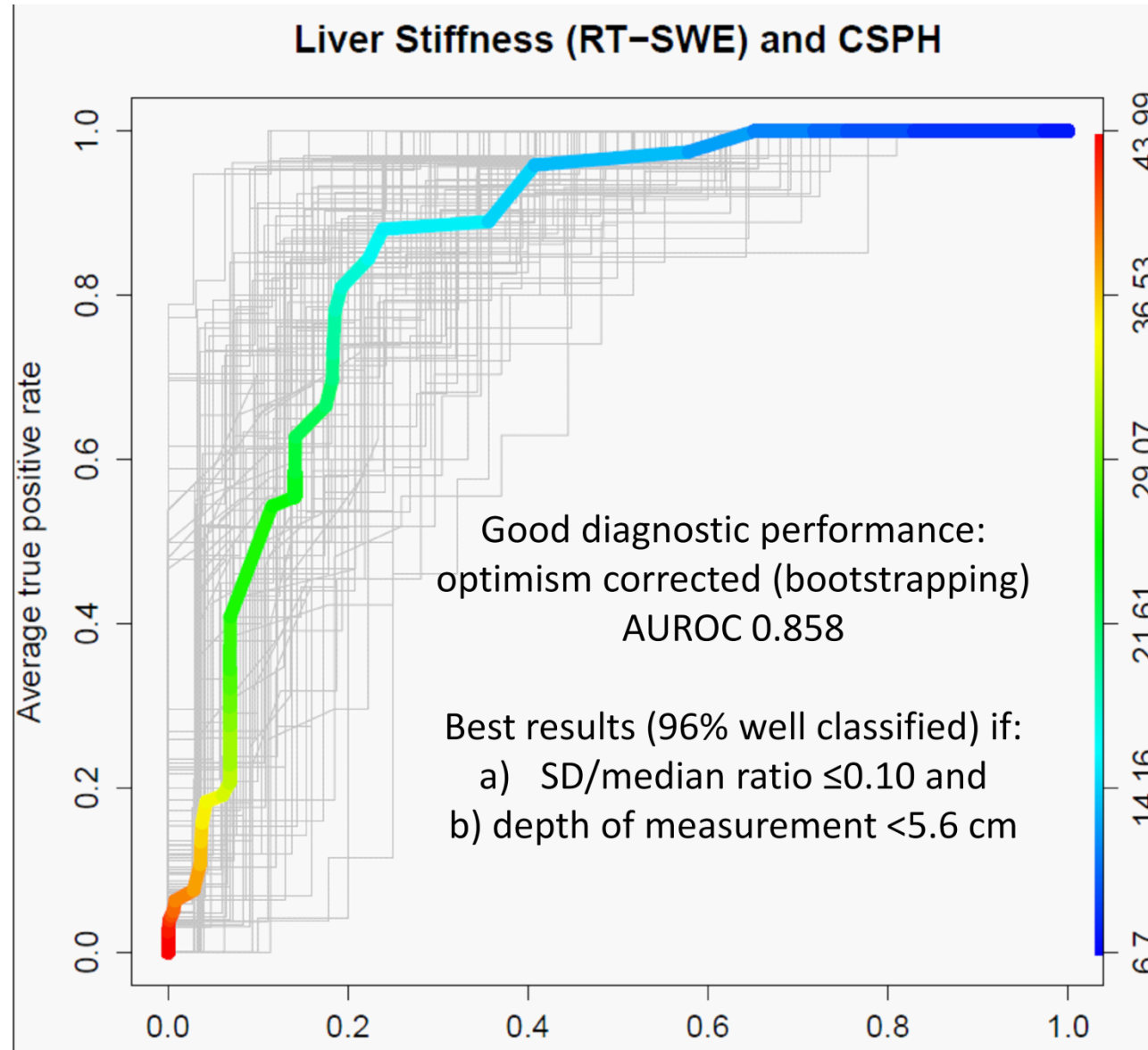


2D Real Time ShearWave™ Elastography
(SuperSonic Imagine)

Point Shear Wave Elastography

2D Shear Wave Elastography
(Others: General Electrics; Toshiba)

TE and 2D-SWE Have Similar Accuracy for Portal Hypertension



Metanalysis of individual data of patients included in 8 studies is ongoing

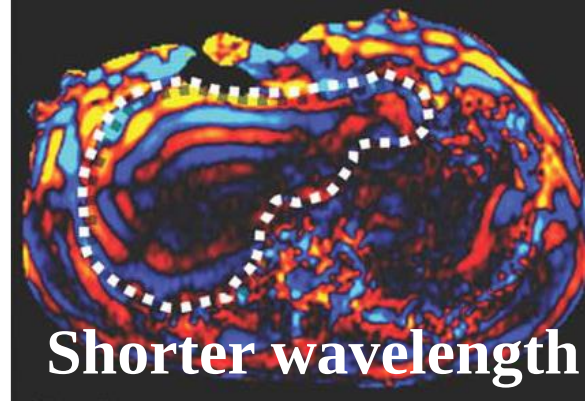
Procopet & Berzigotti et al. J Hepatol 2015

MRE? Data not yet available and needed.....

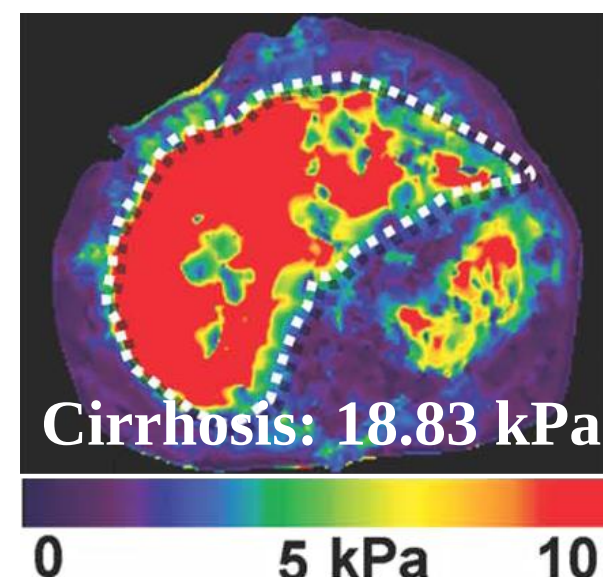
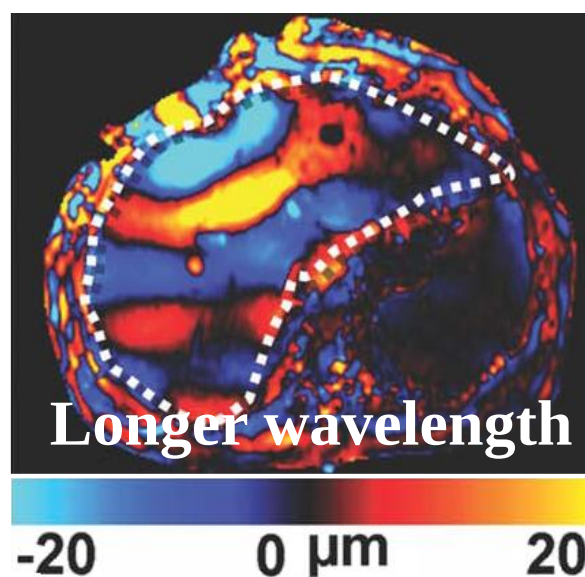
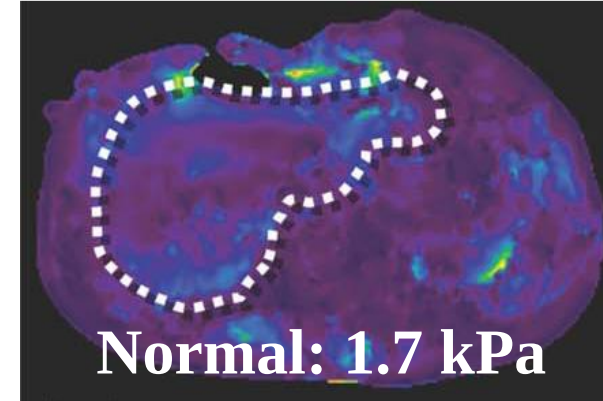
Conventional MR



Wave images at 60 Hz



MR elastography





www.ucl.ac.uk/medicine/liver-and-digestive-health

