



# Quantification of fibrosis and cirrhosis outcomes

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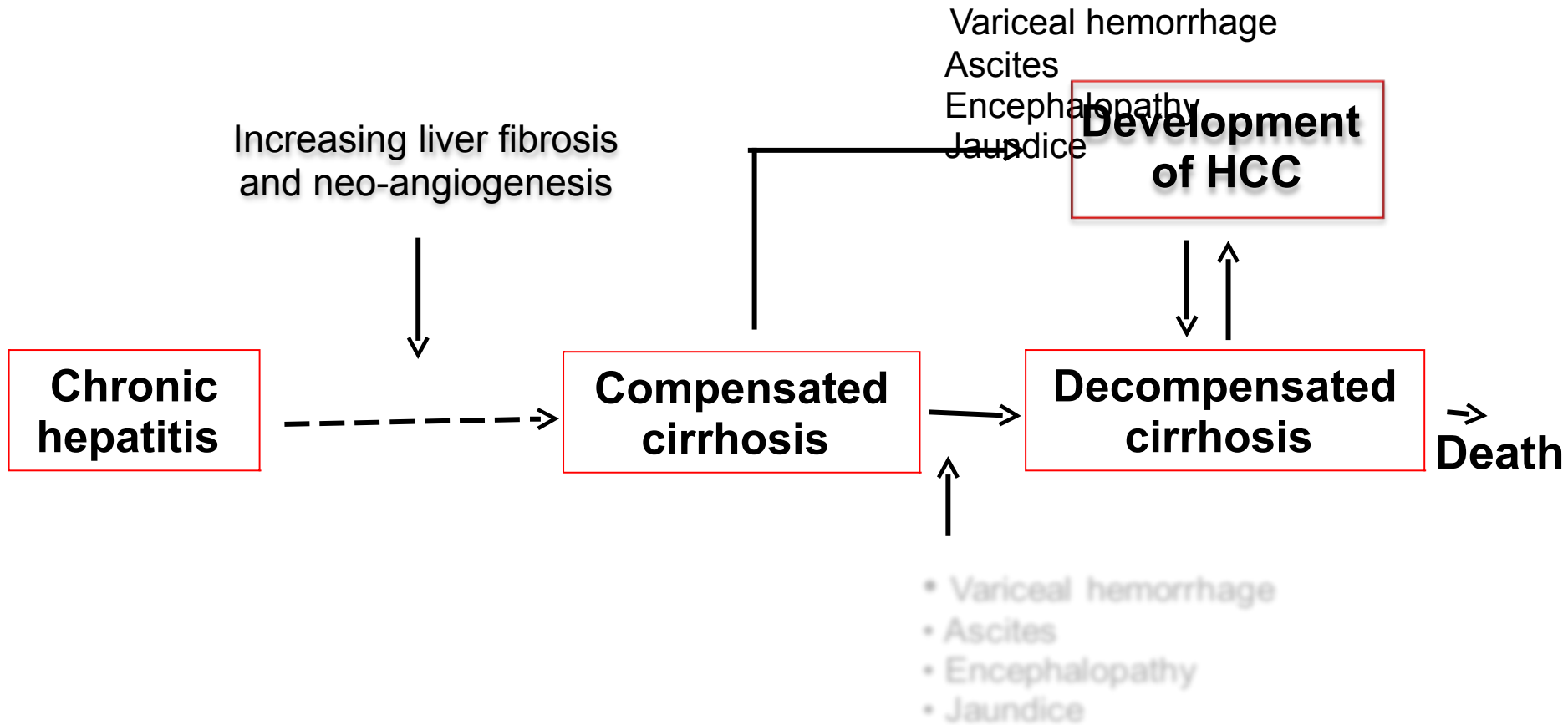
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# The natural history of chronic liver disease



- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice

**Esophageal Varices**



Hepatic Venous Pressure Gradient (HVPG) (mm Hg)



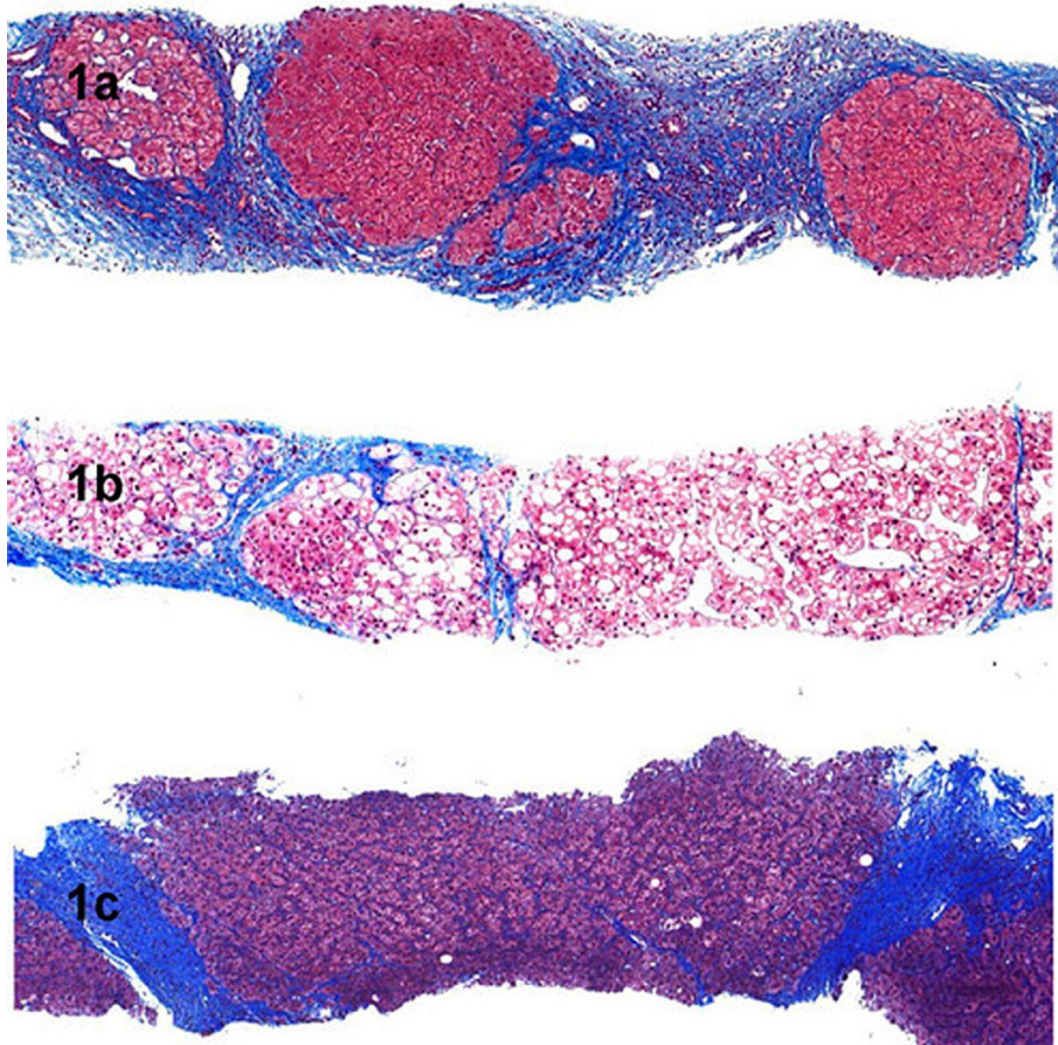
# Cirrhosis is a progression of stages of increasing severity and non-reversibility

	Metavir F4 Ishak S 5-6	Metavir F4 Ishak S 6	Metavir F4 Ishak S 6	Metavir F4 Ishak S 6	Metavir F4 Ishak S 6
<b>Biology:</b>	Fibrogenesis & angiogenesis	Scar X-linking	Acellular scar Nodule size	Insoluble scar & small nodules	Scars & large nodules
<b>HVPG:</b>		> 5	> 10	> 12	≥ 12
<b>Clinical:</b>	none	none	Varices formation	Ascites (without VH)	VH (+ ascites)
<b>Stage:</b>	Early stage cirrhosis	Compensated (stage 1)	Compensated (stage 2)	Decompensated (stage 3)	Decomp (stage 4)

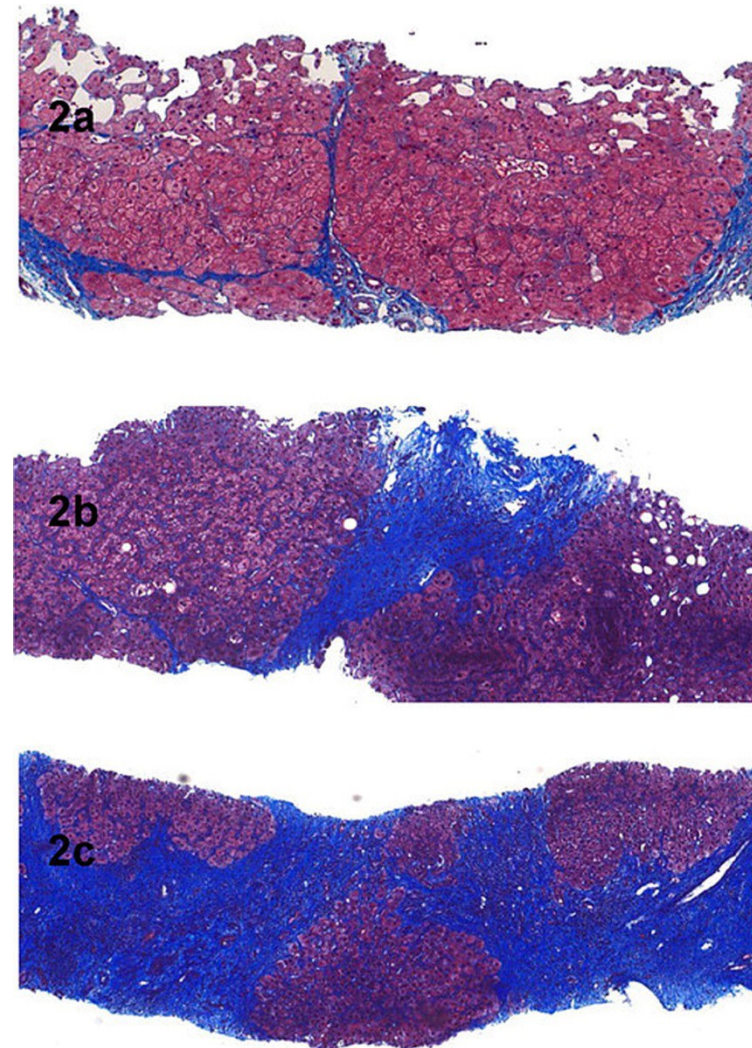


# Histological classification of the severity of cirrhosis

Size of the nodule

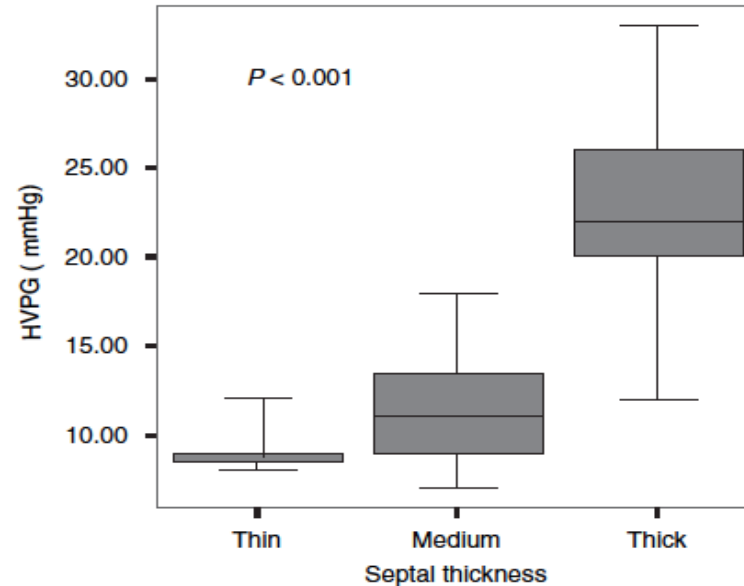
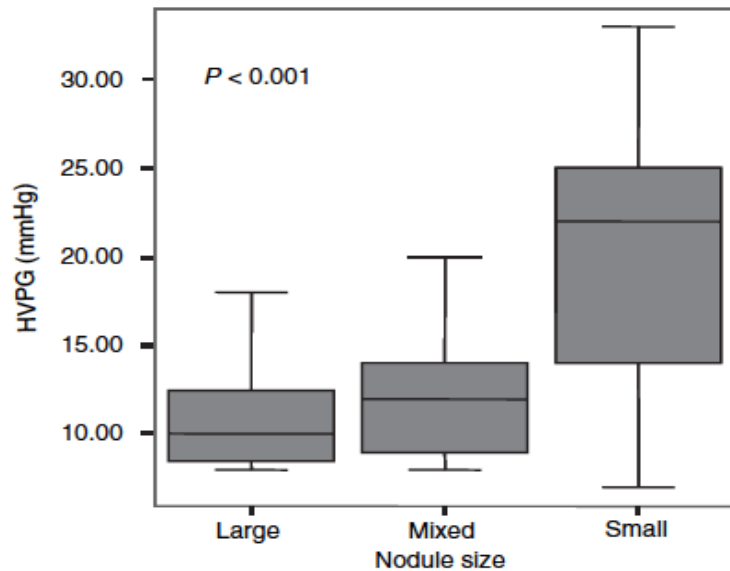
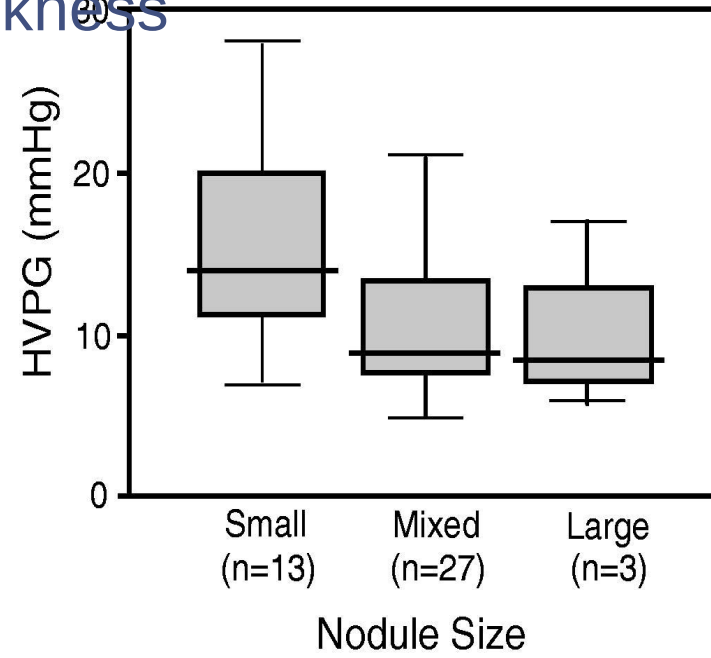
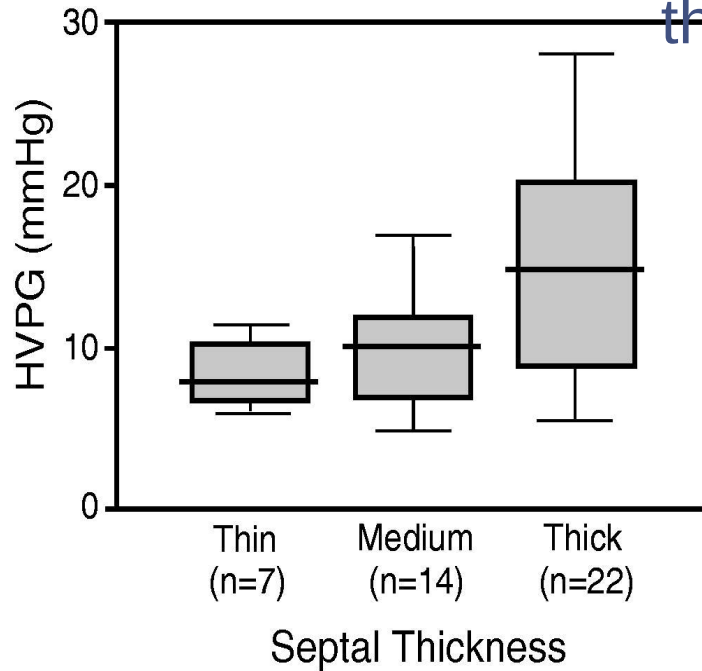


Thickness of septa

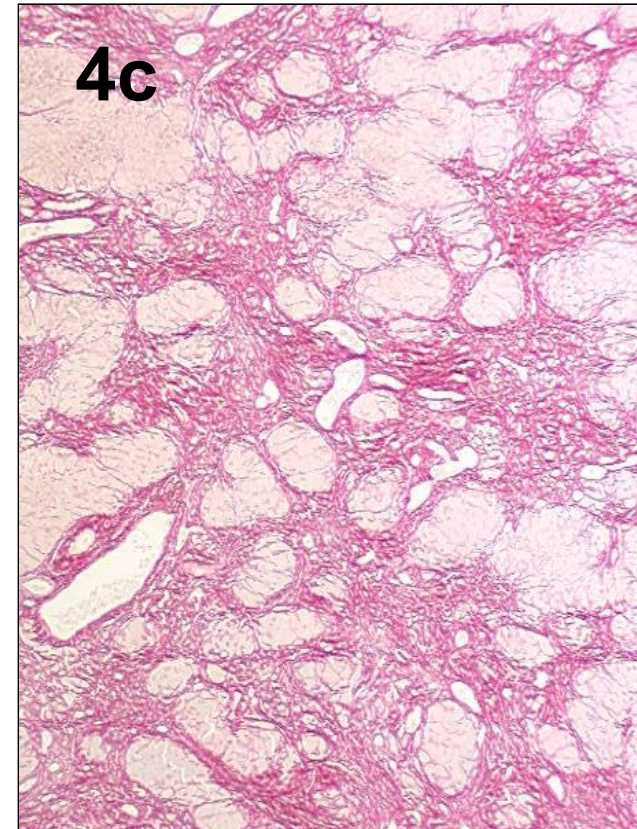
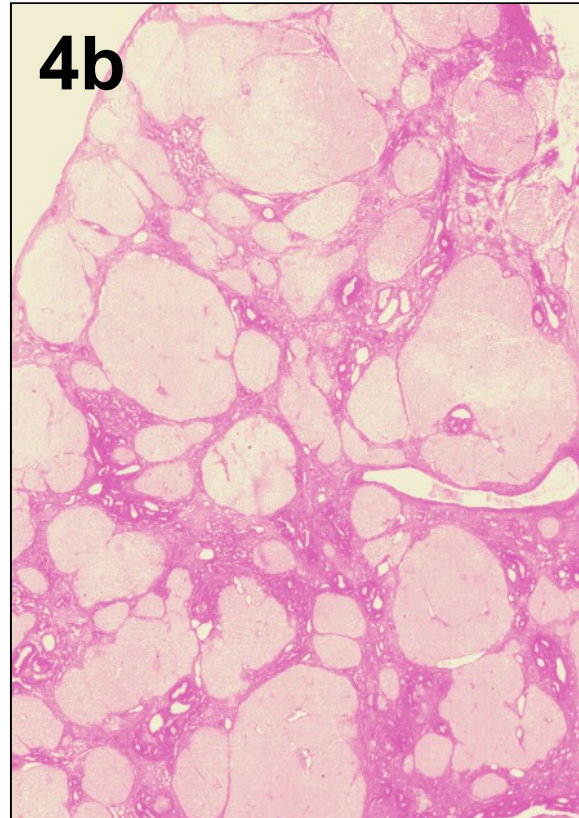
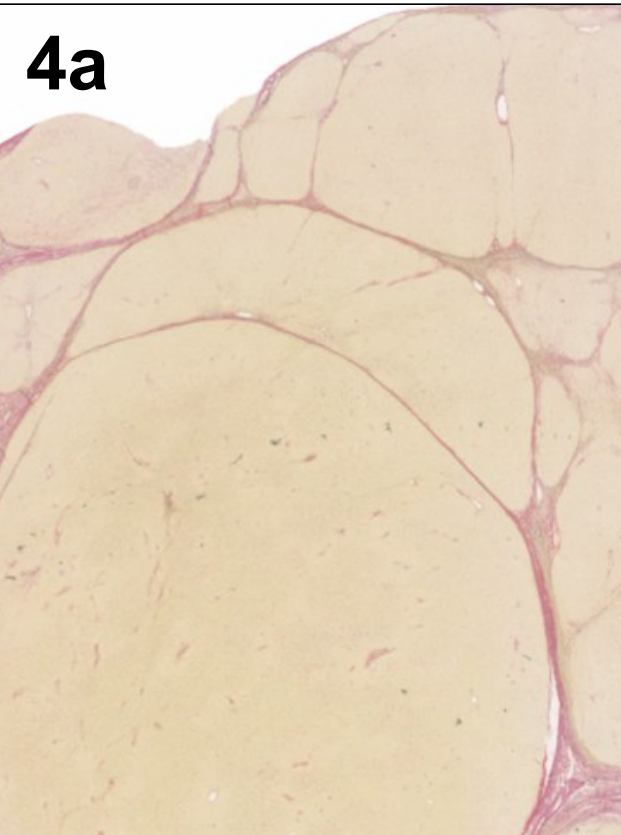




# Distribution of HVPG according to nodule size and septal thickness

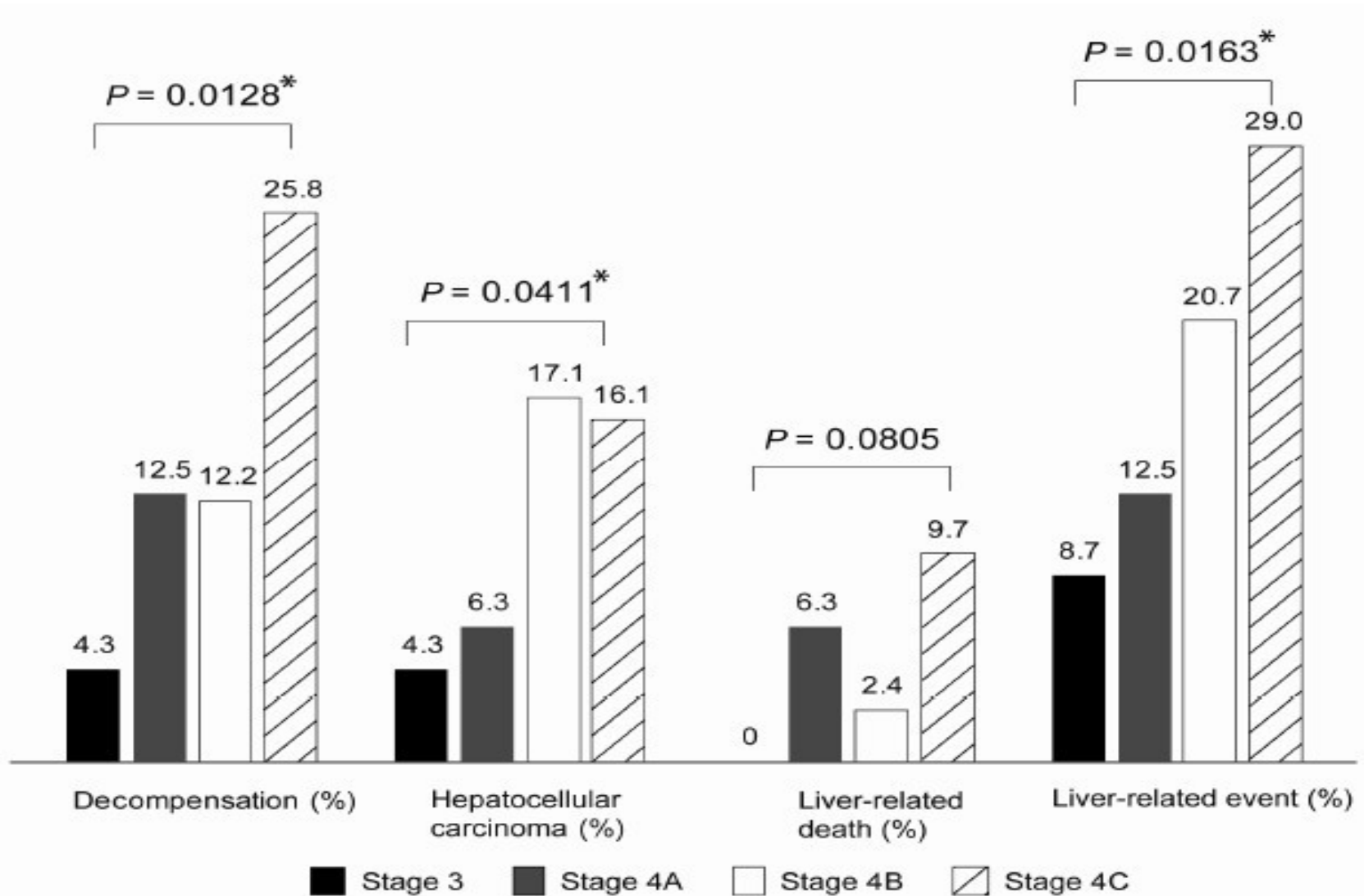


# The Laennec scoring system of cirrhosis



Thickness of septa / size of the nodule

# The Laennec scoring system for stratification of prognosis in patients with liver cirrhosis



# Issues for histological assessment of liver fibrosis

Histological scoring systems categorize architectural changes

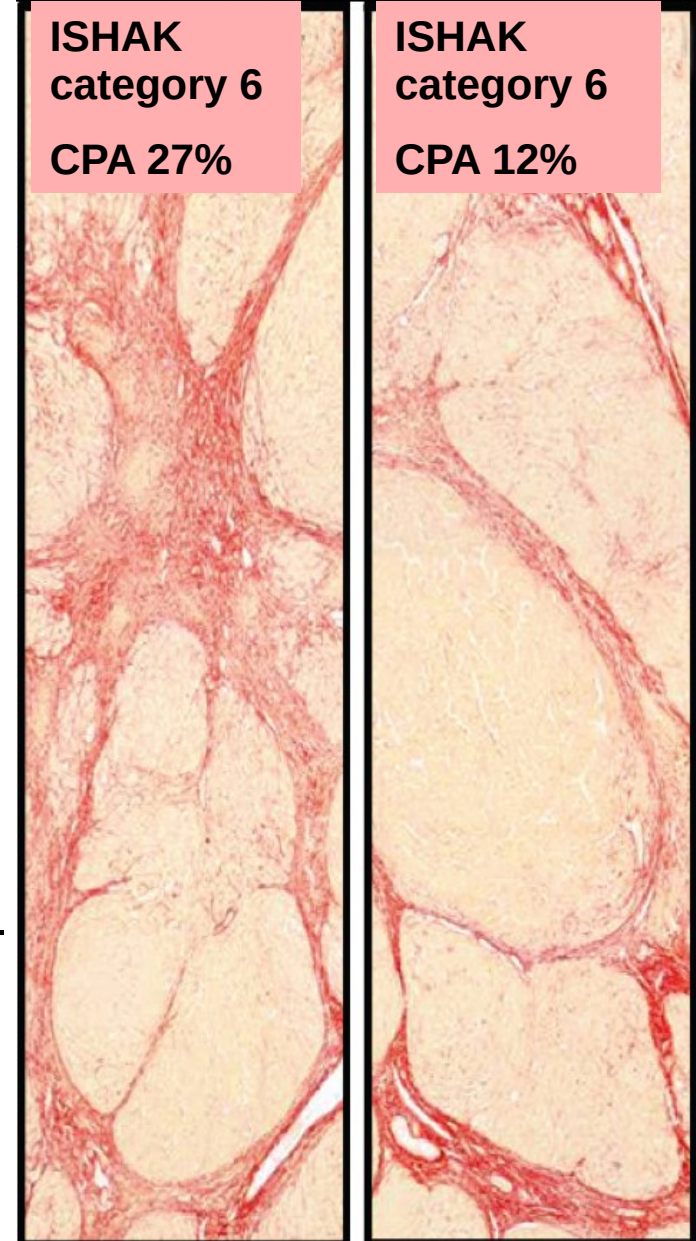
No quantitative progression across worsening categories

No relation to amount of collagen (fibrosis) using trichrome/ reticulin stains which are general connective tissue stains

**Standish, 2006**

Sirius red staining identifies primarily collagen - the major constituent of fibrosis in chronic liver disease

**Puchtler, 1988**





# Correlation between area of fibrosis / Metavir stage

# Correlation between area of fibrosis /Ishak stage

Area of fibrosis (%)

METAVIR STAGE	Area of fibrosis by image analysis (mean + SEM)
F0	2 ± 0.14
F1	3.4 ± 0.25
F2	5.8 ± 1.7
F3	14.7 ± 3.77
F4	25.1 ± 4.44


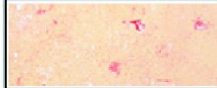
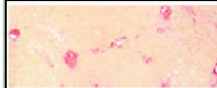
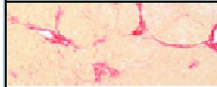
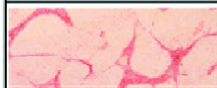
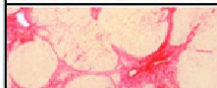
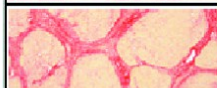
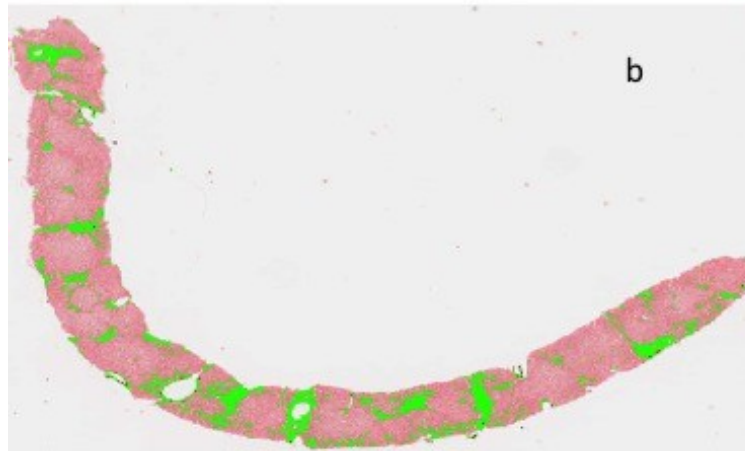
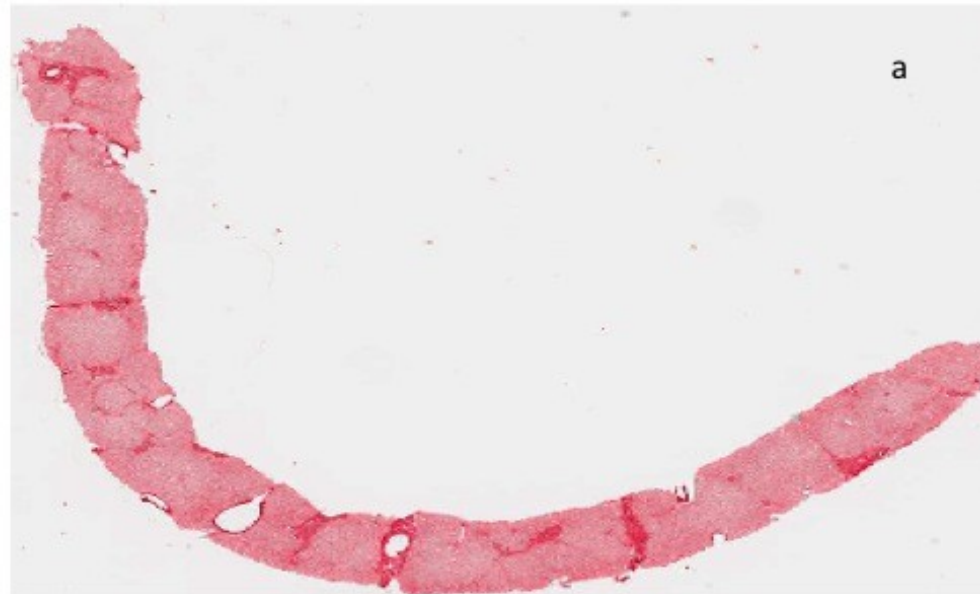
Appearance	Ishak stage: Categorical description	Ishak stage: Categorical assignment	Fibrosis measurement*
	No fibrosis (normal)	0	1.9%
	Fibrous expansion of some portal areas ± short fibrous septa	1	3.0%
	Fibrous expansion of most portal areas ± short fibrous septa	2	3.6%
	Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging	3	6.5%
	Fibrous expansion of portal areas with marked bridging (portal to portal (P-P) as well as portal to central (P-C))	4	13.7%
	Marked bridging (P-P and/or P-C), with occasional nodules (incomplete cirrhosis)	5	24.3%
	Cirrhosis, probable or definite	6	27.8%

Figure 1 Stage component of the Ishak system. \*Proportion (%) of area of illustrated section showing Sirius red staining for collagen (collagen proportionate area).

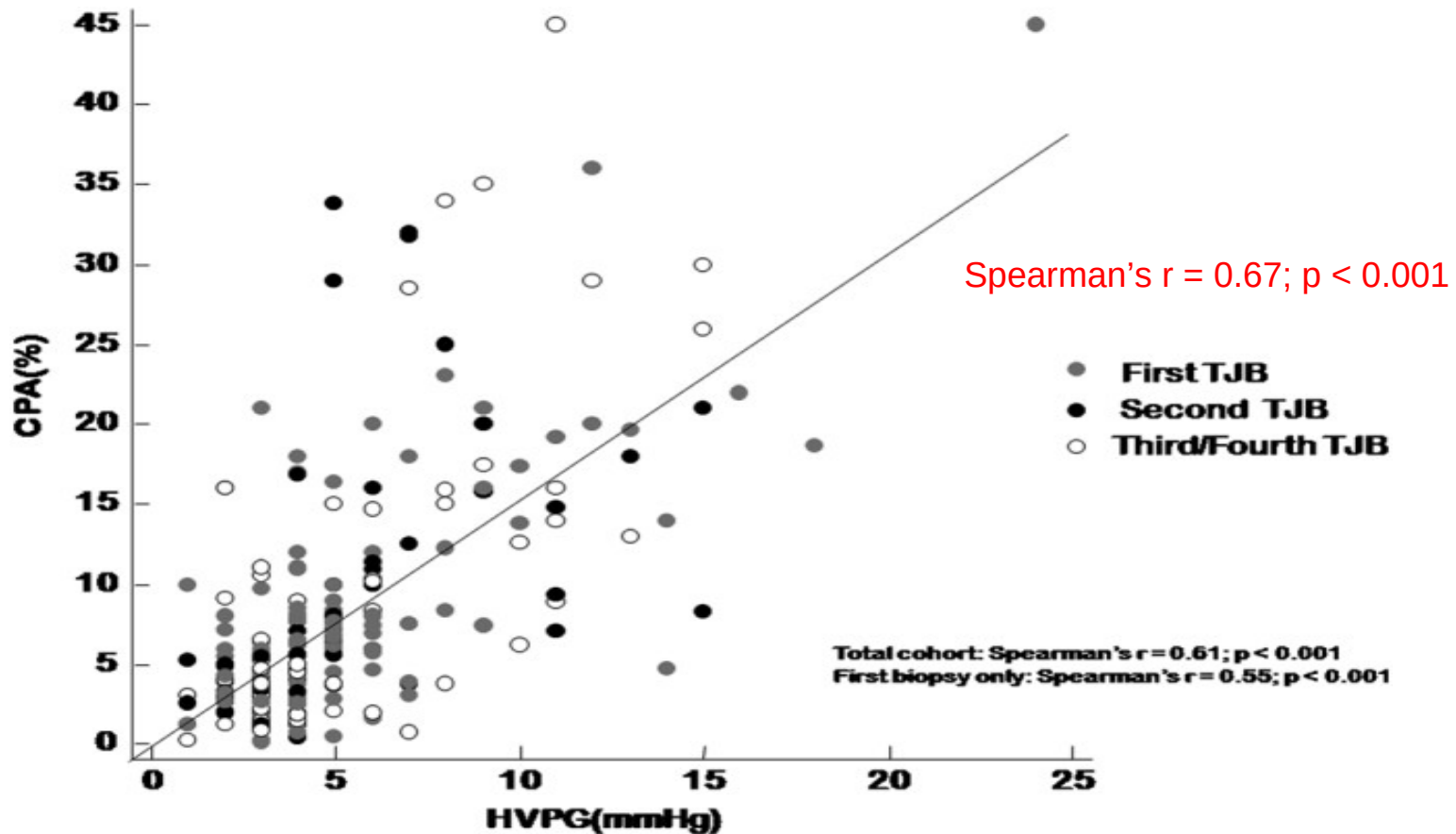
# Computer assisted Digital Image Analysis (DIA)

Using segmentation of digital images to measure collagen proportionate area (CPA)

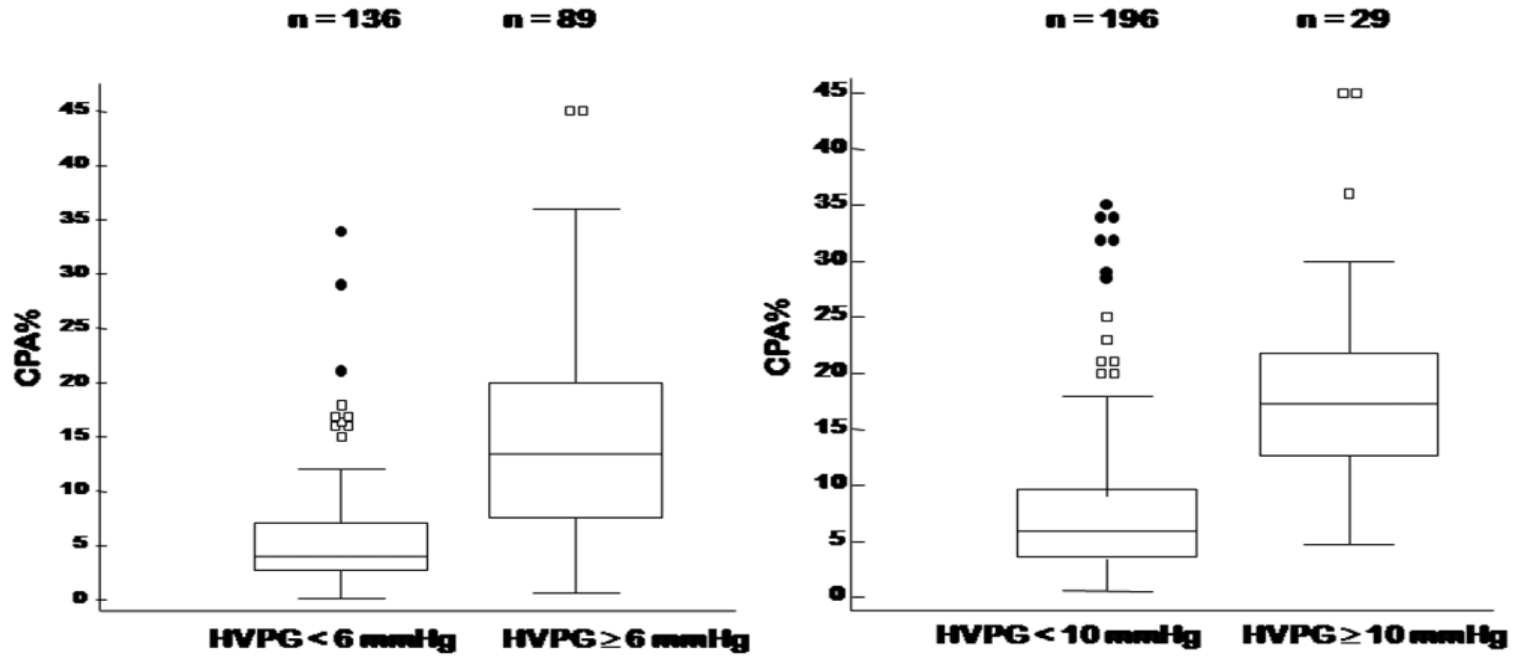


# Computer-Assisted Image Analysis of Liver Collagen: Relationship to Ishak Scoring and Hepatic Venous Pressure Gradient

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# Relationship between CPA and HVPG



	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
<b>Predictor of HVPG ≥ 6 mm Hg</b>				
Ishak grading score		<0.0001	1.214 (0.940-1.567)	0.138
Ishak staging score		<0.0001	1.372 (0.979-1.923)	0.067
Collagen proportionate area (%)		<0.0001	1.206 (1.094-1.331)	<b>&lt;0.001</b>
<b>Predictor HVPG ≥ 10 mm Hg</b>				
Ishak grading score		0.003	1.126 (0.812-1.561)	0.477
Ishak staging score		<0.0001	1.577 (1.000-2.482)	0.05
Collagen proportionate area (%)		<0.0001	1.105 (1.026-1.191)	<b>0.009</b>

# Invasive and non invasive evaluation of disease progression in chronic viral hepatitis

Search for predictor of progression rate to cirrhosis

Search for early predictor of decompensation

Search for early predictor of HCC

Spleen-related Non Invasive Indexes and Algorithms

Spleen stiffness measurement

Liver stiffness measurement

Serum markers: Direct/Indirect

Serum markers: predictors of liver related outcomes

Liver biopsy (PC or TJ): quantitative staging of CPA

Early to advanced liver fibrosis

Cirrhosis without clinical manifestations

Cirrhosis with clinical manifestations

Liver Failure

Advanced chronic liver disease (ACLD)

PHASE 1

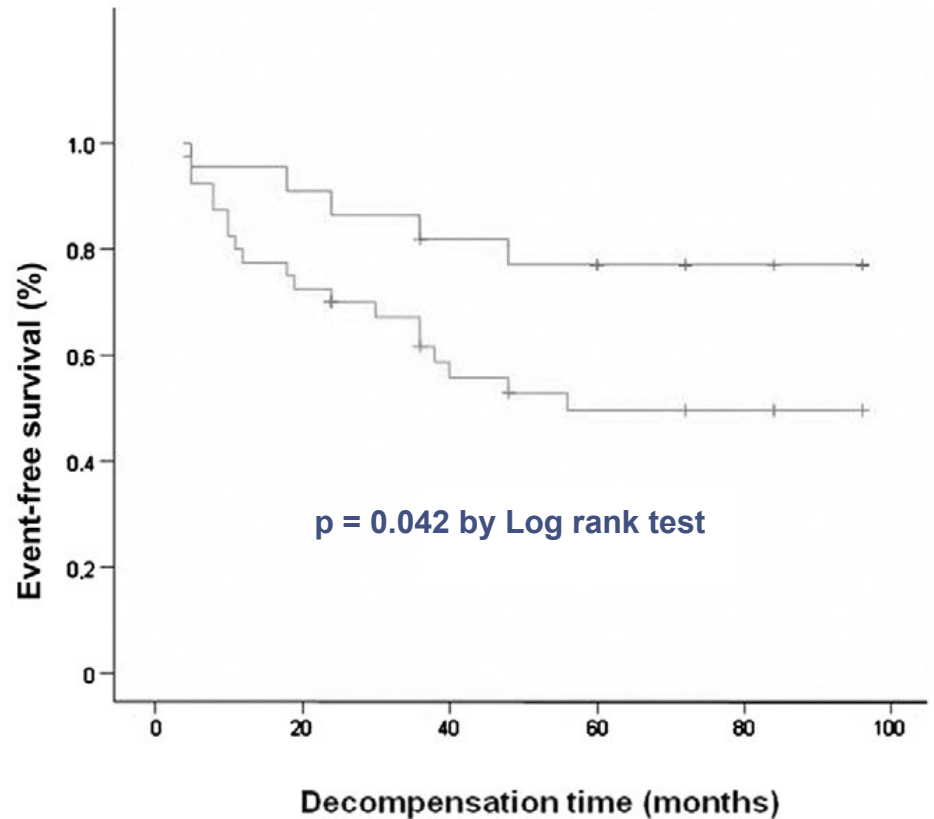
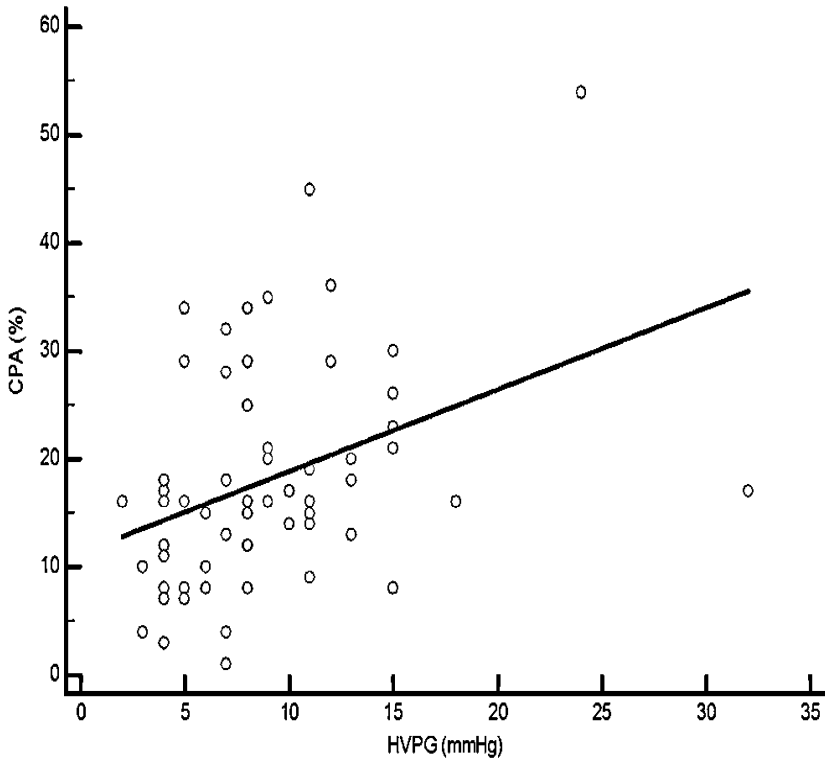
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# CPA correlates with HVPG and predict decompensation in patients with recurrent HCV infection and liver cirrhosis

## CPA correlates with HVPG

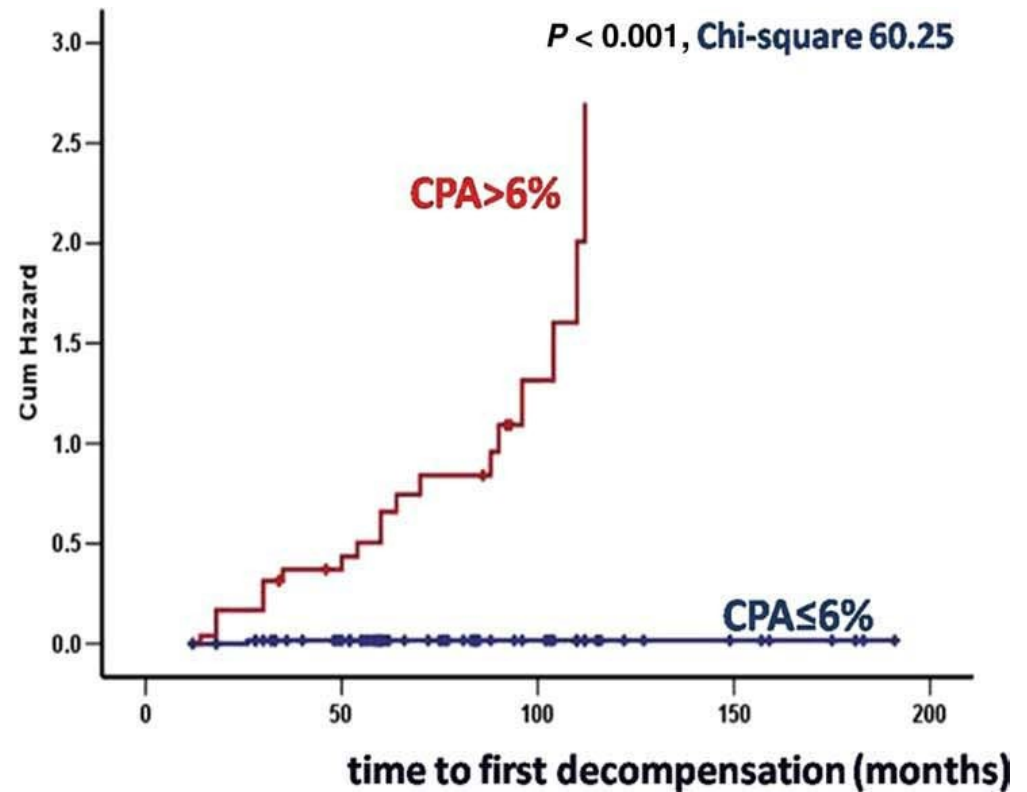
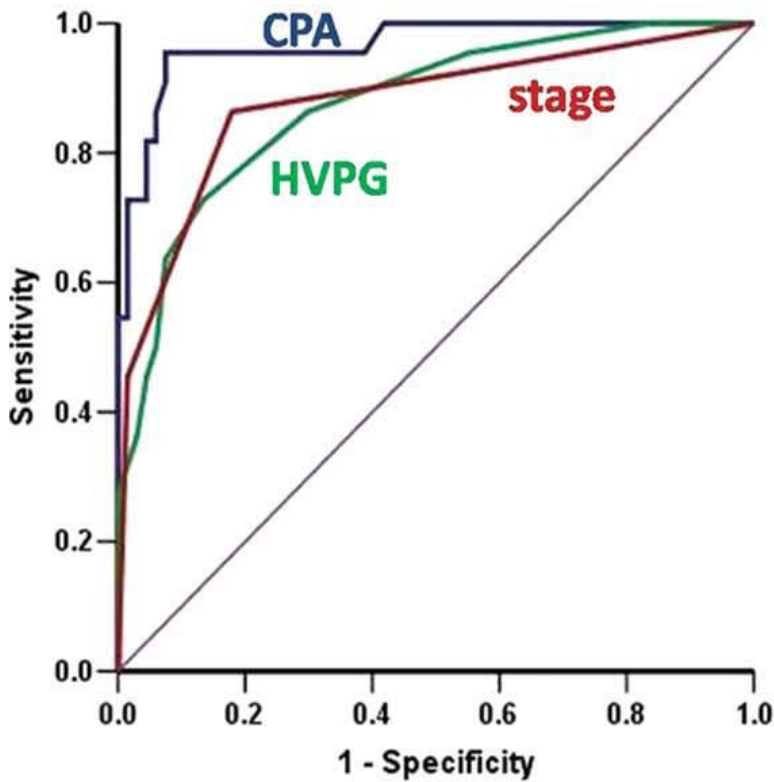
## CPA predicts decompensation



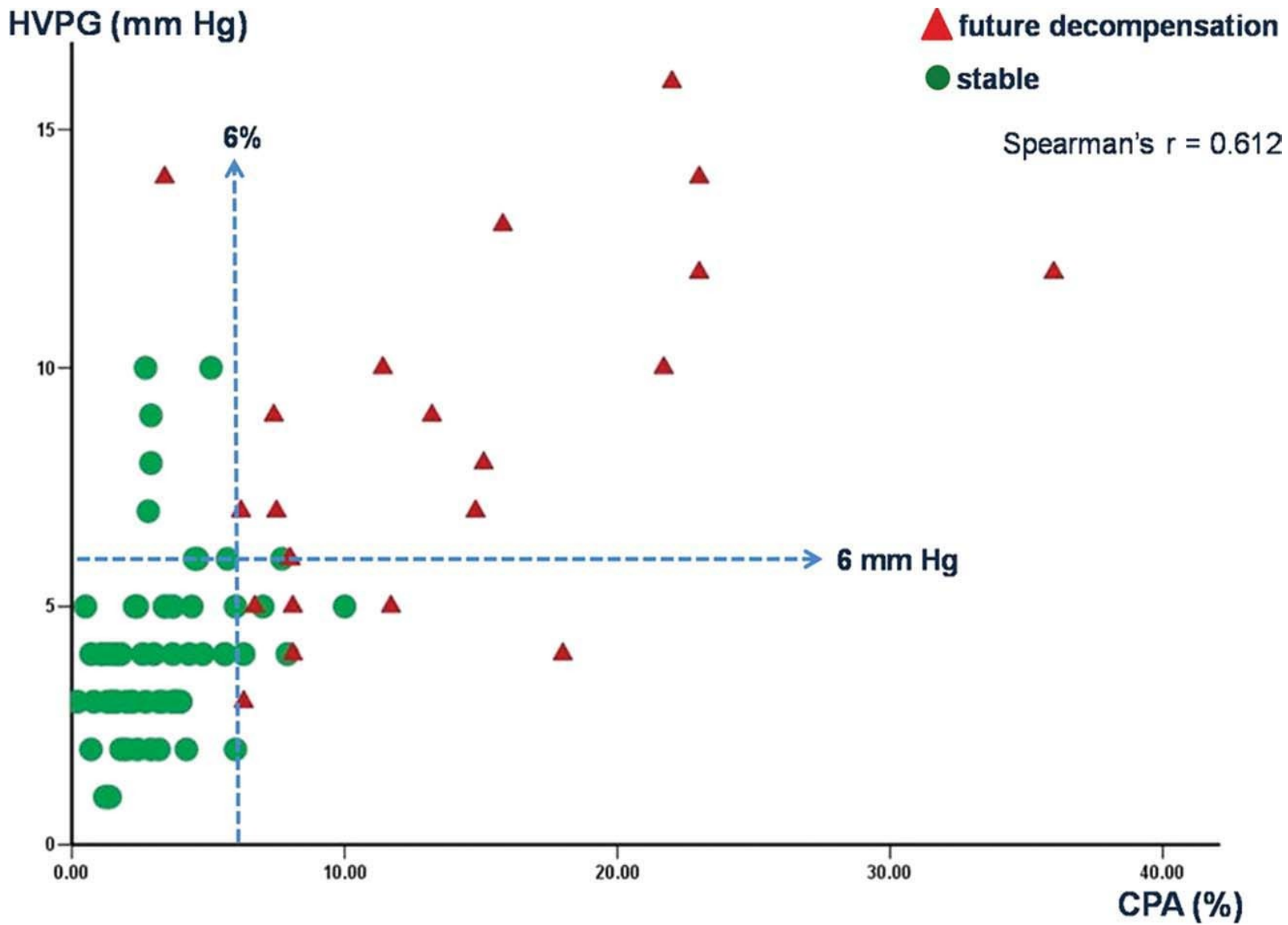
# Clinical and histological associations with CSPH in 43 patients with recurrent HCV infection, and Ishak stage 5 or 6 after OLT

	Univariate analysis			Multivariate analysis	
	HVPG			OR (95% CI)	P-value
	< 6 mmHg	≥ 6 mmHg	P-value		
Ishak grading score	5 (3-6)	6 (4-7)	0.188		
Ishak staging score = 6	4/14 (28.6%)	13/28 (46.4%)	0.323		
CPA (%)	12.0 (7.5-17.2)	17.4 (13.0-24.0)	0.096	1.057 (0.978-1.142)	0.165
CPS	6.0 (5-7)	5 (5-8)	0.354		
	HVPG			OR (95% CI)	P-value
	< 10 mmHg	≥ 10 mmHg	P-value		
	Ishak grading score	6 (4-6)	6 (4.5-7)	0.723	
Ishak staging score = 6	11/29 (37.9%)	5/13 (38.5%)	0.823		
CPA (%)	15.7 (8.2-19.0)	19.2 (16.0-28.7)	0.054	1.085 (1.004-1.172)	<b>0.040</b>
CPS	5 (5-7)	6.0 (5-10)	0.550		

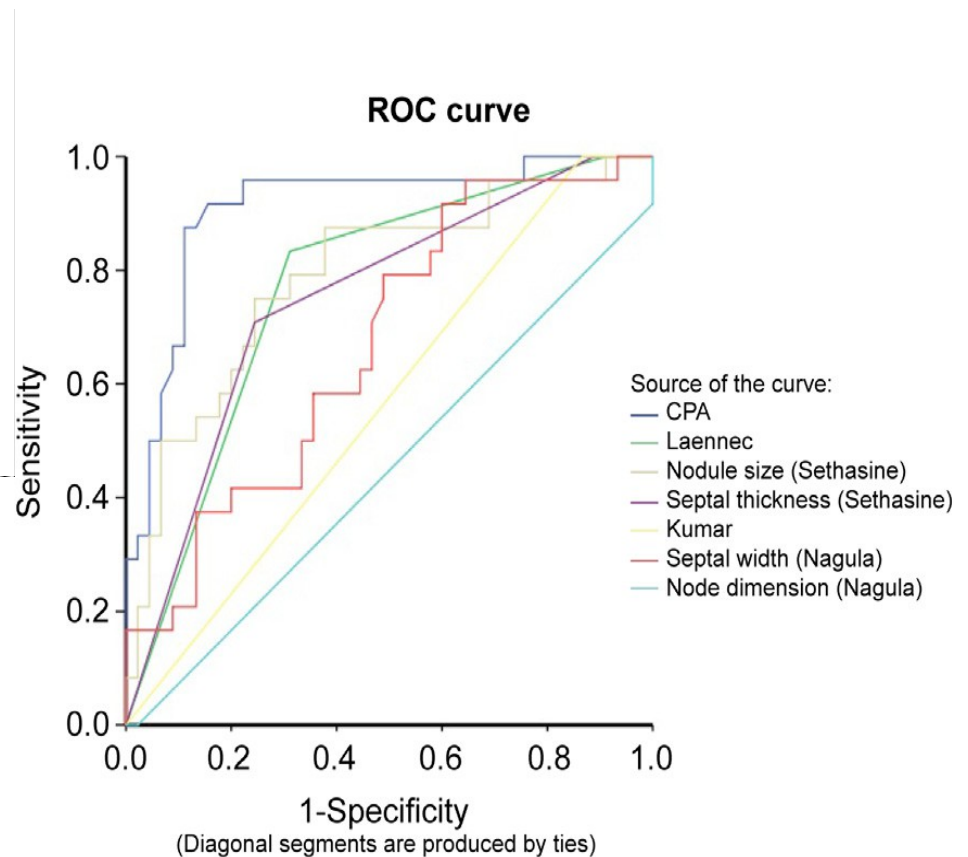
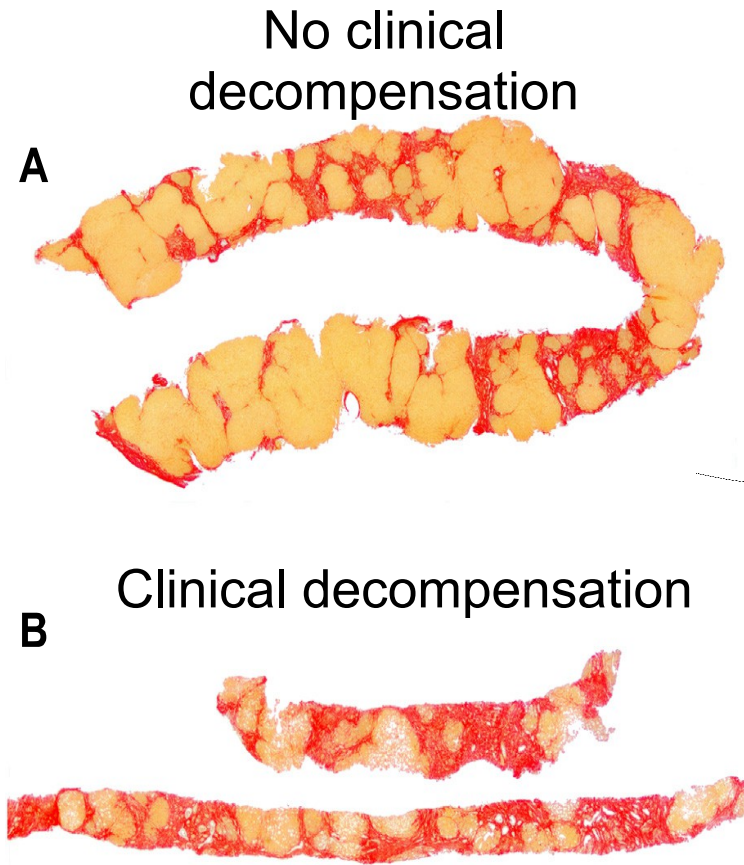
# Digital Image Analysis of Liver Collagen Predicts Clinical Outcome of Recurrent Hepatitis C Virus 1 Year After Liver Transplantation







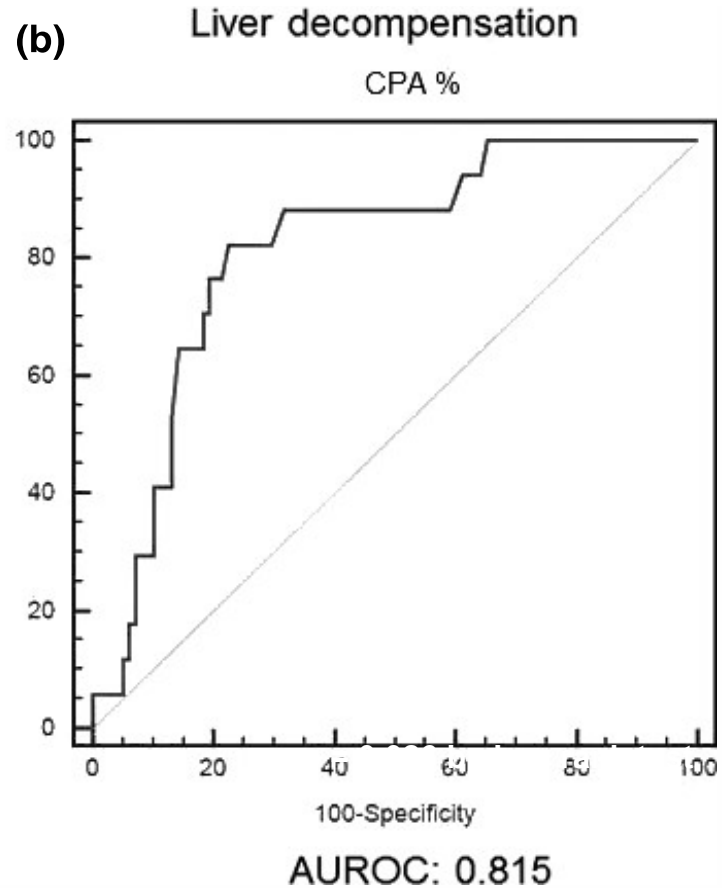
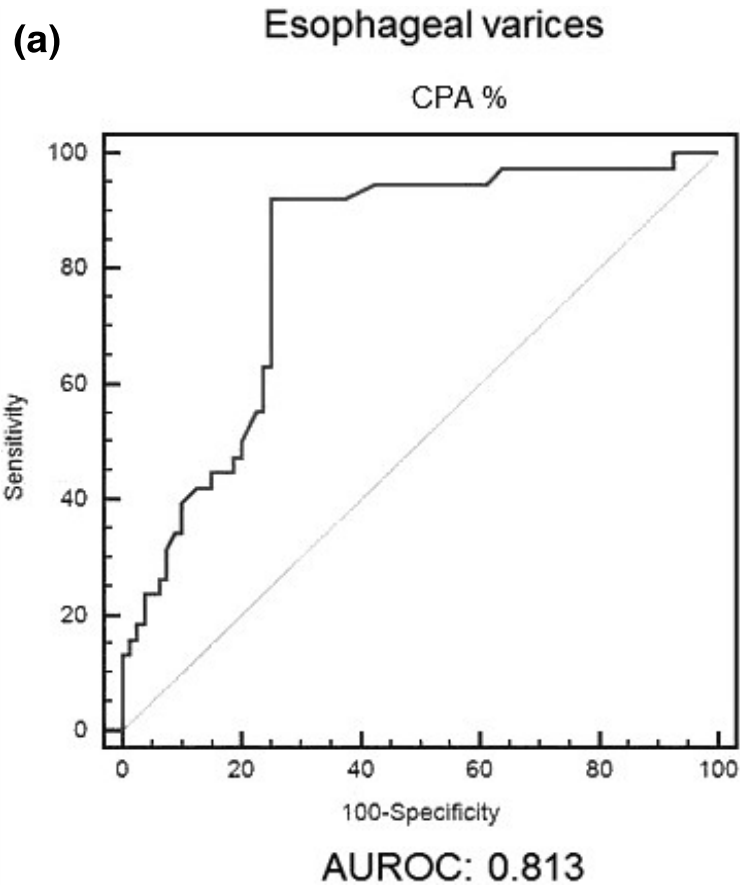
# Collagen proportionate area (CPA) predicts clinical decompensation in patients with liver cirrhosis



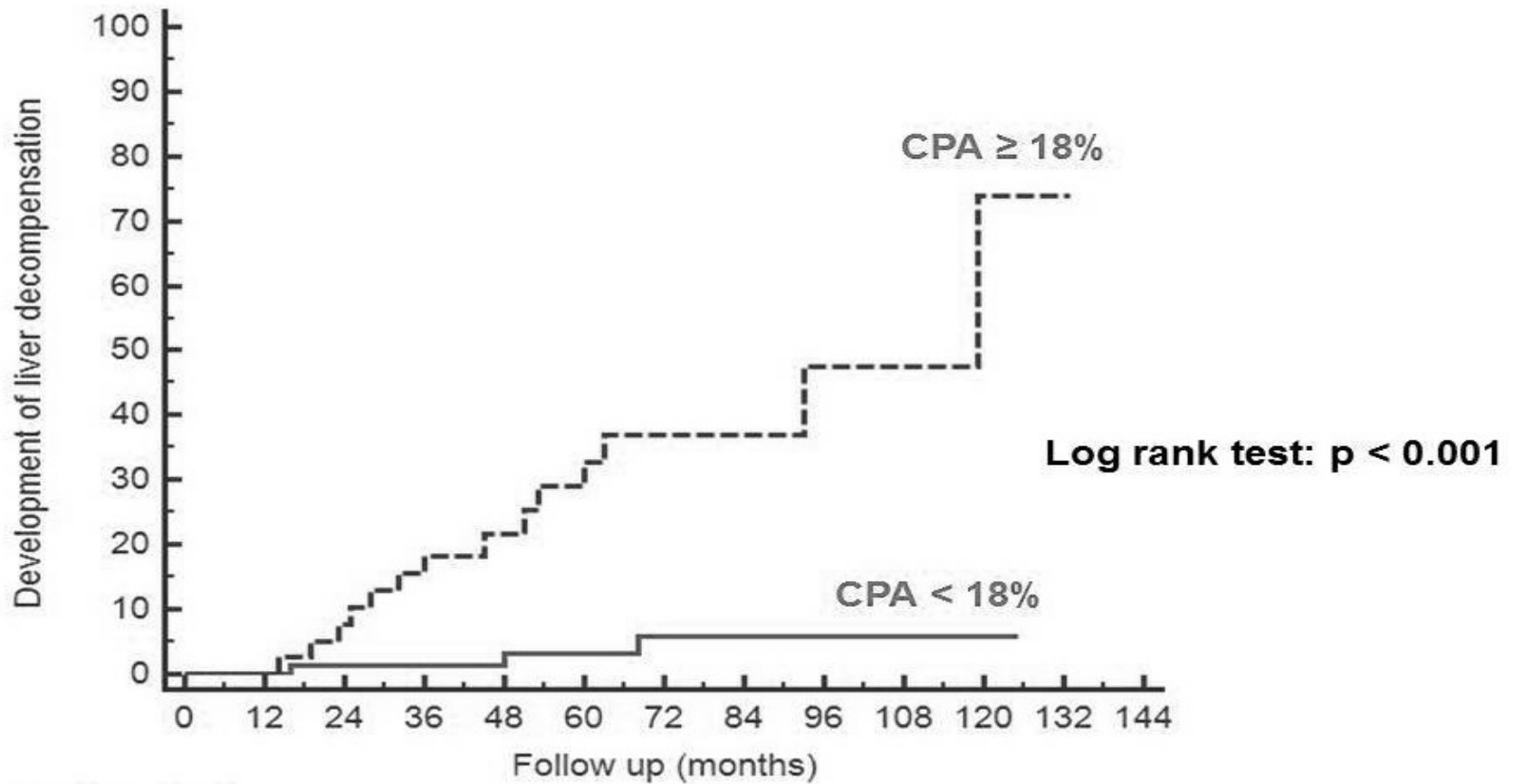
Predictors of clinical decompensation at the  
time of baseline biopsy in 69 patients with cirrhosis

Variable	OR	95% CI	p value
<b>Model 1</b>			
CPA	1.249	1.101-1.417	0.001
Laennec			n.s.
<b>Model 2</b>			
CPA	1.245	1.119-1.385	<0.001
Kumar			n.s.
<b>Model 3</b>			
CPA	1.249	1.101-1.416	0.001
Septal thickness			n.s.
Nodular size			n.s.
<b>Model 4</b>			
CPA	1.292	1.127-1.482	<0.001
Septal thickness			n.s.
Nodular size			n.s.
<b>Model 5</b>			
CPA	1.196	1.054-1.357	0.005
MELD	1.383	1.111-1.720	0.004

# Collagen proportionate area (CPA) predicts portal hypertension and clinical decompensation in patients with HCV cirrhosis



# Free of events survival in patients with HCV cirrhosis according to CPA



Number at risk

Group: CPA  $<$  18%

74 74 72 60 50 40 35 23 13 5 2 0 0

Group: CPA  $\geq$  18%

41 39 35 27 22 16 14 7 3 3 1 1 0

## Risk factors for liver decompensation (LD) in 118 patients with biopsy proven HCV cirrhosis, prospectively evaluated by CPA

	No LD 98 pts* (85.6%)	LD 17 pts (14.4%)	Univariate analysis <i>P</i> -value	Multivariate analysis	
				HR (95% CI)	<i>P</i> -value
Age (years, mean ± s.d.)	56.5 ± 9.4	60.0 ± 7.2	0.148	–	
Gender (% males)	58 (59.1)	7 (41.1)	0.153	–	
Platelets (×10 <sup>9</sup> /L, mean ± s.d.)	142.7 ± 44.4	107.3 ± 40.0	0.003	1.00 (0.98–1.02)	0.223
AST (IU/L, mean ± s.d.)	113.2 ± 67.1	108.8 ± 53.2	0.800		
ALT (IU/L, mean ± s.d.)	155.2 ± 94.1	133.6 ± 72.2	0.389		
Prothrombin time (%), mean ± s.d.)	90.2 ± 13.3	93.7 ± 10.4	0.325		
Bilirubin (mg/dL, mean ± s.d.)	0.9 ± 0.4	1.0 ± 0.5	0.258		
Albumin (g/dL, mean ± s.d.)	4.2 ± 0.4	3.7 ± 0.5	<0.001	0.12 (0.04–0.43)	<b>0.001</b>
CPA ≥18% (%)	28 (28.6)	14 (82.3)	<0.001	3.99 (1.04–11.45)	<b>0.036</b>
Presence of oesophageal varices (%)	24 (24.5)	13 (76.5)	<0.001	8.15 (2.31–28.78)	<b>0.001</b>
No SVR (%)	70 (71.4)	16 (94.1)	0.043	3.68 (0.40–38.05)	0.244

# Liver collagen in cirrhosis correlates with portal hypertension and liver dysfunction

Forty-eight consecutive liver transplantation patients with established cirrhosis

Hepatic venous pressure gradient (HVPG) and serum markers of liver failure determined prior to transplantation.

CPA assessed in the explanted livers.

CPA showed significant correlations with HVPG and with various surrogate markers of hepatic dysfunction including albumin, bilirubin, INR, MELD score and Child-Pugh score.

CPA reliably discriminated HVPG  $\geq 10$  mmHg (AUROC 0.923,  $p < 0.001$ ).

# Take home messages

Collagen continues to accumulate even when the biopsy stage is cirrhosis

CPA measurement is a morphometric methods that continuously quantify collagen accumulation across the full spectrum of disease with no upper limit

CPA scores HCV cirrhosis with a continuous scale and predicts clinical outcomes.

## Research agenda

Evaluate the role of CPA, alone or combined with other tools, on the prediction of liver decompensation in liver disease of different etiology

Evaluate if CPA could act as a histological standard for TE or other noninvasive markers of fibrosis.



Focus



# Replacing a crystal ball with a calculator in predicting liver disease outcomes

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See Articles, pages 934–939 and pages 948–954

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