

*BSG Annual Liver Pathology Update Meeting
Stratford upon Avon
20 November 2014*



in liver pathology?

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Institute of Cellular Medicine, Newcastle University
Newcastle upon Tyne



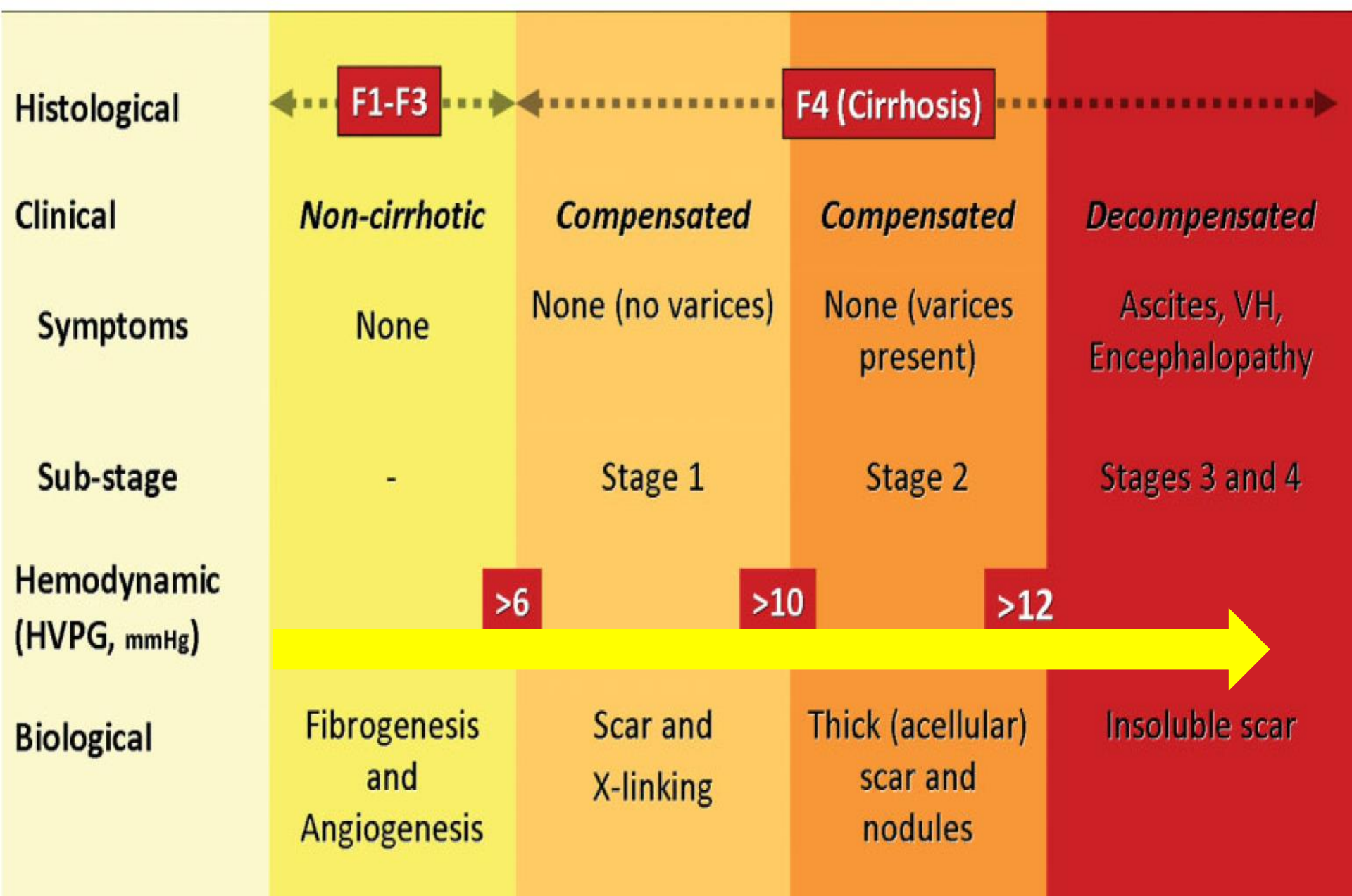
- **Chronic liver disease**
 - **Fibrosis – Cirrhosis**
 - **DILI**
 - **Fatty liver disease**
 - **Biliary disease**
- **Benign tumours**
- **Malignant tumours**

Evaluation of fibrosis - cirrhosis

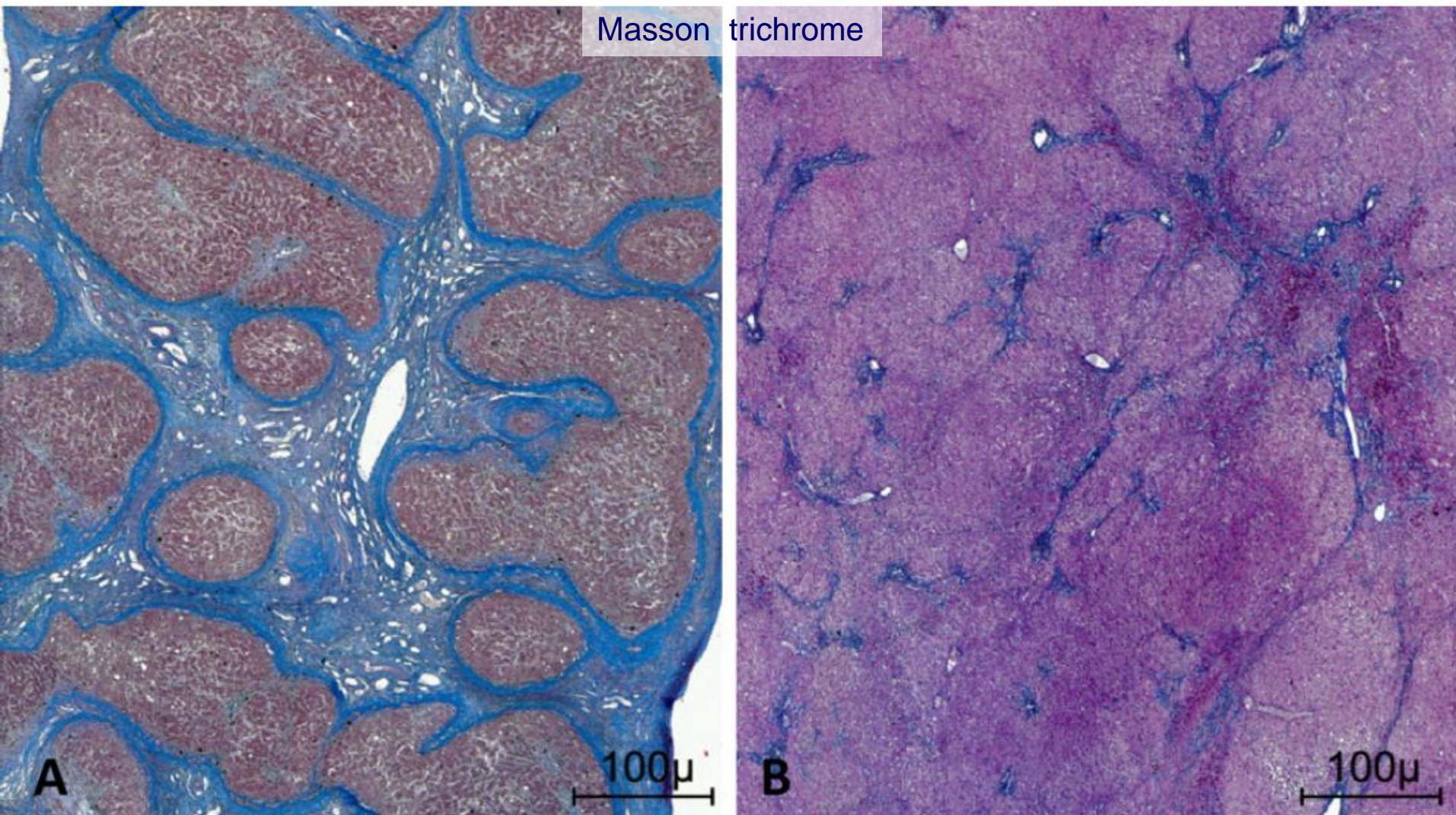
HEPATOLOGY, April 2010

Now There Are Many (Stages) Where Before There Was One: In Search of a Pathophysiological Classification of Cirrhosis

Guadalupe Garcia-Tsao,¹ Scott Friedman,² John Iredale,³ and Massimo Pinzani⁴



All cirrhotoses are not the same !



Laennec staging system for evaluation of hepatic fibrosis

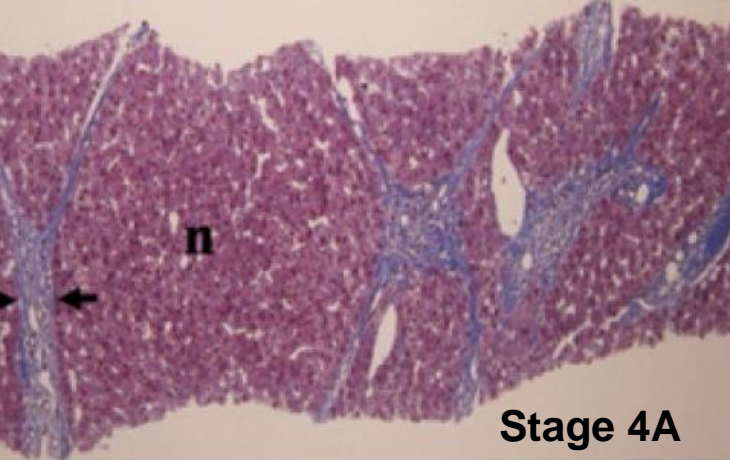
Beyond stage 4.....

Wanless, Blood 2002

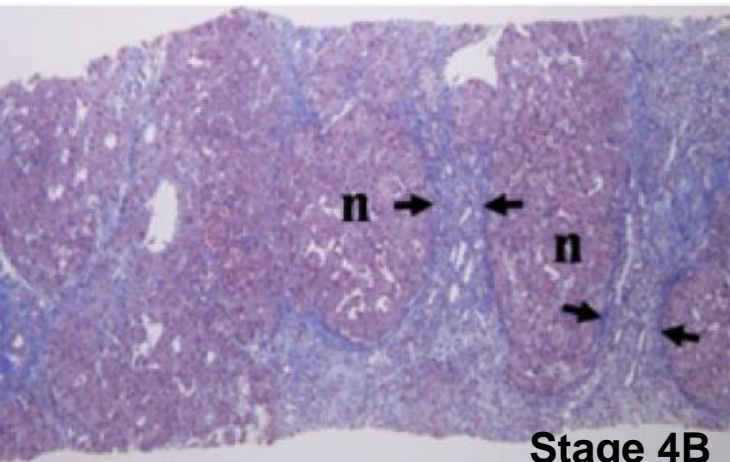
Correlates with HVG levels
and clinical stages of cirrhosis

Nagula, J Hepatol 2006

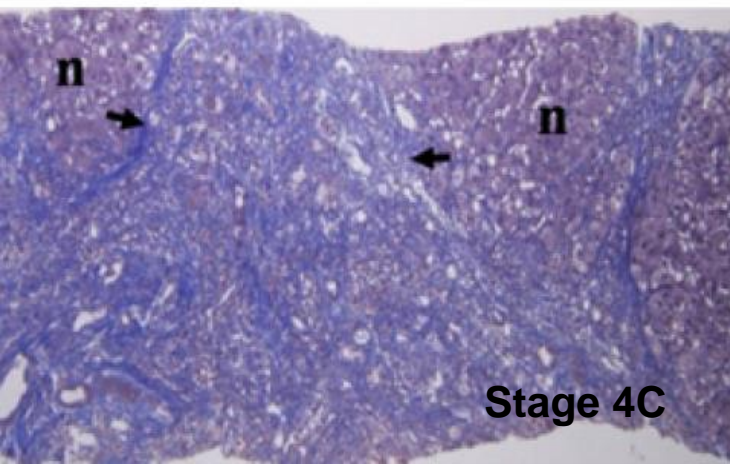
Kim, J Hepatol 2011



Stage 4A



Stage 4B

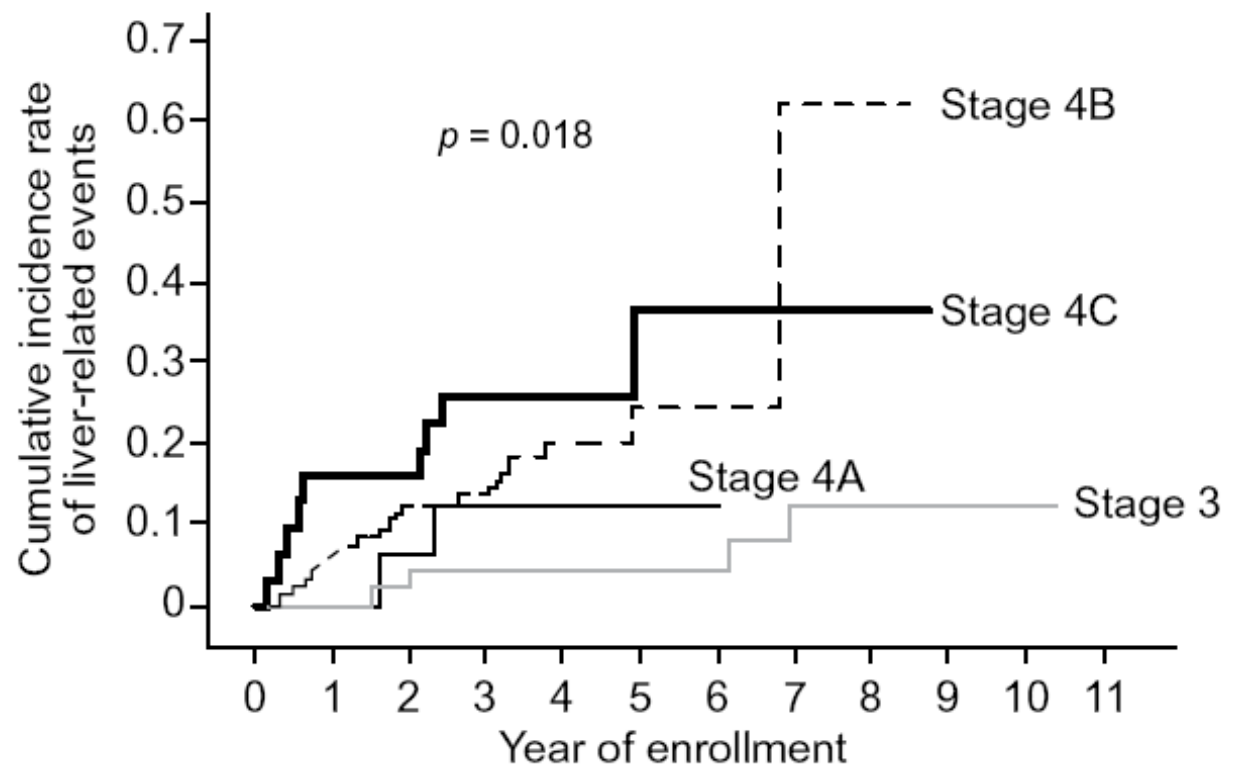
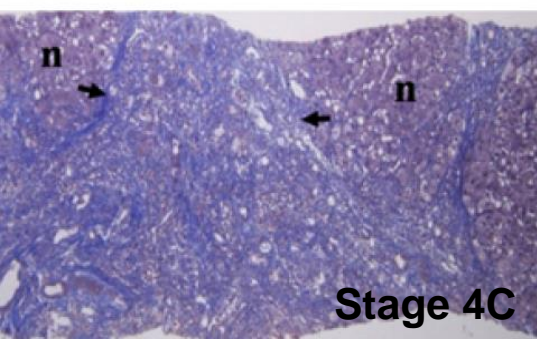
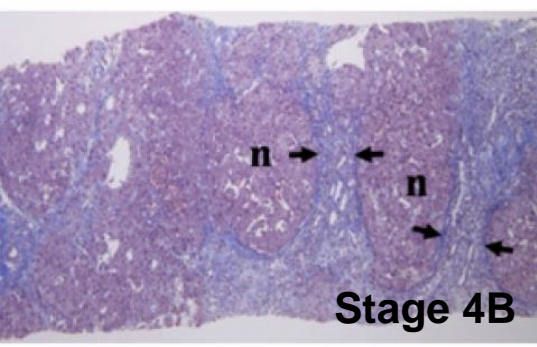
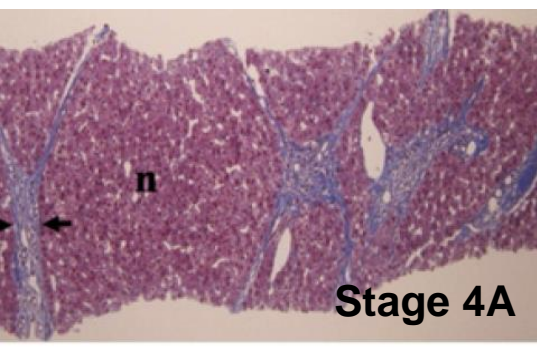


Stage 4C

The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis

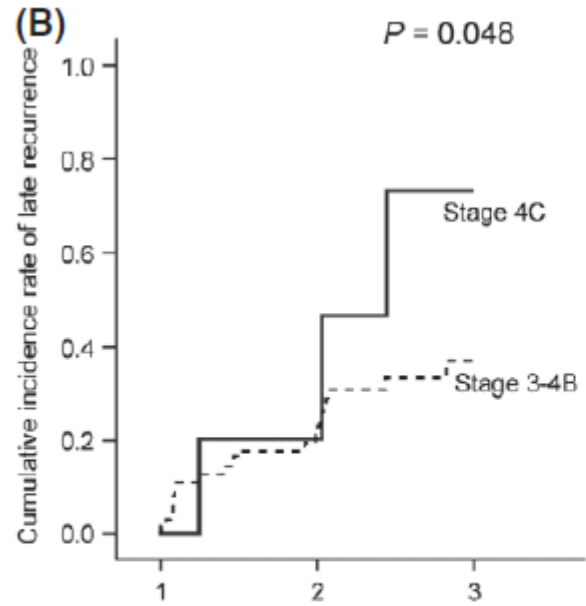
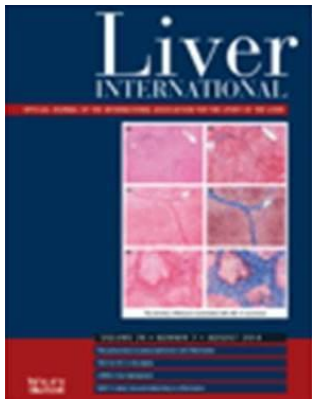
Journal of Hepatology 2012

Seung Up Kim^{1,2,4,†}, Hyun Jung Oh^{1,†}, Ian R. Wanless⁷, Sarah Lee³, Kwang-Hyub Han^{1,2,4,5,*}, Young Nyun Park^{3,4,5,6,*}

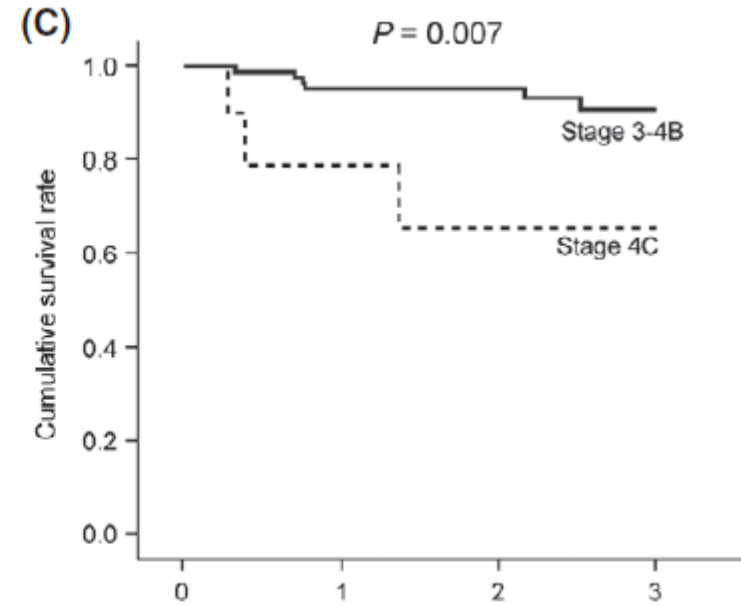


Histological subclassification of cirrhosis can predict recurrence after curative resection of hepatocellular carcinoma *Liver Int* 2014; 34:1008-17

Seung Up Kim^{1,2,5,6}, Kyu Sik Jung¹, Sarah Lee³, Jun Yong Park^{1,2,5,6}, Do Young Kim^{1,2,5,6}, Sang Hoon Ahn^{1,2,5}, Gi Hong Choi^{4,5,6}, Kyung Sik Kim^{4,5,6}, Jin Sub Choi^{4,5,6}, Kwang-Hyub Han^{1,2,5,6,7} and Young Nyun Park^{2,3,7}



No. at risk	Years after enrollment		
	1	2	3
Stage 3-4B	65	53	46
Stage 4C	5	4	2



No. at risk	Years after enrollment			
	0	1	2	3
Stage 3-4B	82	78	78	75
Stage 4C	10	8	7	7

n=92

High histological tumour grade (3-4) correlated with early recurrence and Laennec stage 4c was the only independent risk factor for late recurrence in HBV-related HCC

Evaluation of fibrosis - cirrhosis

Digital quantification of collagen

- objective
- accurate
- assessment of fibrosis as a continuous variable



Collagen proportionate area (CPA)

- better reflects HVPG compared to Ishak score
- predicts prognosis of patients transplanted for CHC
- correlates with noninvasive fibrosis markers

Calvaruso, J Gastroenterol Hepatol 2012

Huang, Liver Int 2013

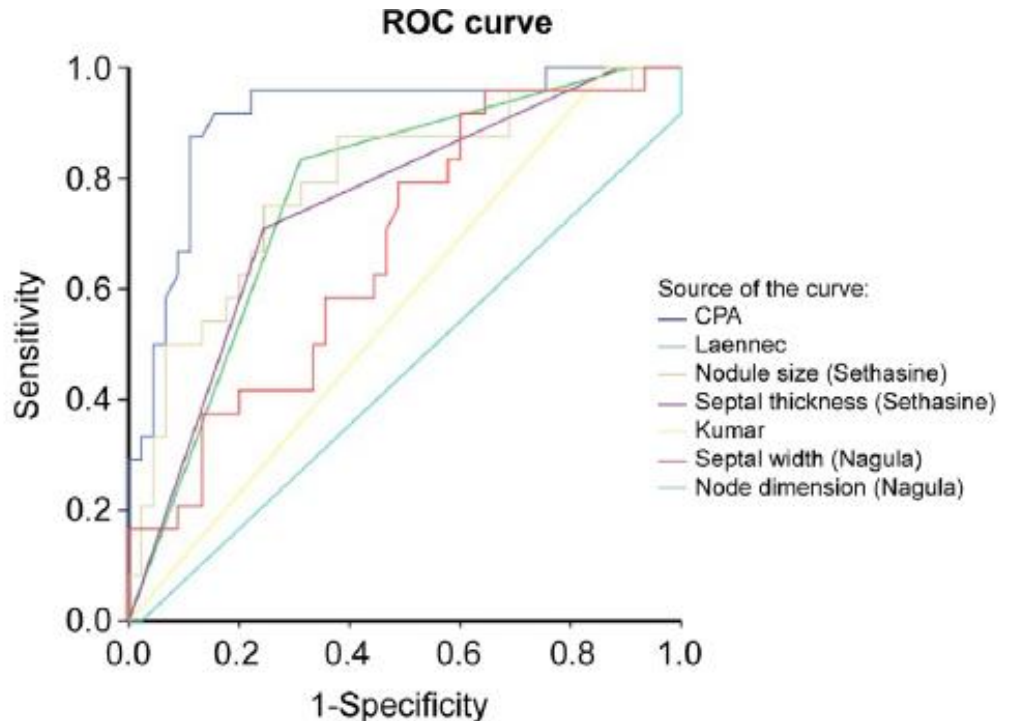
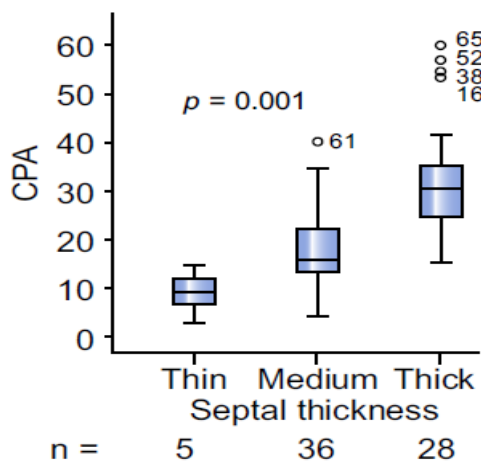
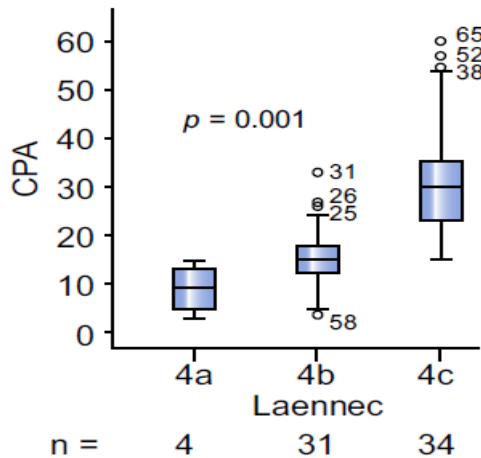
Collagen proportionate area is superior to other histological methods for sub-classifying cirrhosis and determining prognosis

Emmanuel Tsochatzis¹, Sara Bruno², Graziella Isgro¹, Andrew Hall², Eleni Theocharidou¹,
 Pinelopi Manousou², Amar P. Dhillon², Andrew K. Burroughs^{1,*†}, Tu Vinh Luong^{2,*†}

¹The Royal Free Sheila Sherlock Liver Centre, Royal Free Hospital and UCL Institute for Liver and Digestive Health, London, UK; ²Department of Histopathology, UCL Medical School, Royal Free Campus, UK

J Hepatol 2014;60: 948-54

n=69

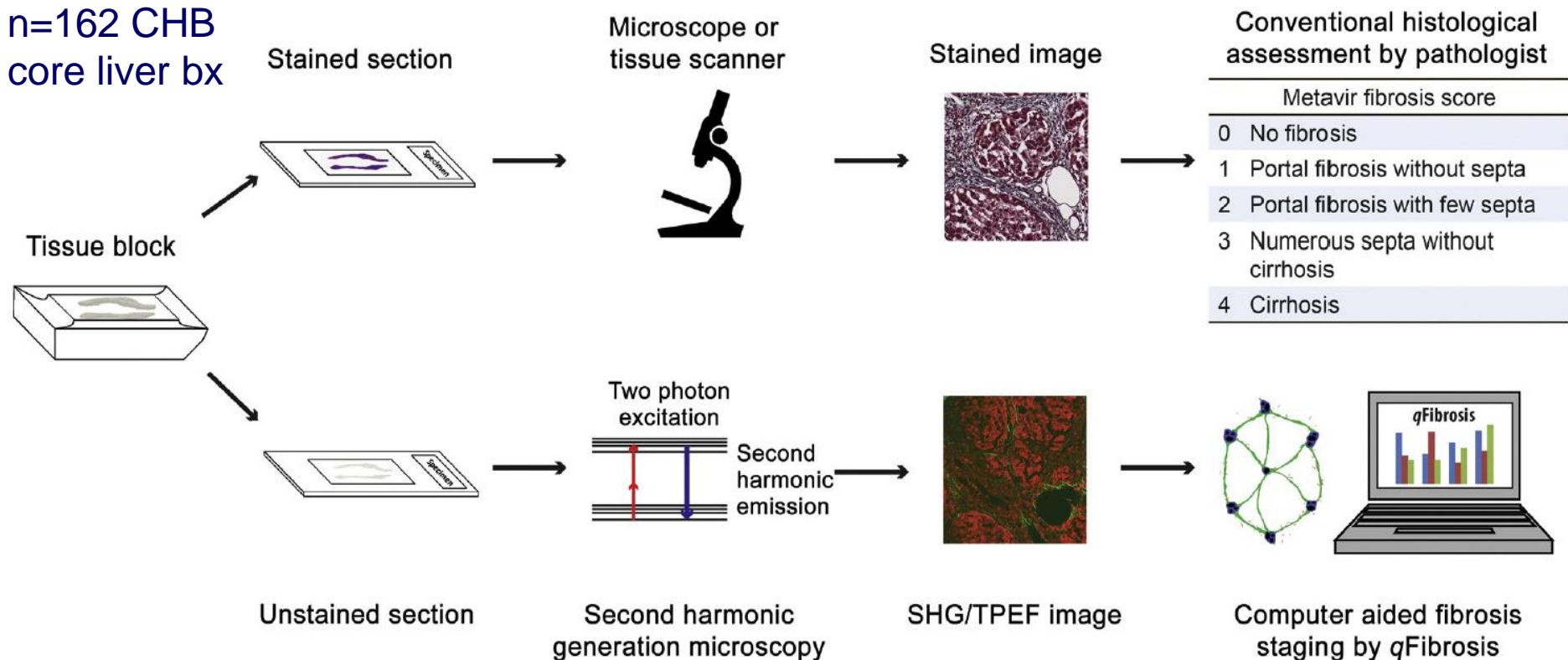


CPA was the only independent predictor of clinical decompensation in patients with cirrhosis

qFibrosis: A fully-quantitative innovative method incorporating histological features to facilitate accurate fibrosis scoring in animal model and chronic hepatitis B patients

Shuoyu Xu^{1,2,3,†}, Yan Wang^{4,5,6,†}, Dean C.S. Tai^{1,‡}, Shi Wang⁷, Chee Leong Cheng⁷ *J Hepatol* 2014;61:260-9

n=162 CHB core liver bx



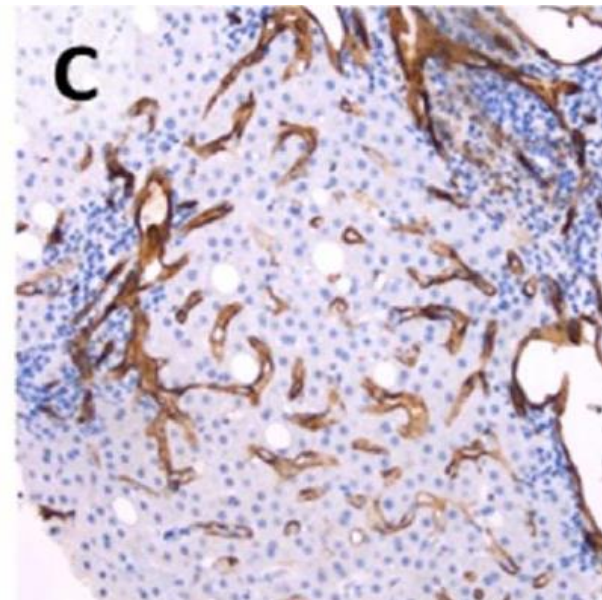
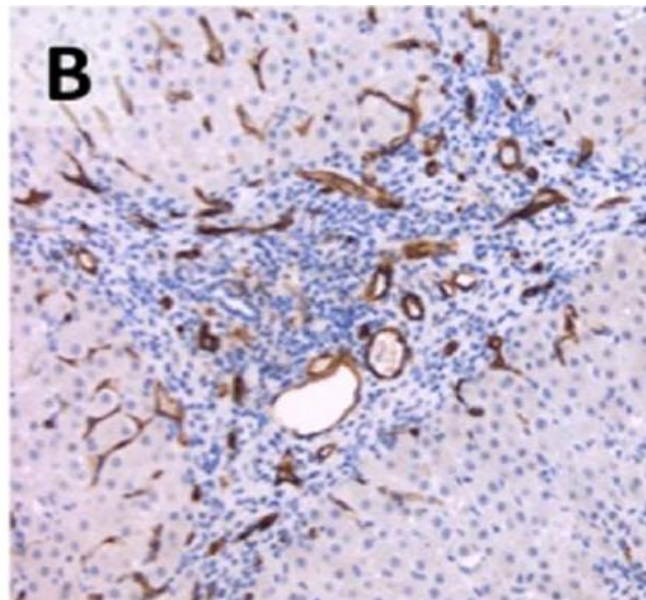
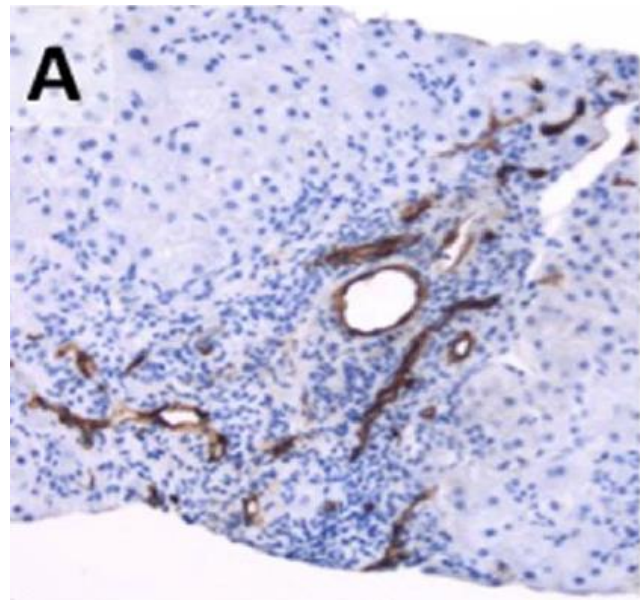
qFibrosis correlates well with Metavir/Ishak fibrosis stages, differentiates between Ishak stages 5 and 6 and is superior to CPA.

Beyond scoring: a modern histological assessment of chronic hepatitis should include tissue angiogenesis

Maria Guido,¹ Marco Pizzi,¹ David Sacerdoti,²
Luciano Giacomelli,¹ Massimo Rugge,¹
Massimo Bolognesi²

- Extent of sinusoidal capillarisation correlates with
 - fibrosis stage and HAI
 - splanchnic haemodynamic parameters
- Angiogenesis is an early event in CLD
- Tissue angiogenesis should be included in the histological assessment of CLD

N=40 CHC





- **Chronic liver disease**
 - Fibrosis – Cirrhosis
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 - Biliary disease
- Benign tumours
- Malignant tumours

Hepatic Histological Findings in Suspected Drug-Induced Liver Injury: Systematic Evaluation and Clinical Associations

Hepatology 2014; 59:661-70

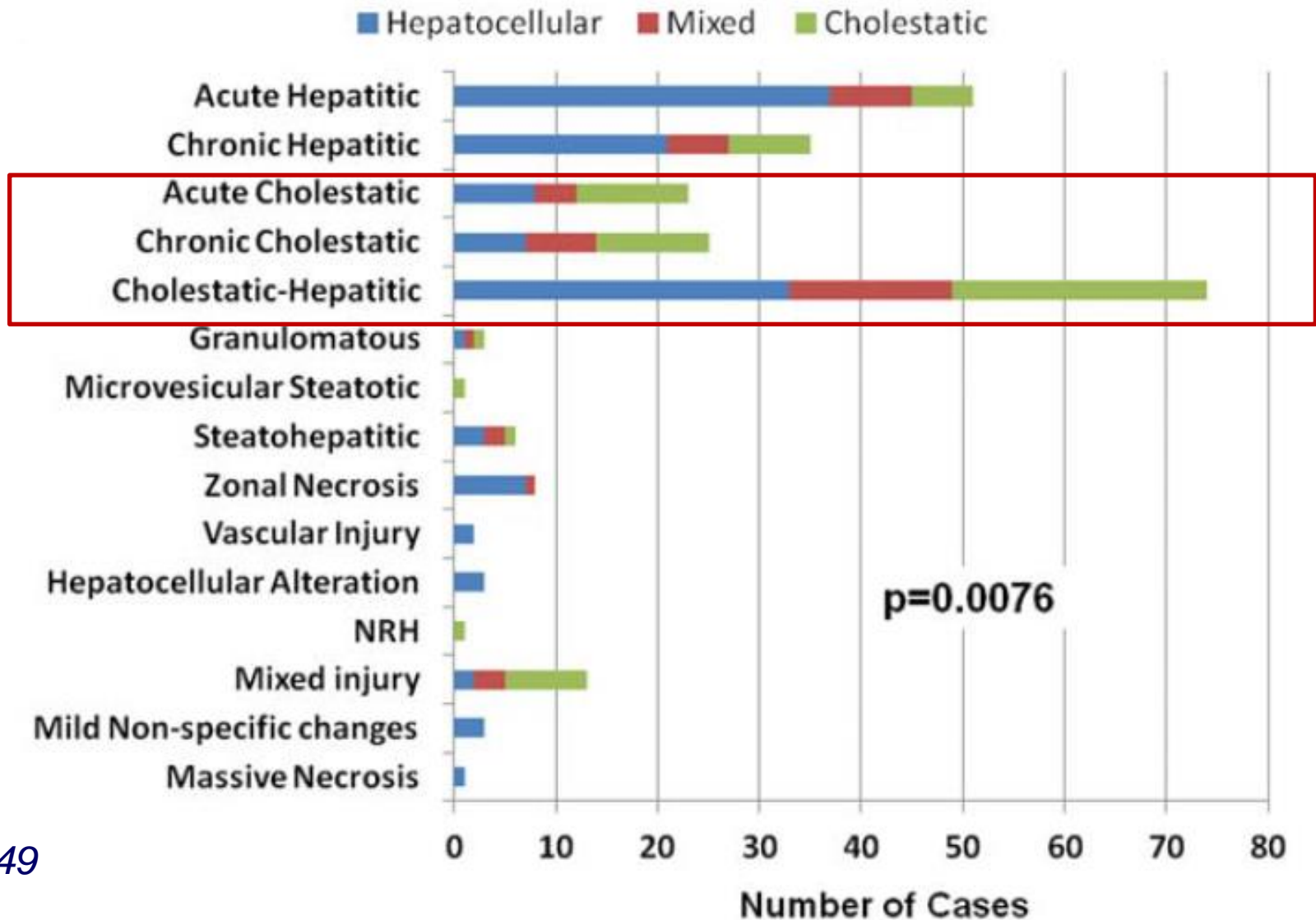
David E. Kleiner,¹ Naga P. Chalasani,² William M. Lee,³ Robert J. Fontana,⁴ Herbert L. Bonkovsky,⁵
for the Drug-Induced Liver Injury Network (DILIN)

n=249

Table 5. Significant Associations of Histological Findings With Outcome

Feature	Severe or Fatal		P Value*	Fatal Outcome		P Value*
	No	Yes		No	Yes	
Total N	162	46		193	15	
Granulomas						
None	57 (35)	28 (62)	0.0010	74 (39)	11 (73)	0.0300
Microgranulomas	97 (60)	13 (29)		106 (55)	4 (27)	
Epith granulomas	8 (5)	4 (9)		12 (6)	0 (0)	
Eosinophils	76 (47)	10 (22)	0.0030	84 (44)	2 (13)	0.0300
Neutrophils	43 (27)	22 (49)	0.0060			
Degree of necrosis, mean	0.36	0.89	0.0100	0.43	1.13	0.0200
Fibrosis stage, mean	1.15	1.73	0.0030	1.18	2.53	<0.0001
Type of steatosis						
Macrovesicular	84 (82)	12 (39)	<0.0001	95 (77)	1 (9)	<0.0001
Mixed	9 (9)	10 (32)		14 (11)	5 (46)	
Microvesicular	10 (10)	9 (29)		14 (11)	5 (46)	
Cholangiolar cholestasis	2 (1)	6 (13)	0.0020	5 (3)	3 (20)	0.0100
Ductular reaction	52 (32)	24 (53)	0.0100	65 (34)	15 (73)	0.0040
Portal venopathy				4 (2)	2 (17)	0.0400

DILI: Relationship between pathological and biochemical injury patterns



$n=249$



<http://livertox.nih.gov/>

Free database of drugs linked to liver injury launched in 2012

Up-to-date and accurate information and case registry of DILI

>1000 medications, herbals and dietary supplements.



- **Chronic liver disease**

Fibrosis – Cirrhosis

DILI

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Biliary disease

- Benign tumours

- Malignant tumours

Differentiation between acute and chronic steatosis

- Lipid-droplet associated proteins of the perilipin/PAT-family
- *perilipin, adipophilin, TIP47, MLDP*
are differentially expressed in hepatic steatosis
- Perilipin is expressed *de novo*
- Lipid-droplet maturation studied *in vitro* (cultured hepatocytes)
- 120 liver biopsies with steatosis of different aetiology

Straub, Hepatol 2008

Straub, Mod Pathol 2010

Pawella, J Hepatol 2014; 60:633-42

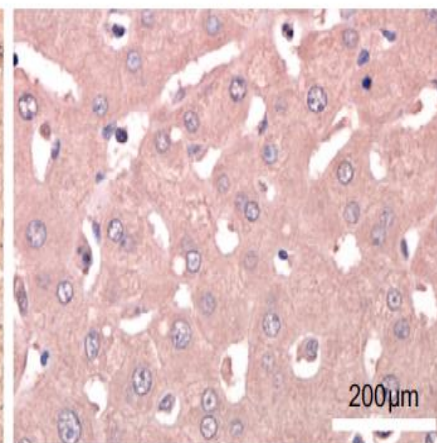
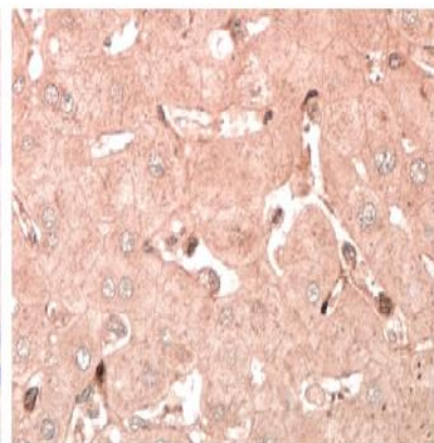
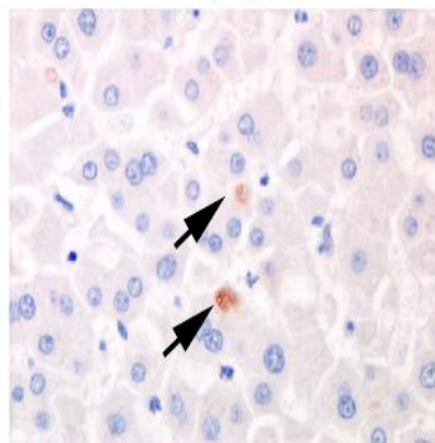
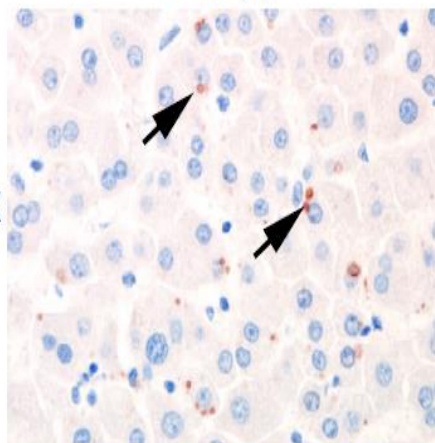
Perilipin

Adipophilin

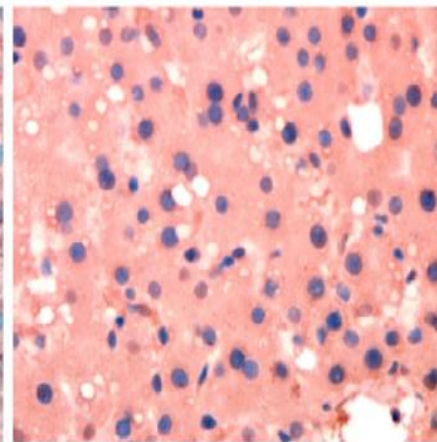
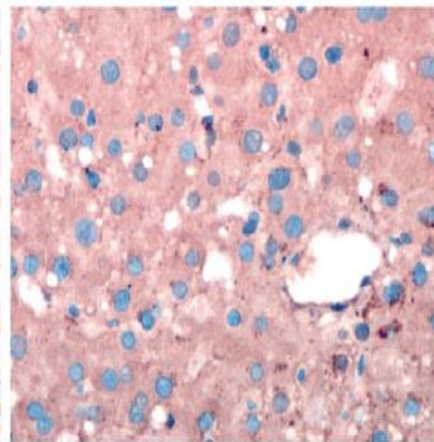
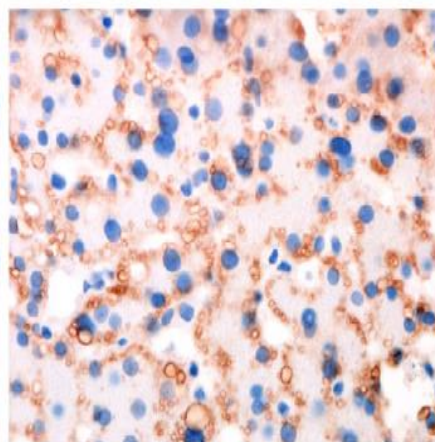
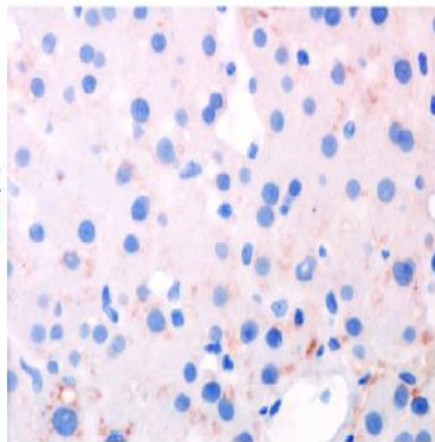
TIP47

MLDP

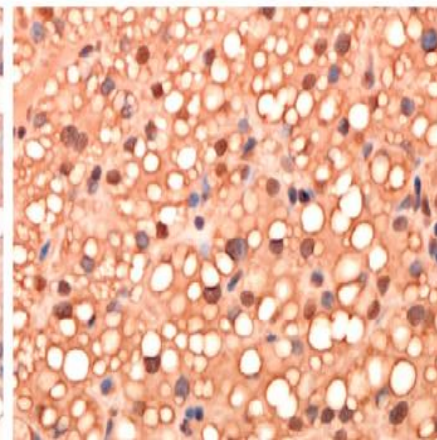
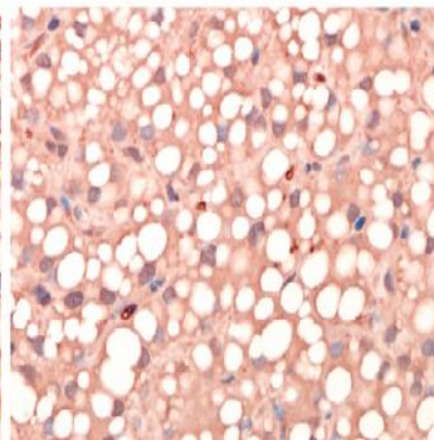
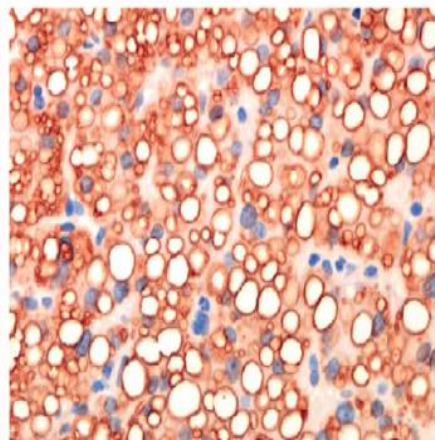
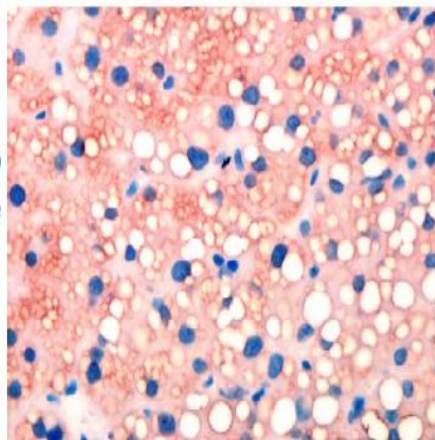
LTX



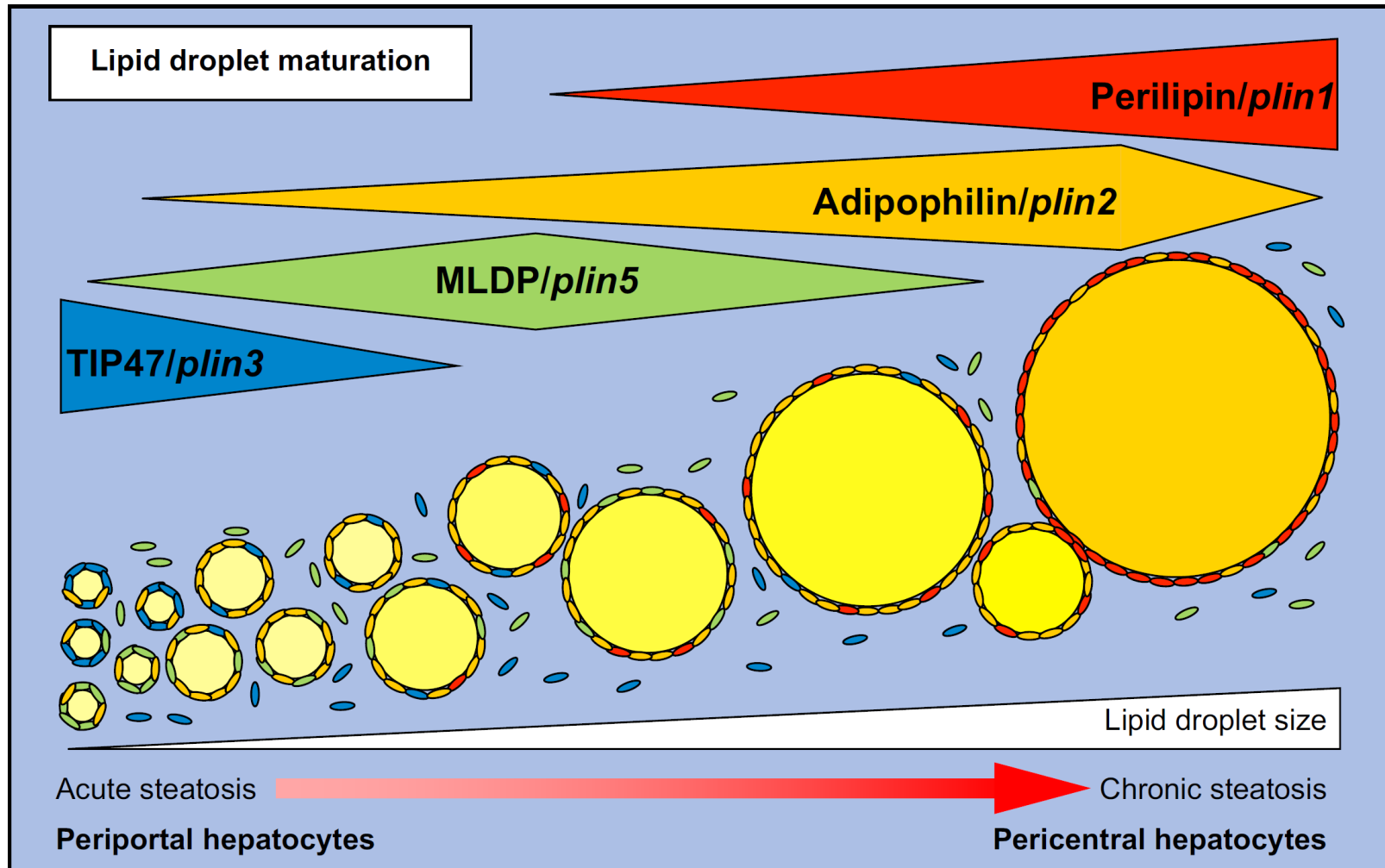
+ 2 wk
PN



+ 10 mo
cortisone



Lipid droplet maturation



Perilipin might be used for the differential diagnosis of chronic vs. acute steatosis

Scoring activity in Nonalcoholic Fatty Liver Disease (NAFLD)

NAS–NASH Activity Score

- Steatosis (S: 0-3)

0: <5%, 1: 5-33%, 2: 33-66%, 3: >66%

- Lobular Inflammation (LI: 0-3)

0: 0, 1: 1-2, 2: 2-4, 3: >4 foci/x20

- Ballooning (B: 0-2)

0: none,

1: mild, few

2: moderate-marked, many

NAS = S + LI + B, range 0-8

NAS

1-2: no NASH

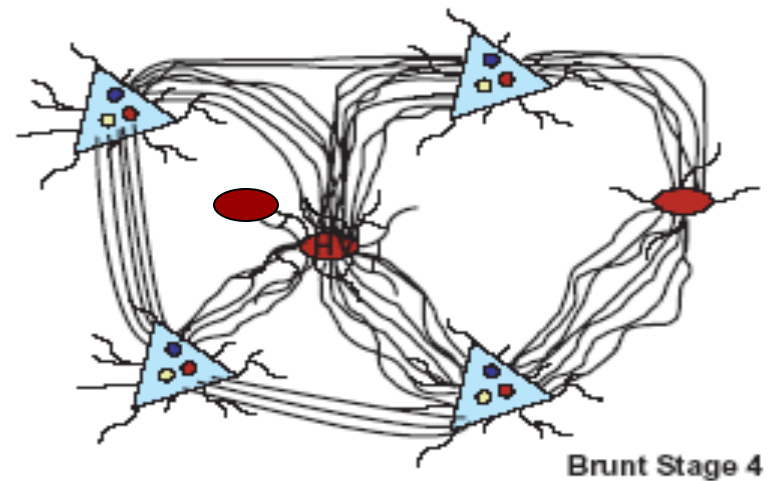
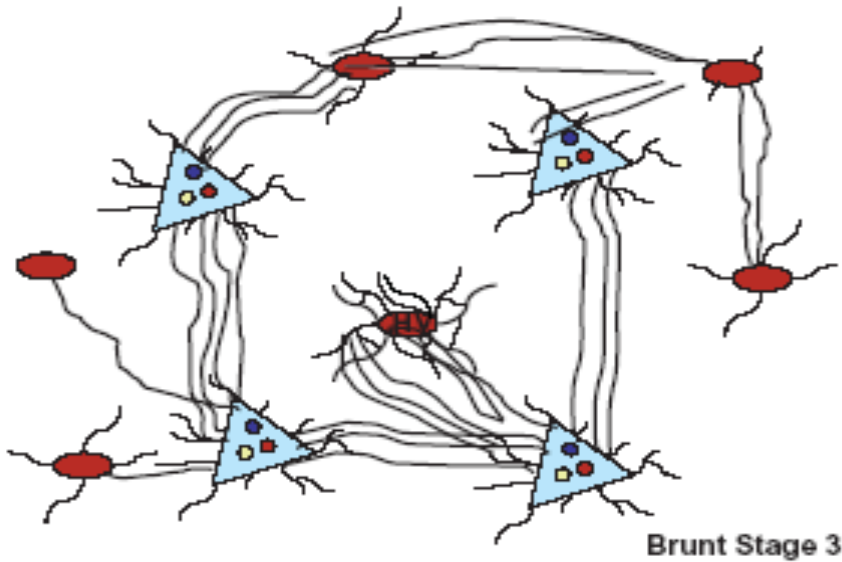
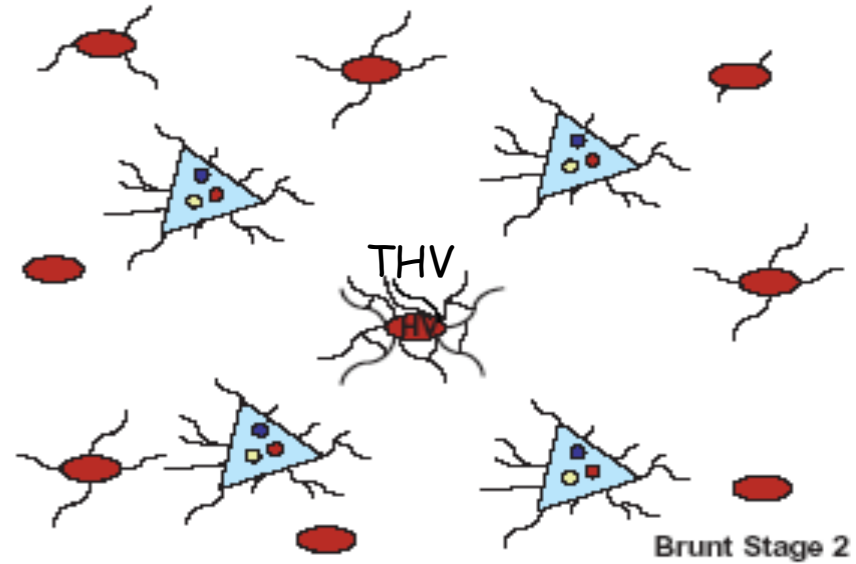
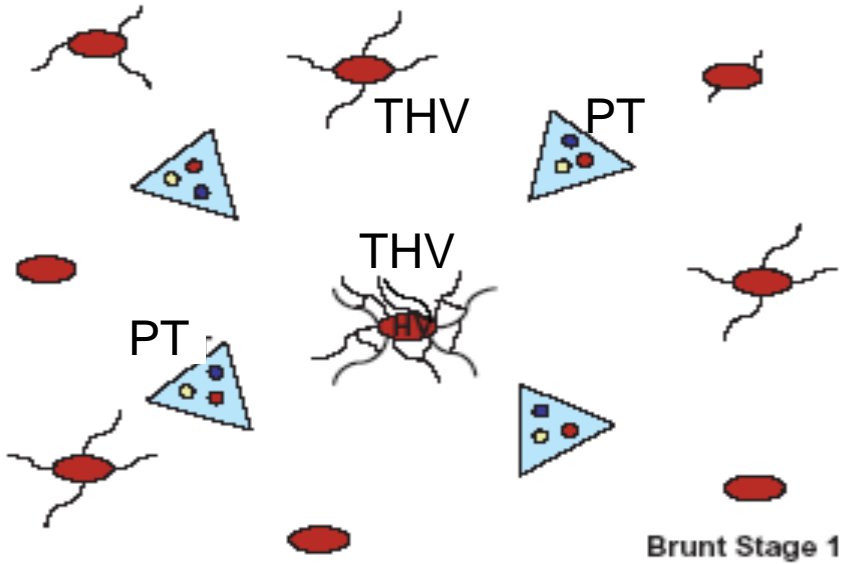
3-4: borderline NASH

5-8: NASH

Kleiner , Hepatology 2005

Pathology Committee of NASH, Clinical Research Network-CRN, NIH–**NASH CRN**)

Staging fibrosis in NAFLD

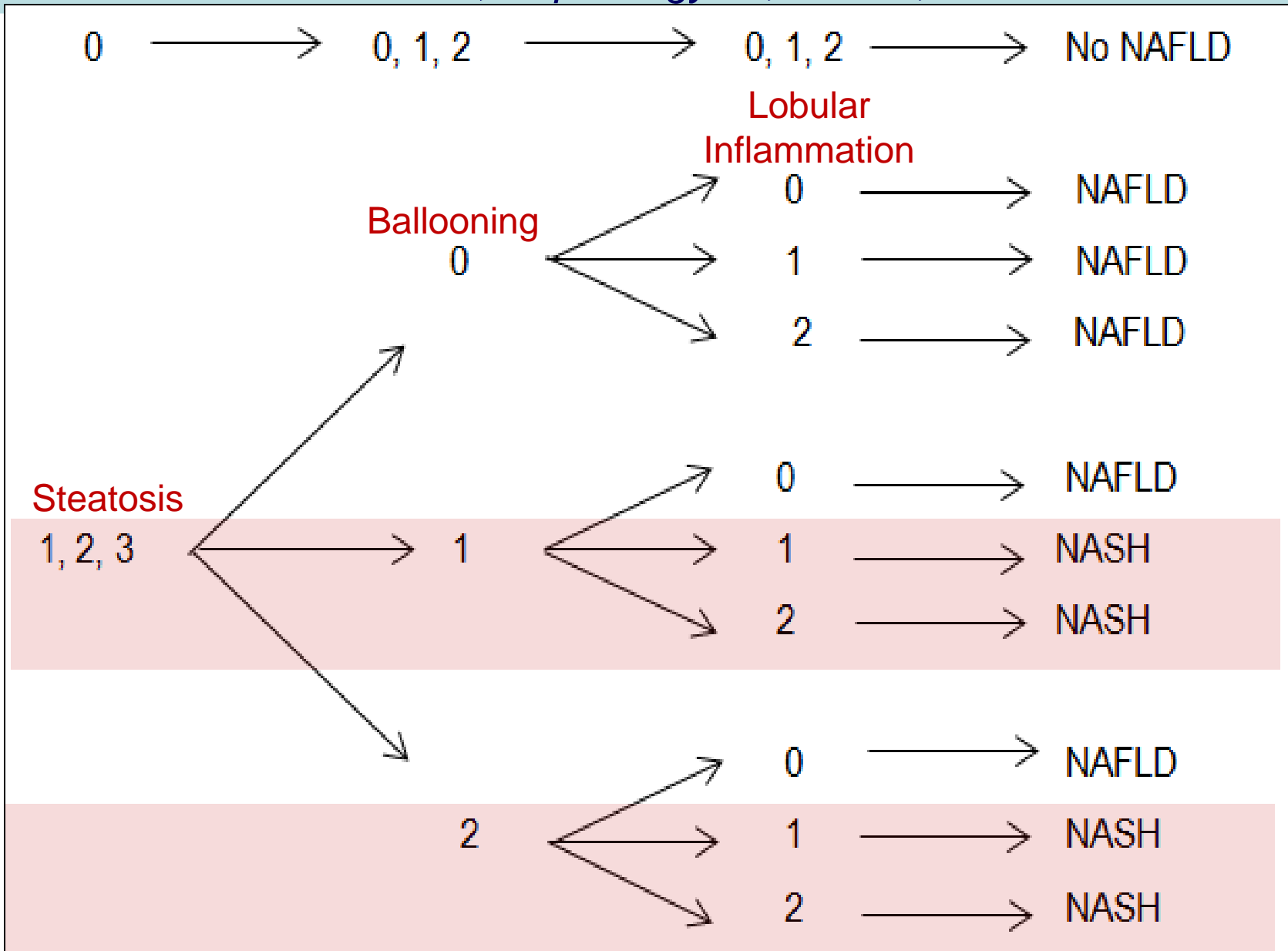


Scoring activity and staging fibrosis in NAFLD

- NASH CRN thresholds do not always correlate with histological diagnosis
- NASH CRN system **has not been validated in routine**
- **Used only for research purposes** in clinical trials

Algorithm for disease classification in NAFLD

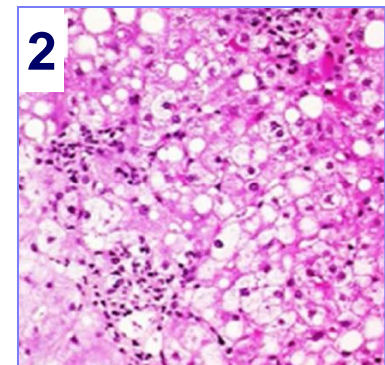
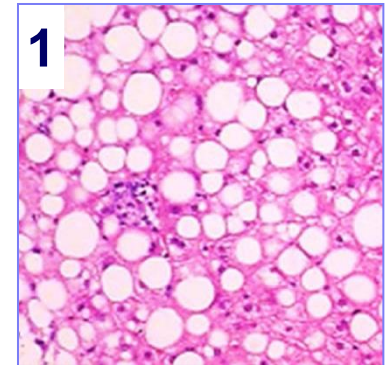
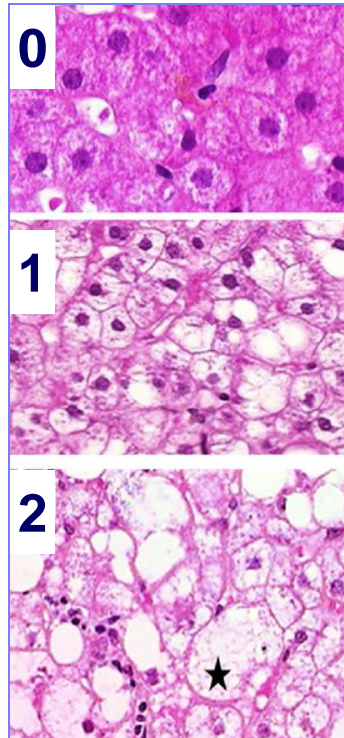
Bedossa et al, Hepatology 50; 1751-9, 2012



Scoring NAFLD in morbidly obese patients

Bedossa et al, Hepatology 2012

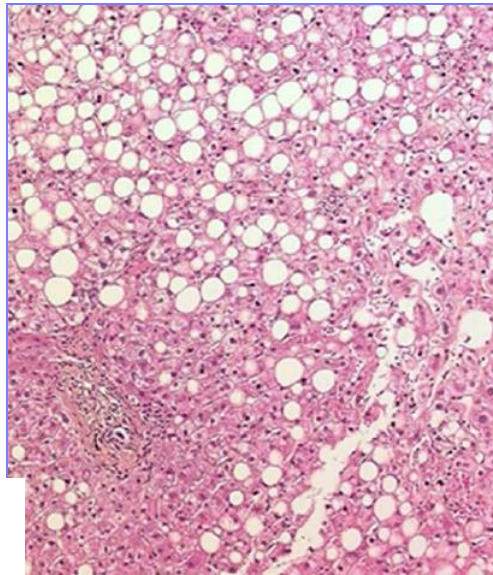
- Simple algorithm for categorizing liver injury in NAFLD
- Exclusion of steatosis (0-3) from grading of disease activity
- **Activity grade** (0-4): sum of **ballooning** (0-2) and **lobular inflammation** (0-2)



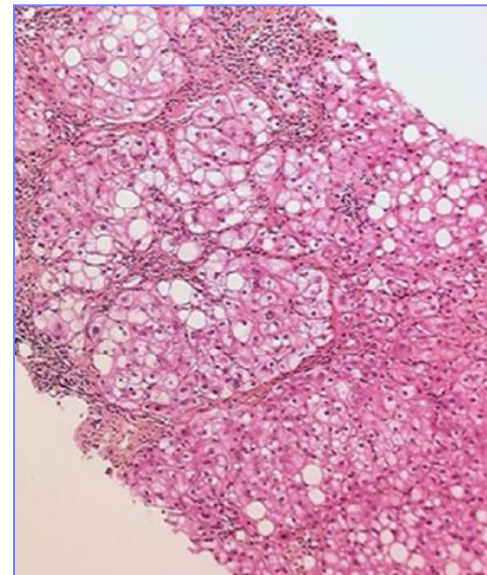
Scoring NAFLD in morbidly obese patients

Bedossa et al, Hepatology 2012

- Simple algorithm for categorizing liver injury in NAFLD
- Exclusion of steatosis (0-3) from grading of disease activity lobular
- Activity grade (0-4): sum of ballooning (0-2) and inflammation (0-2)
- Fibrosis stage: as in NASH-CRN
- **SAF score: Steatosis (0-3), Activity (0-4), Fibrosis (0-4)**



$S_3 A_{2(1+1)} F_1$



$S_1 A_{4(2+2)} F_4$

**Utility and Appropriateness of the
Fatty Liver Inhibition of Progression (FLIP)
Algorithm and Steatosis, Activity, and Fibrosis (SAF)
Score in the Evaluation of Biopsies of Nonalcoholic
Fatty Liver Disease**

Pierre Bedossa and the FLIP Pathology Consortium* *HEPATOLOGY* 2014;60:565-575

**Table 2. Agreement for Diagnosis Before and After Use of
Algorithm in the Two Groups of Pathologists**

		κ Score	Biopsy With Full Agreement Between Pathologists (%)	Biopsy With Agreement With Reference Diagnosis (%)
Group 1 6 expert liver pathologists	Baseline classification	0.54	26/40 (65%)	31/40 (<u>77%</u>)
	Algorithmic classification	0.66	34/40 (85%)	39/40 (<u>97%</u>)
Group 2 10 general pathologists	Baseline classification	0.35	18/40 (45%)	17/40 (<u>42%</u>)
	Algorithmic classification	0.61	28/40 (70%)	30/40 (<u>75%</u>)

**Utility and Appropriateness of the
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Pierre Bedossa and the FLIP Pathology Consortium* *HEPATOLOGY* 2014;60:565-575

Interobserver agreement using SAF score

Steatosis	$\kappa = 0.61$	Substantial
Activity	$\kappa = 0.75$	Substantial
Ballooning	$\kappa = 0.8$	
Lobular Inflamm.	$\kappa = 0.72$	
Fibrosis (1a,b,c-2-3-4)	$\kappa = 0.53$	Moderate
Fibrosis (1-2-3-4)	$\kappa = 0.83$	Perfect

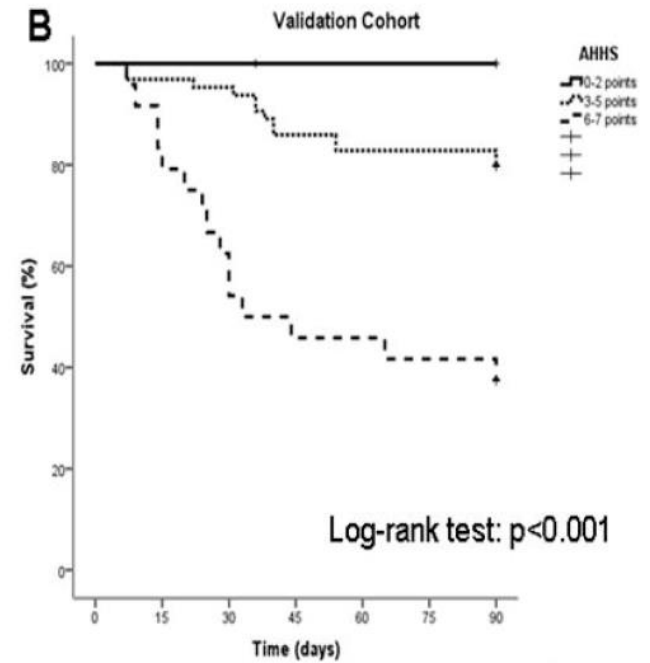
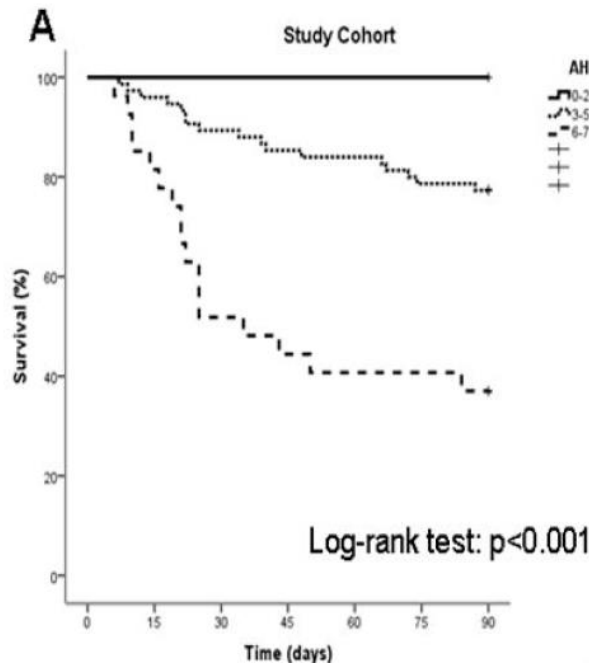
SAF score : highly reproducible semiquantitative features

Scoring activity in Alcoholic Liver Disease

- In ALD the use of grading systems is very limited
- 2014: Semiquantitative histological score with prognostic value
 - **Alcoholic Hepatitis Histological Score (AHHS 0-7)**
 - lobular infiltration by polymorphs
 - bilirubinostasis
 - megamitochondria
 - stage of fibrosis

Altamirano, Gastroenterology 2014; 146: 1231

90-day survival





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 - Benign tumours
 - Malignant tumours

Staging and Grading Primary Biliary Cirrhosis

Human Pathology (2013) 44, 1107–1117

Evaluation of a new histologic staging and grading system for primary biliary cirrhosis in comparison with classical systems ☆, ☆☆ ☆

Yuko Kakuda MD^a . . . Yasuni Nakanuma

Division of Pathology, Kanazawa University Hospital, Kanazawa 920-8641, Japan

J Clin Gastroenterol 2013;47:174–181

Application and Validation of a New Histologic Staging and Grading System for Primary Biliary Cirrhosis

Kenichi Harada, MD, PhD, Maylee Hsu, MD, PhD,* Hiroko Ikeda, MD, PhD,†*

*Mikio Zeniya, MD, PhD,‡ and Yasuni Nakanuma, MD, PhD**

Staging and Grading Primary Biliary Cirrhosis

Table 1 Scoring for the staging of PBC

Score	Criterion
A. Fibrosis	
0	No portal fibrosis or fibrosis limited to portal tracts
1	Portal fibrosis with periportal fibrosis or incomplete septal fibrosis
2	Bridging fibrosis with variable lobular disarray
3	Liver cirrhosis with regenerative nodules and extensive fibrosis
B. Bile duct loss	
0	No bile duct loss
1	Bile duct loss in less than one-third of portal tracts
2	Bile duct loss in one-third to two-thirds of portal tracts
3	Bile duct loss in more than two-thirds of portal tracts
C. Deposition of orcein-positive granules^a	
0	No deposition of granules
1	Deposition of granules in a couple of zone 1 hepatocytes at less than one-third of portal tracts
2	Deposition of granules in a variable number of zone 1 hepatocytes at one-third to two-thirds of portal tracts
3	Deposition of granules in most zone 1 hepatocytes at more than two-thirds of portal tracts

Staging and Grading Primary Biliary Cirrhosis

Table 1 Scoring for the staging of PBC

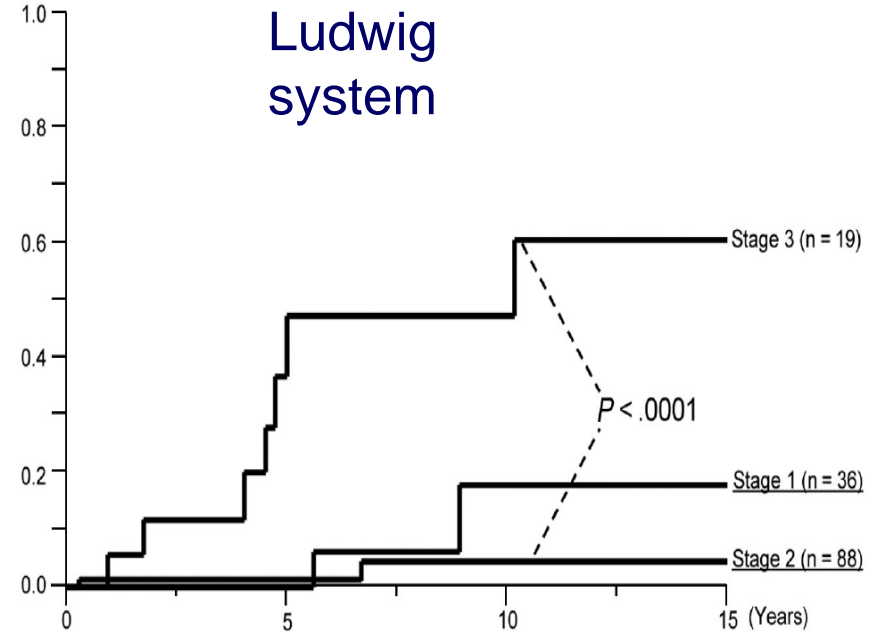
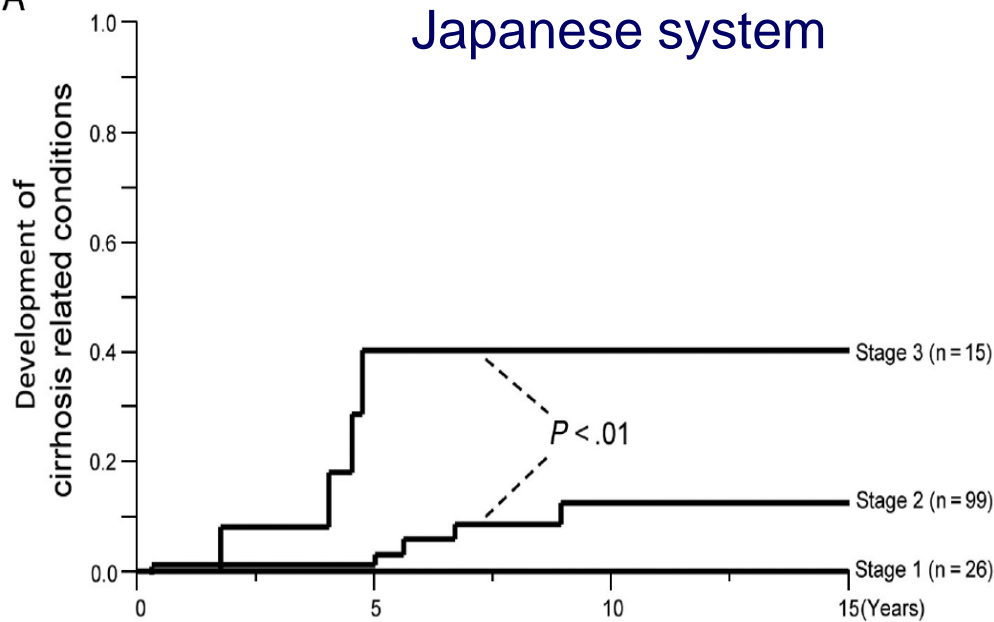
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3	Deposition of granules in most zone 1 hepatoc

Table 2 Grading of the necroinflammatory activity of PBC

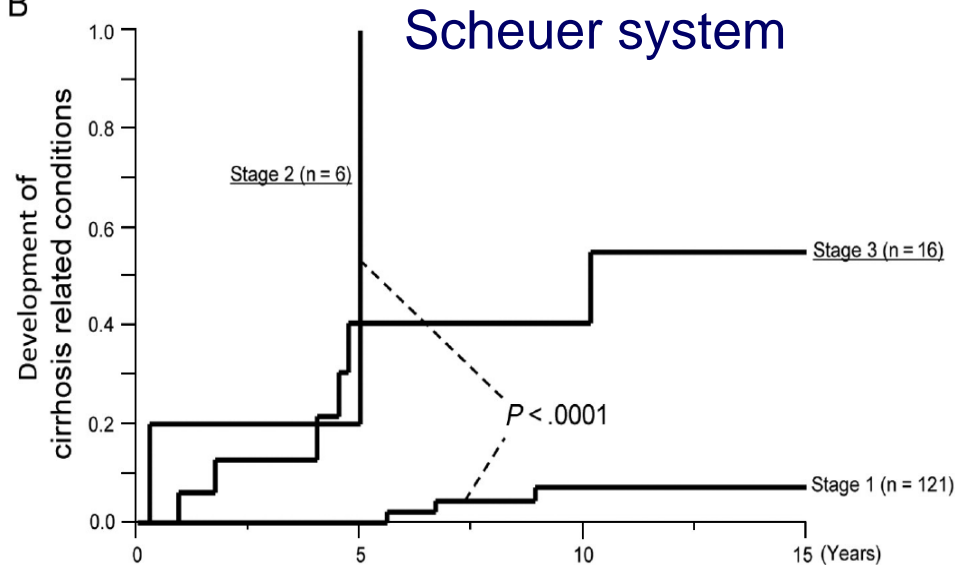
Grade	Criteria
A. CA (cholangitis activity)	
0 (no activity)	No cholangitis but mild damage to the epithelium of the duct may be present
1 (mild activity)	1 evident chronic cholangitis in the specimen
2 (moderate activity)	≥2 bile ducts with evident chronic cholangitis
3 (marked activity)	≥1 CNSDC in the specimen
B. HA (hepatitis activity)	
0 (no activity)	No interface hepatitis and no or minimal lobular hepatitis
1 (mild activity)	Interface hepatitis affecting 10 continuous hepatocytes at a limiting plate in 1 portal tract or fibrous septa and mild-to-moderate lobular hepatitis
2 (moderate activity)	Interface hepatitis affecting 10 continuous hepatocytes at limiting plates in ≥2 portal tracts or fibrous septa and mild-to-moderate lobular hepatitis
3 (marked activity)	Interface hepatitis affecting 20 continuous hepatocytes at limiting plates in more than half of the portal tracts and moderate lobular hepatitis or bridging/zonal necrosis

Rates of development of cirrhosis-related conditions

A



B

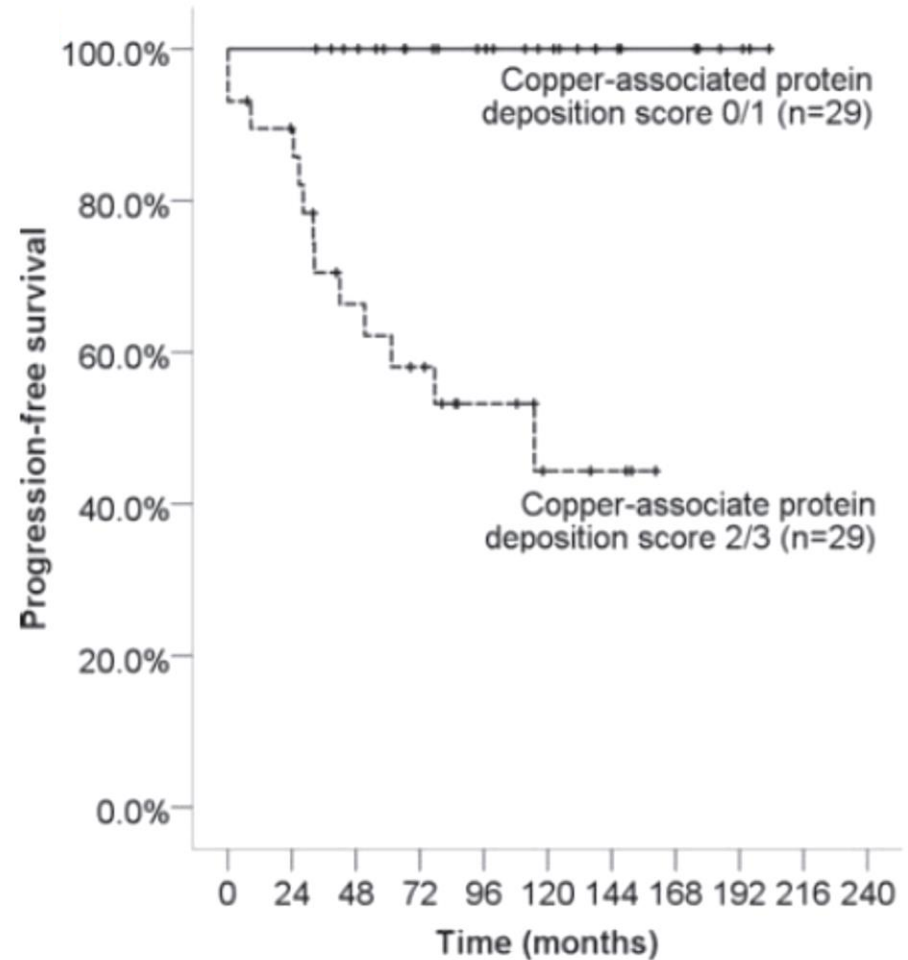
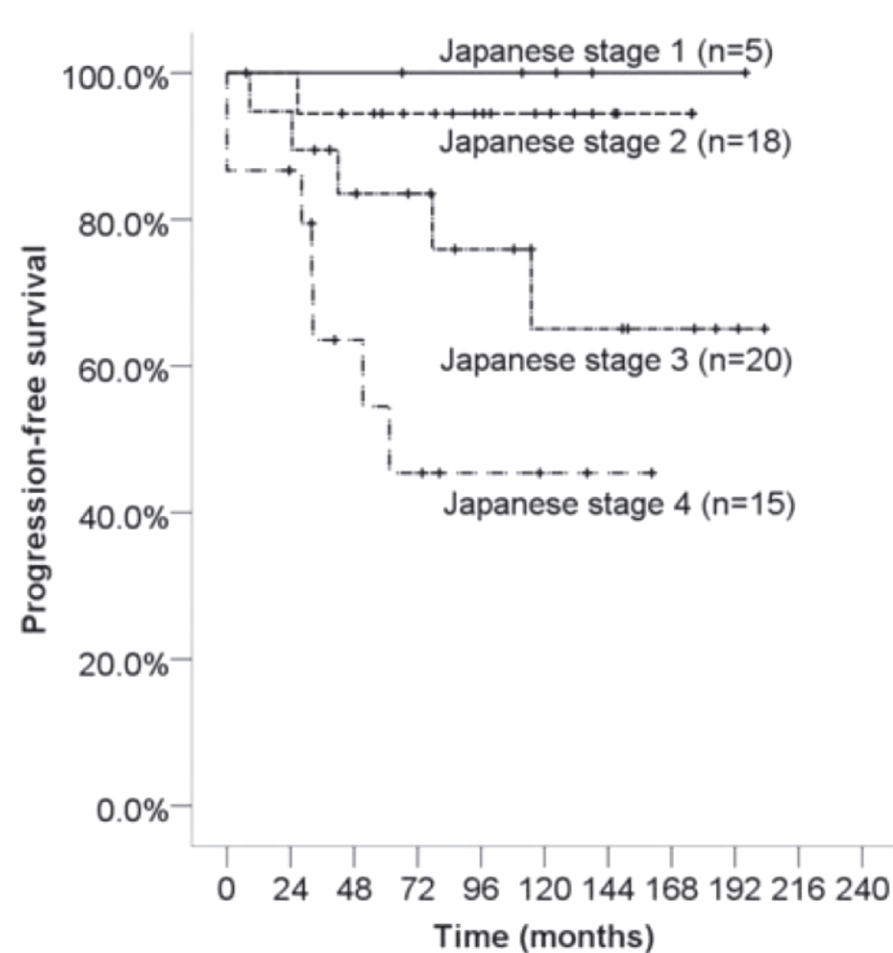


The new system

- correlates with clinical and pathological features
- reflects liver dysfunction

n=152

Japanese staging correlated with progression-free survival in PBC



n=58, follow-up 16.9 years

Chan, Histopathology 2014; 65:174-186

**Copper-associated protein deposition score:
most powerful histologic prognostic parameter**

Primary biliary cirrhosis: proposal for a new simple histological scoring system

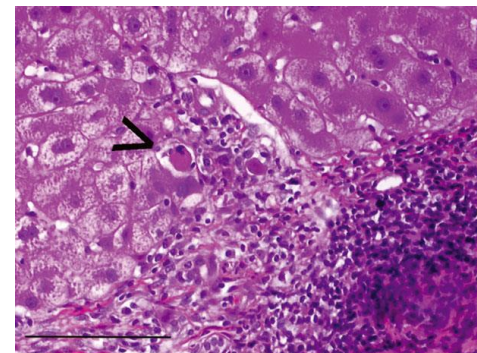
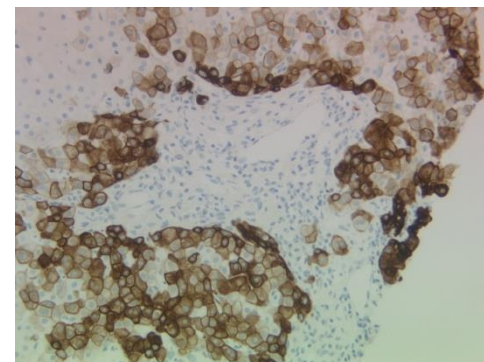
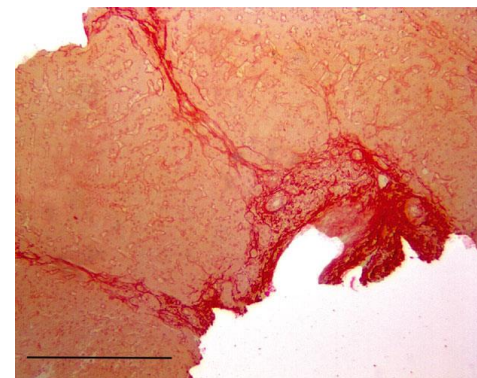
Dominique Wendum^{1,2}, Pierre-Yves Boëlle^{2,3}, Pierre Bedossa⁴, Elie-Serge Zafrani⁵, Frédéric Charlotte^{2,6}, Marie-Christine Saint-Paul⁷, Sophie Michalak⁸, Olivier Chazouillères^{2,9} and Christophe Corpechot⁹

Liver Int 2014 June 17

- Fibrosis (0-4)
- Bile duct ratio (n PT with BD/n PT)
- Interface hepatitis, lymphocytic (0-3)

Table 3. Interobserver agreement for fibrosis, interface hepatitis, bile duct ratio and Ludwig's and Scheuer's stages

	Interobserver agreement
Fibrosis	
5-class system	0.36
4-class system	0.56
3-class system	0.64
Interface hepatitis	0.59
Bile duct ratio	
Before Keratin 7 immunostaining	0.50
After Keratin 7 immunostaining	0.63
Ludwig's stage	0.32
Scheuer's stage	0.31



Primary biliary cirrhosis: proposal for a new simple histological scoring system

Dominique Wendum^{1,2}, Pierre-Yves Boëlle^{2,3}, Pierre Bedossa⁴, Elie-Serge Zafrani⁵, Frédéric Charlotte^{2,6}, Marie-Christine Saint-Paul⁷, Sophie Michalak⁸, Olivier Chazouillères^{2,9} and Christophe Corpechot⁹

Liver Int 2014 June 17

- **F**ibrosis (0-4)
- **B**ile duct ratio (n PT with BD/n PT)
- **I**nterface hepatitis, lymphocytic (0-3)

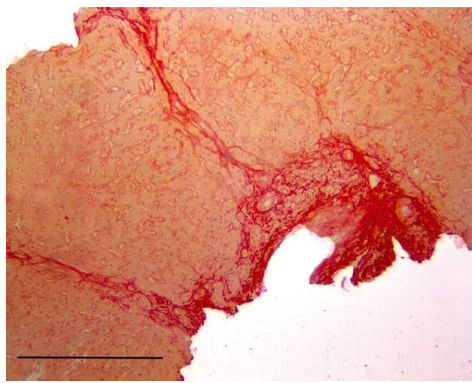
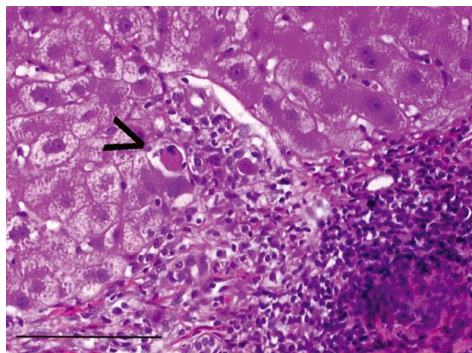
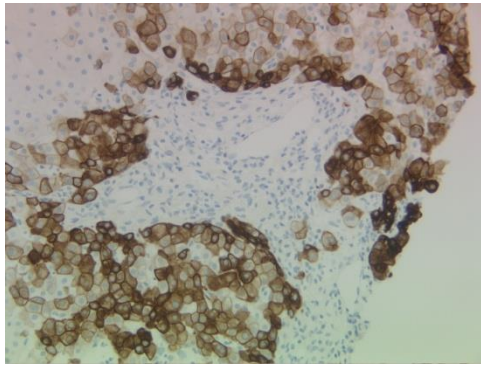


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CORRESPONDENCE

Primary Biliary “Cirrhosis”: Time to Replace a Misnomer

Wahl, Hepatology Sept 10, 2014

this diagnosis term has become a misnomer, as Rubin et al. called it already in 1965,² and should be replaced.

Rubin E, Schaffner F, Popper H. Primary biliary cirrhosis. Chronic non-suppurative destructive cholangitis. Am J Pathol 1965;46:387-407.



- Chronic liver disease
- **Benign liver tumours**
- Malignant tumours

D.D. of FNH and I-HCA

Modern Pathol 2014; 27:62-72

Diagnostic utility and limitations of glutamine synthetase and serum amyloid-associated protein immunohistochemistry in the distinction of focal nodular hyperplasia and inflammatory hepatocellular adenoma

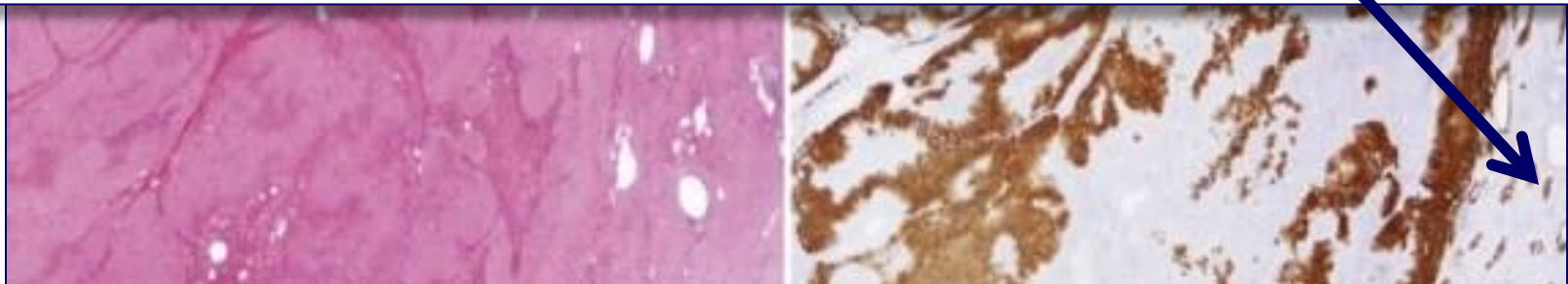
Nancy M Joseph¹, Linda D Ferrell¹, Dhanpat Jain², Michael S Torbenson³, Tsung-Teh Wu⁴, Matthew M Yeh⁵ and Sanjay Kakar^{1,6}

FNH

Glutamine synthetase (GS)



Comparison of pattern and extent of immunoreactivity within the tumour to that in the adjacent liver



D.D. of FNH and I-HCA

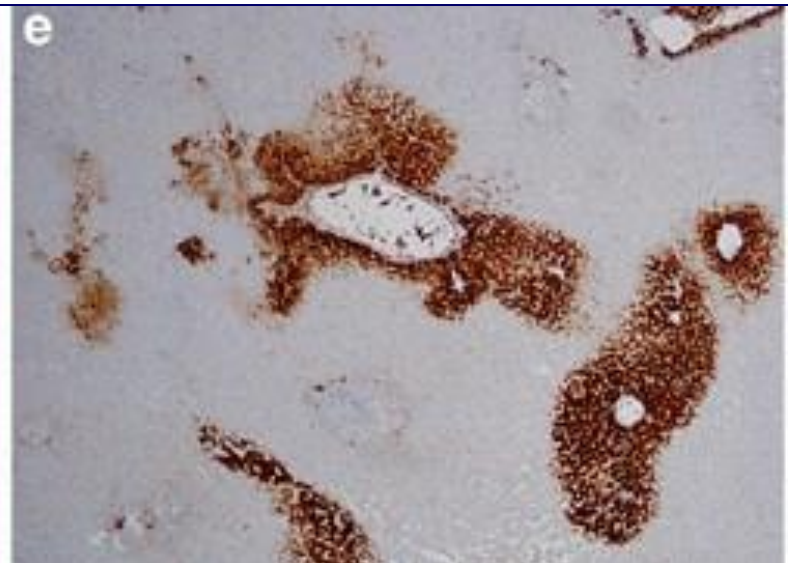
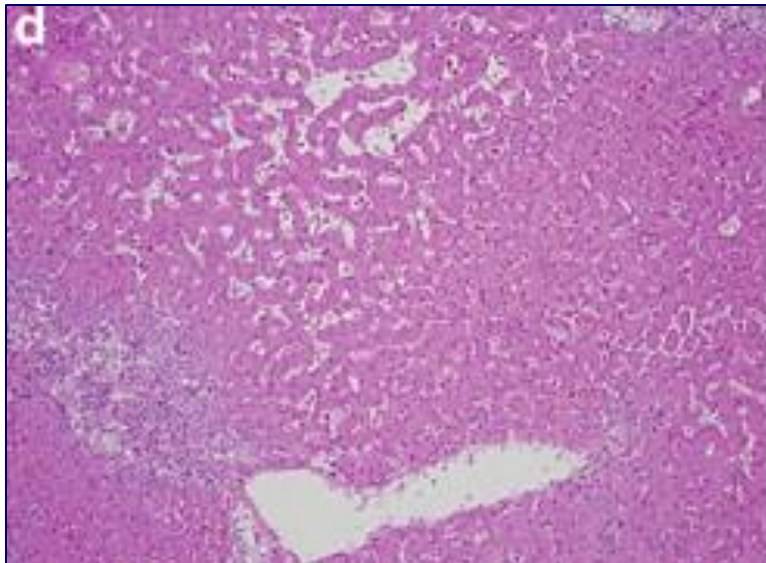
Modern Pathol 2014; 27:62-72

Diagnostic utility and limitations of glutamine synthetase and serum amyloid-associated protein immunohistochemistry in the distinction of focal nodular hyperplasia and inflammatory hepatocellular adenoma

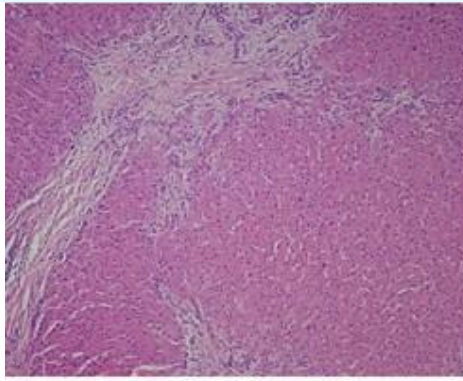
Nancy M Joseph¹, Linda D Ferrell¹, Dhanpat Jain², Michael S Torbenson³, Tsung-Teh Wu⁴, Matthew M Yeh⁵ and Sanjay Kakar^{1,6}

I-HCA

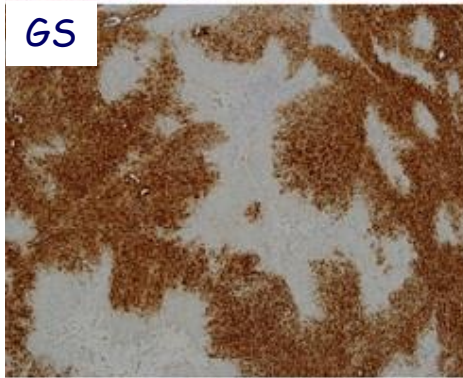
Glutamine synthetase (GS)



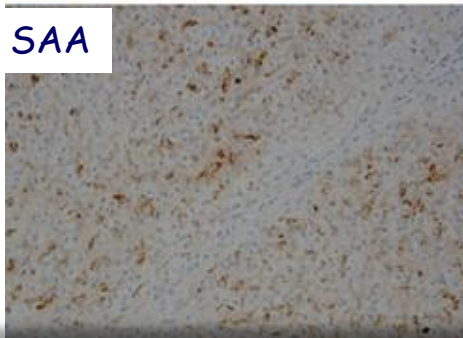
IHC of FNH and HCA



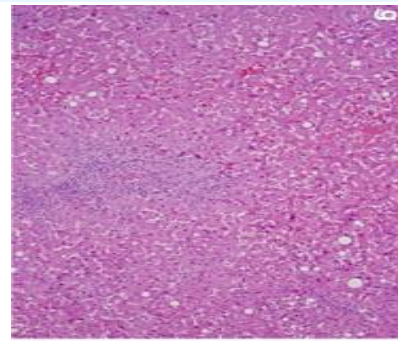
GS



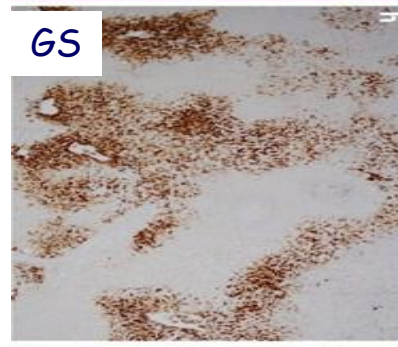
SAA



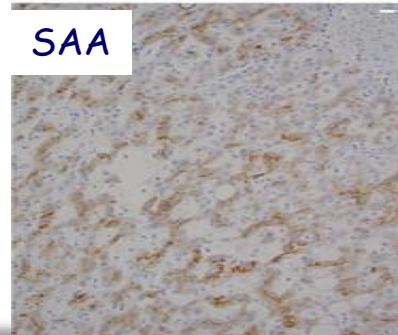
17.5% of **FNH**
show SAA positivity



GS



SAA



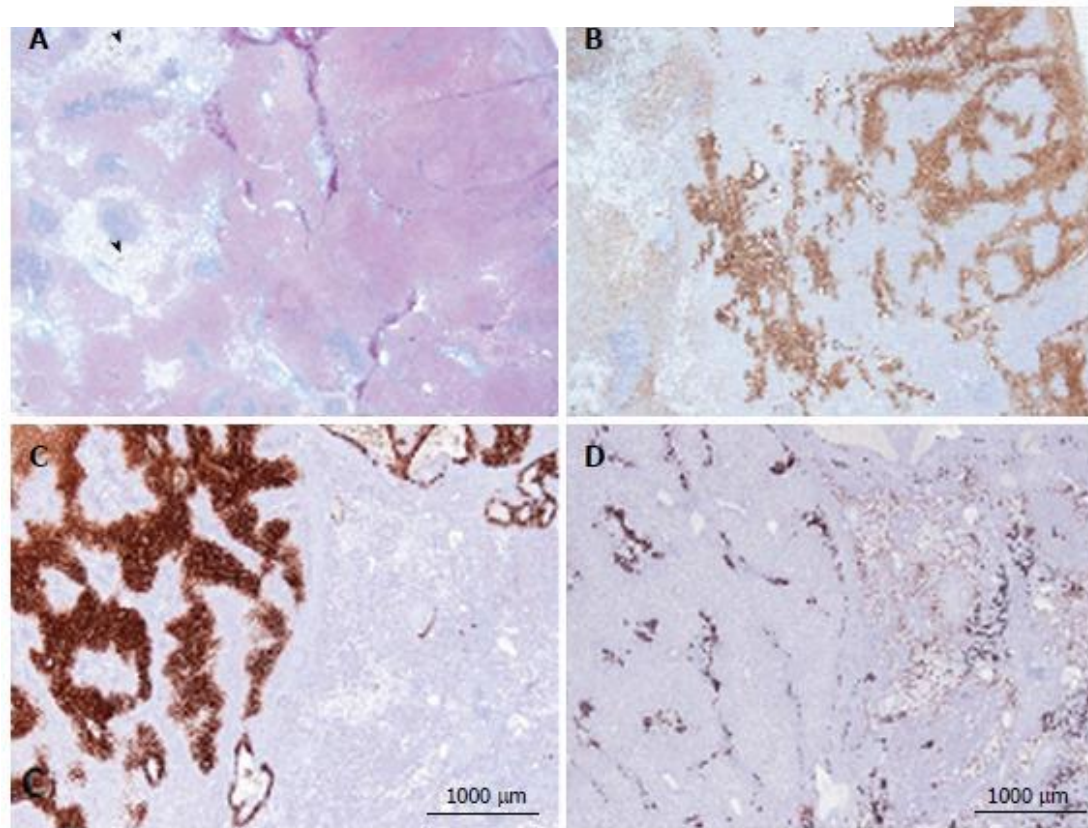
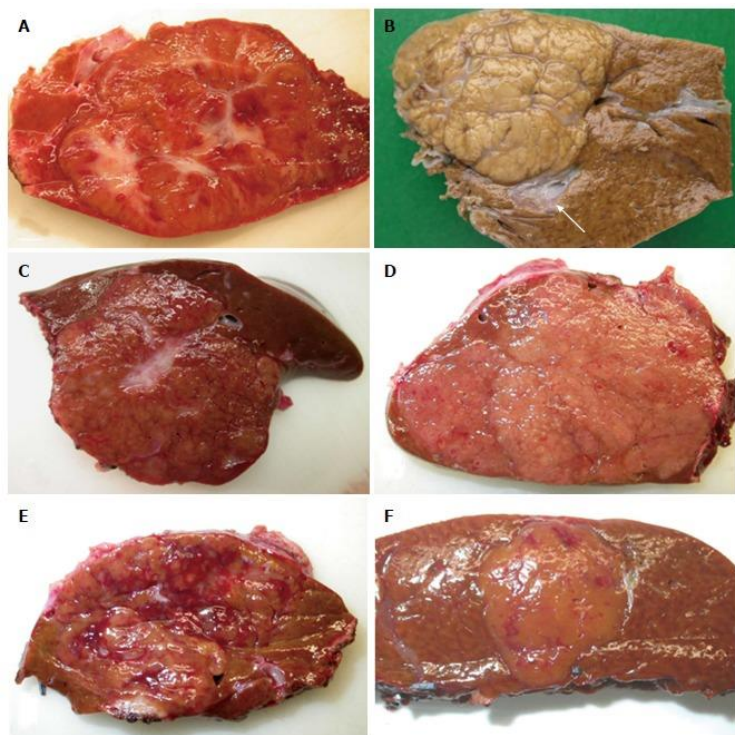
15% of **I-HCA** show
FNH-like GS pattern
(map-like)

Christine Sempoux, Charles Balabaud, Paulette Bioulac-Sage

MINIREVIEWS

Pictures of focal nodular hyperplasia and hepatocellular adenomas

FNH



Christine Sempoux, Charles Balabaud, Paulette Bioulac-Sage

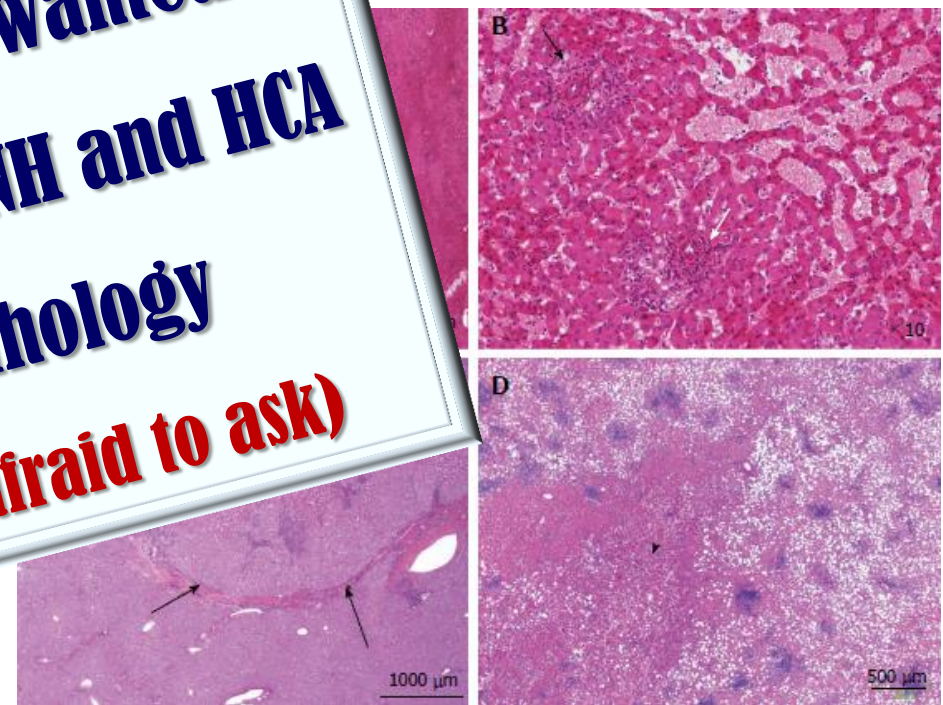
MINIREVIEWS

Pictures of focal nodular hyperplasia and hepatocellular adenomas



HCA

**Everything you wanted to
know about FNH and HCA
histopathology
(but were afraid to ask)**





- Chronic liver disease
- Benign liver tumours
- **Malignant liver and biliary tract tumours**
 - **HCC**
 - Intrahepatic cholangiocarcinoma

IHC markers for diagnosing HCC

Most frequently used:

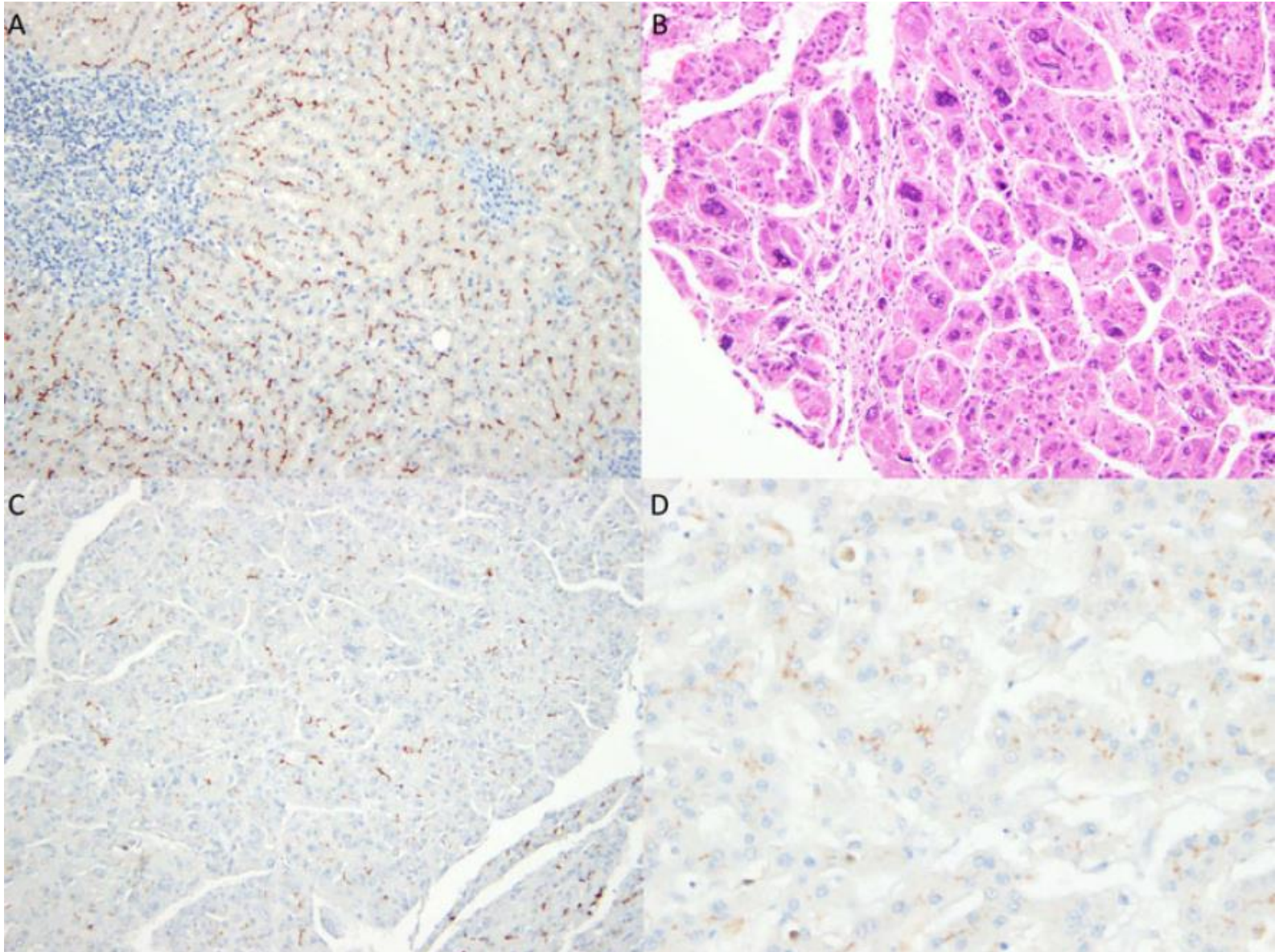
- HepPar1
 - arginase 1
 - polyclonal CEA
 - CD10
- } Hepatocellular differentiation
- } Canalicular markers

Yan, Am J Surg Pathol 2010

- Glypican-3 (GPC-3) → - marks HCC, but generally not benign hepatocytes
- therapeutic target in HCC

Filmus & Capurro, FEBS J 2013

Bile Salt Export Pump as a marker of HCC



Bile Salt Export Pump as a marker of HCC

Marker	Grade 1-2 HCC, n=39 (%)	Grade 3-4 HCC, n=9 (%)	ChCa, n=41 (%)	Metastatic tumors, n=24 (%)	Sensitivity	Specificity	PPV	NPV
BSEP	36 (92)	7 (78)	0	0	90%	100%	100%	93%
CD10	28 (72)	6 (67)	0	0	74%	100%	100%	84%
pCEA	32 (82)	7 (78)	0	0	81%	100%	100%	88%
HepPar-1	36 (92)	7 (78)	1 (2)	1 (4)	90%	97%	96%	93%
ARG	37 (95)	8 (89)	2 (5)	2 (8)	94%	94%	92%	95%
GPC-3	20 (51)	6 (67)	1 (2)	1 (4)	54%	97%	93%	74%

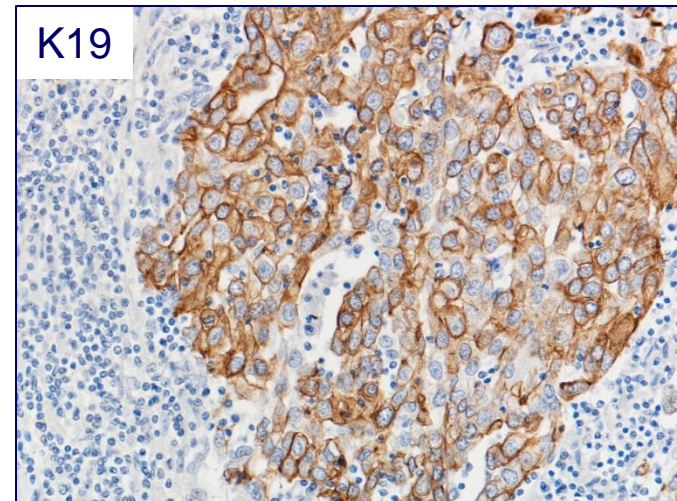
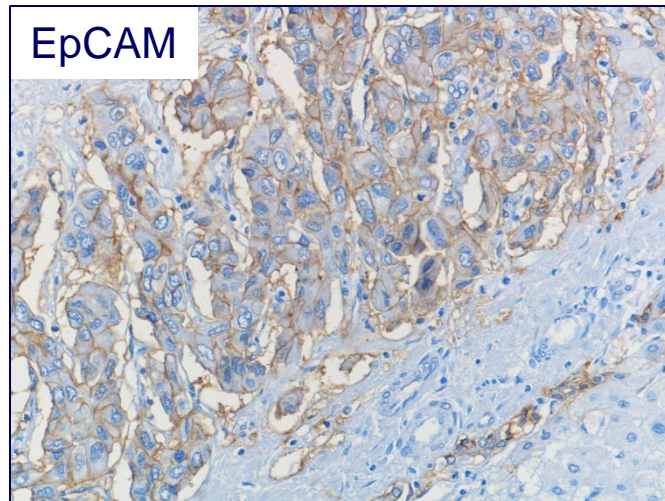
Lagana, Histopathology 2014 Nov 6, in press

BSEP is a highly sensitive and specific marker for HCC

No need to identify a “canalicular” pattern!

HCC expressing “stemness”-related markers

- HCC that express “stemness”-related markers (keratin 19, EpCAM, CD133, CD117) show more aggressive behaviour and have poor prognosis



Durnez, Histopathology 2006
Yamashita, Cancer Res 2008
Theise, WHO 2010
Kim, Hepatology 2013
Chan, Histopathology 2014

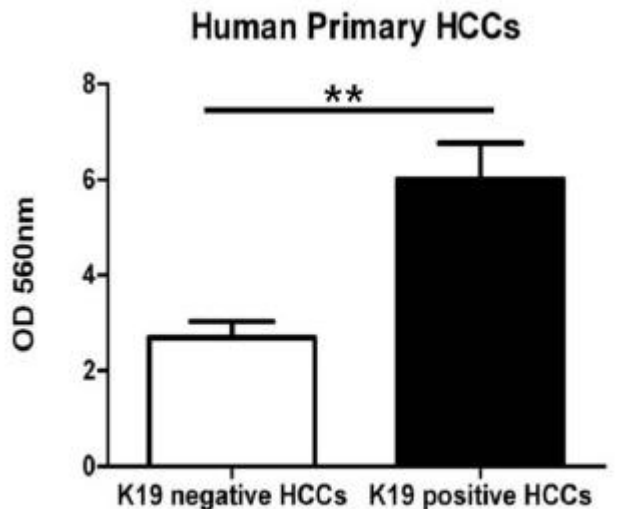
Keratin 19: a key role player in the invasion of human hepatocellular carcinomas

Olivier Govaere,¹ Mina Komuta,¹ Johannes Berkers,¹ Bart Spee,¹ Carl Janssen,¹ Joost van den Oord,¹ Massimo Pinzani,¹⁰ Tania Roskams[†]

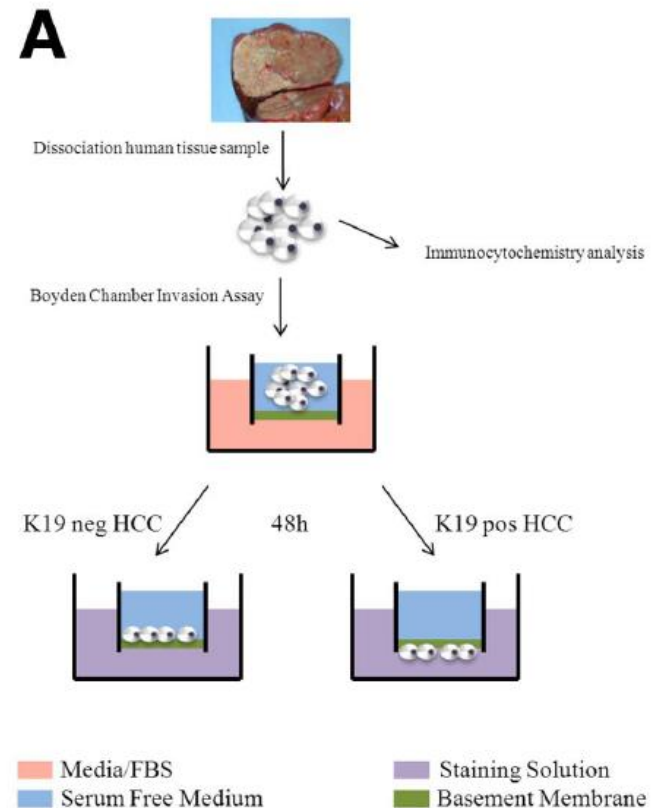
IHC 241 HCC, molecular profiling (mRNA, microRNA), *in vitro* assays

Keratin 19 expression in HCC

- confers an **invasive phenotype**



Cell Invasion Assay, 24-well (8 μ m), t=48h (n=12)



Keratin 19: a key role player in the invasion of human hepatocellular carcinomas

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Joost van den Oord,¹ Massimo Pinzani,¹⁰ Tania Roskams[†]

IHC 241 HCC, molecular profiling (mRNA, microRNA), *in vitro* assays

Keratin 19 expression in HCC

- confers an **invasive phenotype** by intersecting with pathways involved in cytoskeleton dynamics and cell motility
- is associated with **chemoresistance**

K19-positive HCC should be diagnosed and treated as a separate entity of HCCs (?)

HCC expressing “stemness”-related markers

- **SALL4**, an oncofetal antigen, is a new marker of HCC with progenitor-like gene signatures

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 368;24

ORIGINAL ARTICLE

Oncofetal Gene *SALL4* in Aggressive Hepatocellular Carcinoma

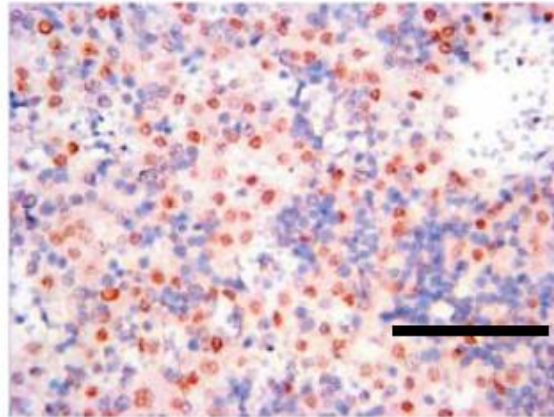
Kol Jia Yong, B.Sc., Chong Gao, M.D., Ph.D., Joline S.J. Lim, M.B., B.S.,
Benedict Yan, M.B., B.S., Henry Yang, Ph.D., Todor Dimitrov, Ph.D.,
Akira Kawasaki, M.D., Ph.D., Chee Wee Ong, M.Sc., Kwong-Fai Wong, Ph.D.,
Sanghoon Lee, Ph.D., Sharada Ravikumar, M.D., Ph.D., Supriya Srivastava, M.D.,
Xi Tian, B.S., Ronnie T. Poon, M.B., B.S., Ph.D., Sheung Tat Fan, M.D., D.Sc.,
John M. Luk, D.Med.Sc., Yock Young Dan, M.B., B.S., Ph.D.,
Manuel Salto-Tellez, M.D., Li Chai, M.D., and Daniel G. Tenen, M.D.

SALL4 expression in HCC

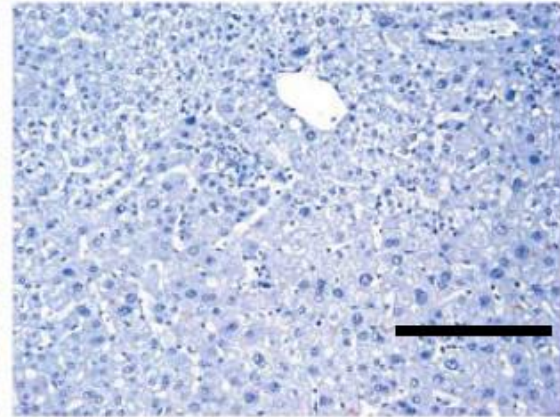
- **SALL4** is absent from normal liver

A Human Fetal and Adult Liver Specimens

19-Wk Fetal Liver

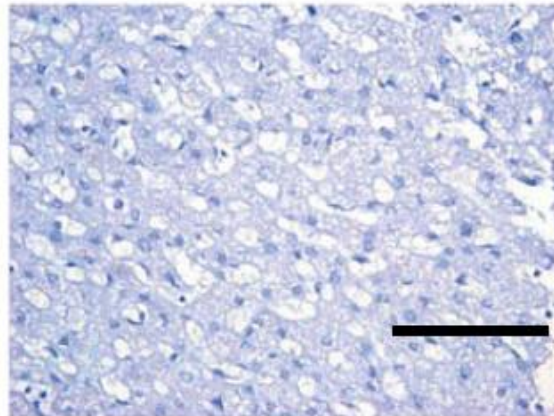


Adult Liver

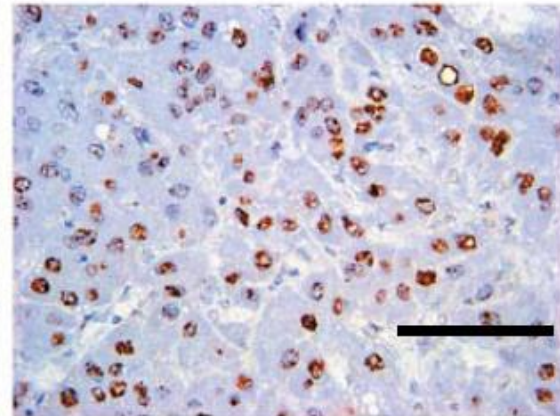


B Matched Non-neoplastic and Neoplastic Liver Specimens

Matched Non-neoplastic Tissue



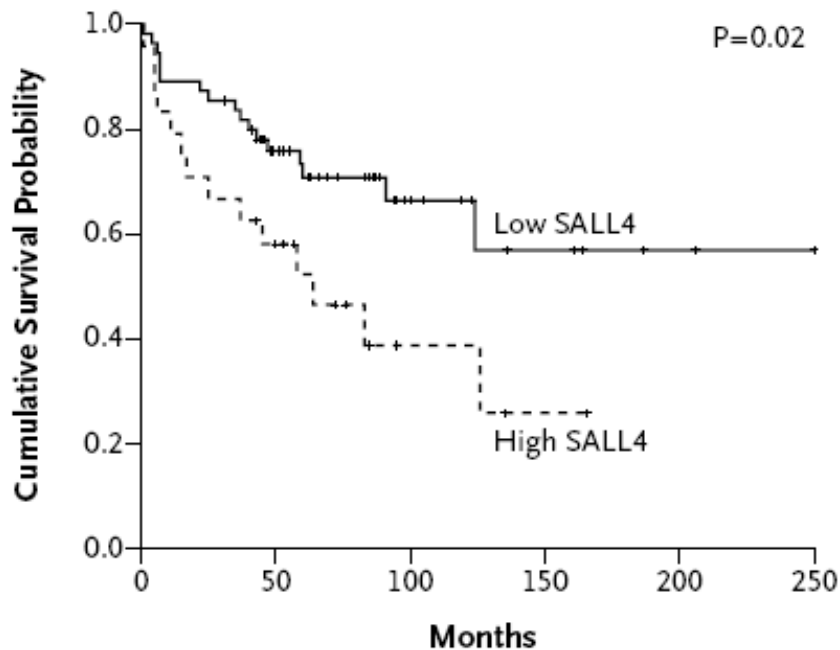
Tumor Tissue



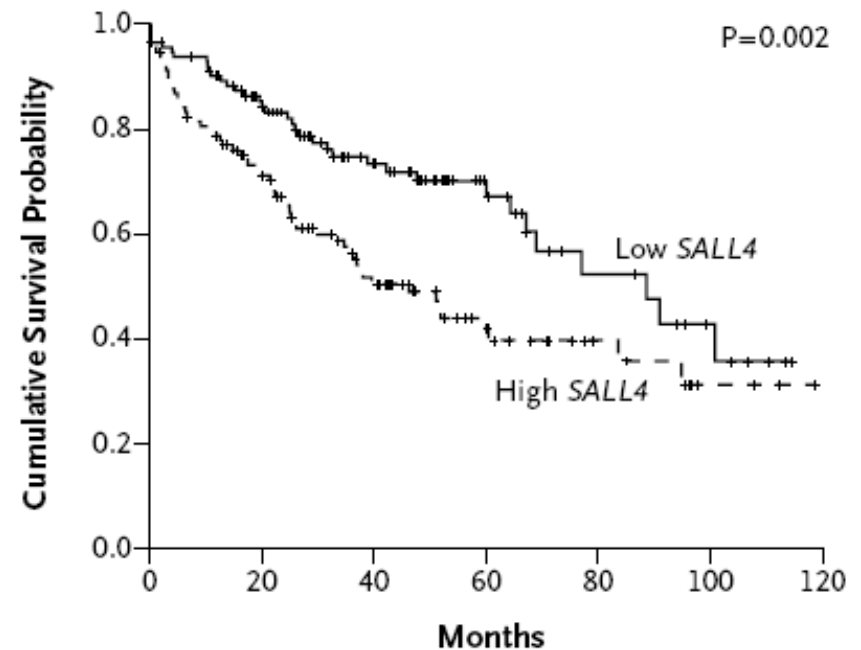
SALL4 expression in HCC

- Overexpression of proliferation- and metastasis-related genes in SALL4 (+) HCC

A Overall Survival, Singapore Cohort



B Overall Survival, Hong Kong Cohort



- SALL4 immunopositivity is a marker of poor prognosis in HCC

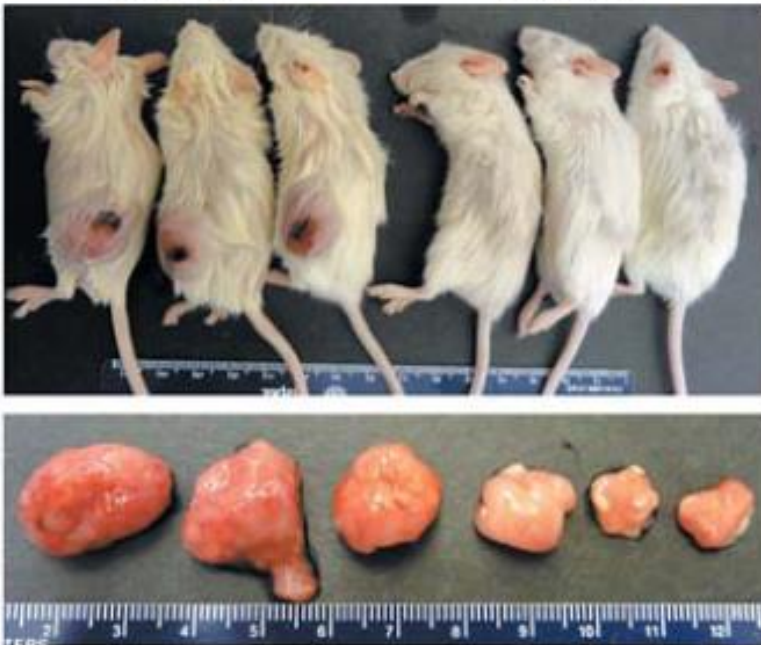
SALL4 expression in HCC

The absence of SALL4 expression from healthy adult liver enhances the **potential of SALL4 as a treatment target in HCC**

E SNU-398 Cells

TAT-Mutant
Peptides

TAT-Nonmutant
Peptides



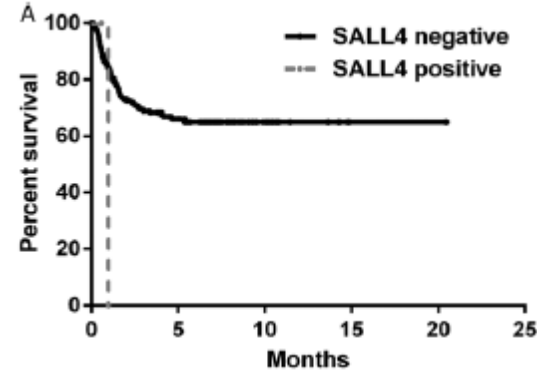
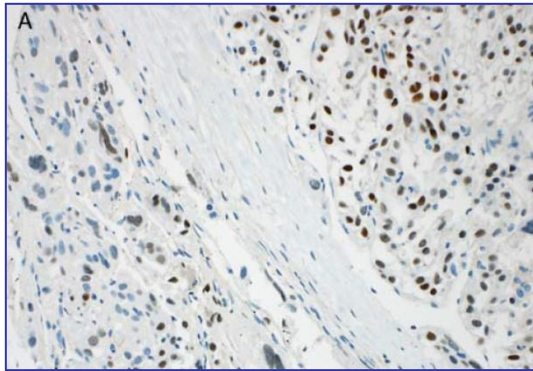
Inhibition of tumour formation by specific targeting of SALL4 in xenograft models

Yong, *NEJM* 2013
Zeng SS, *J Hepatol* 2014

SALL4 Immunoreactivity Predicts Prognosis in Western Hepatocellular Carcinoma Patients but Is a Rare Event

A Study of 236 Cases

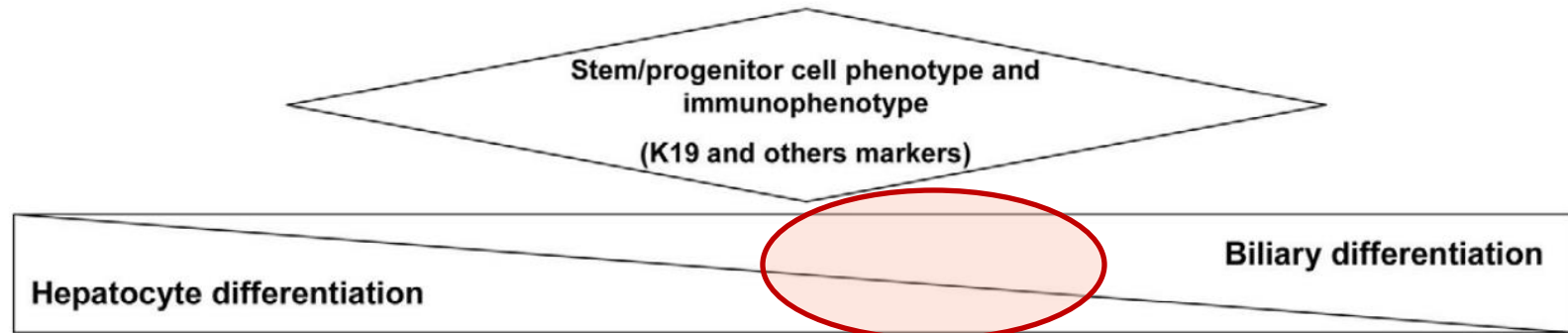
Ta-Chiang Liu, MD, PhD, Neeta Vachharajani, MBBS,†
William C. Chapman, MD,† and Elizabeth M. Brunt, MD**



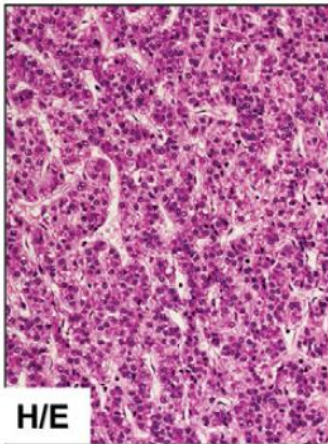
- 1.3% SALL4+ (3/236 HCC)
- correlation with high grade

universal application of SALL4 as a biomarker for HCC should be performed with caution.

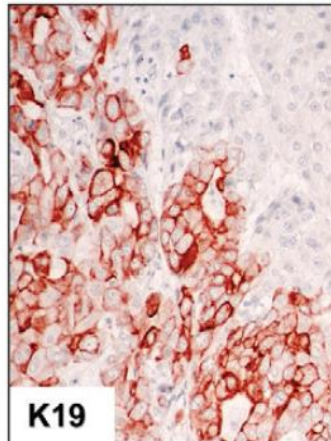
A new approach to histopathological classification of primary liver carcinoma



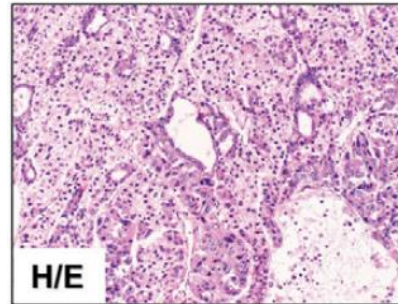
HCC: Hepatocellular phenotype



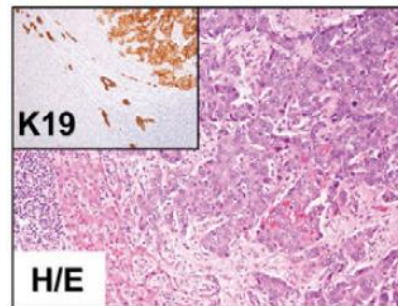
HCC: Hepatocellular phenotype with stem/progenitor cell immunophenotype



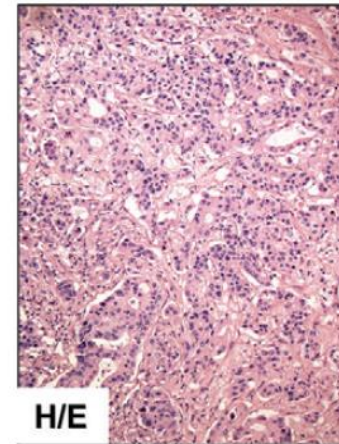
Mixed hepatobiliary carcinoma, classical type



Mixed hepatobiliary carcinoma with stem/progenitor cell phenotype and immunophenotype



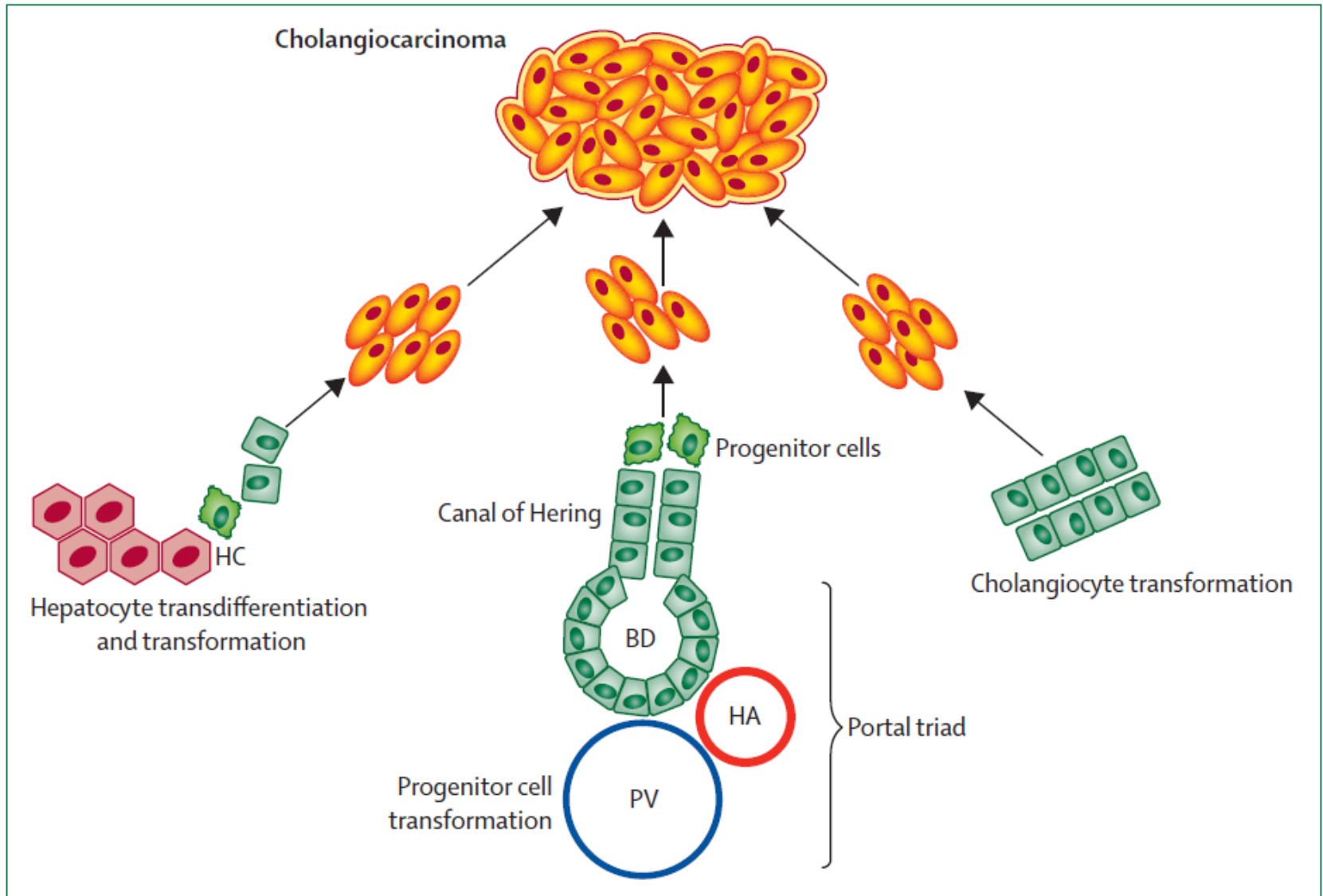
Cholangiocarcinoma: Biliary phenotype



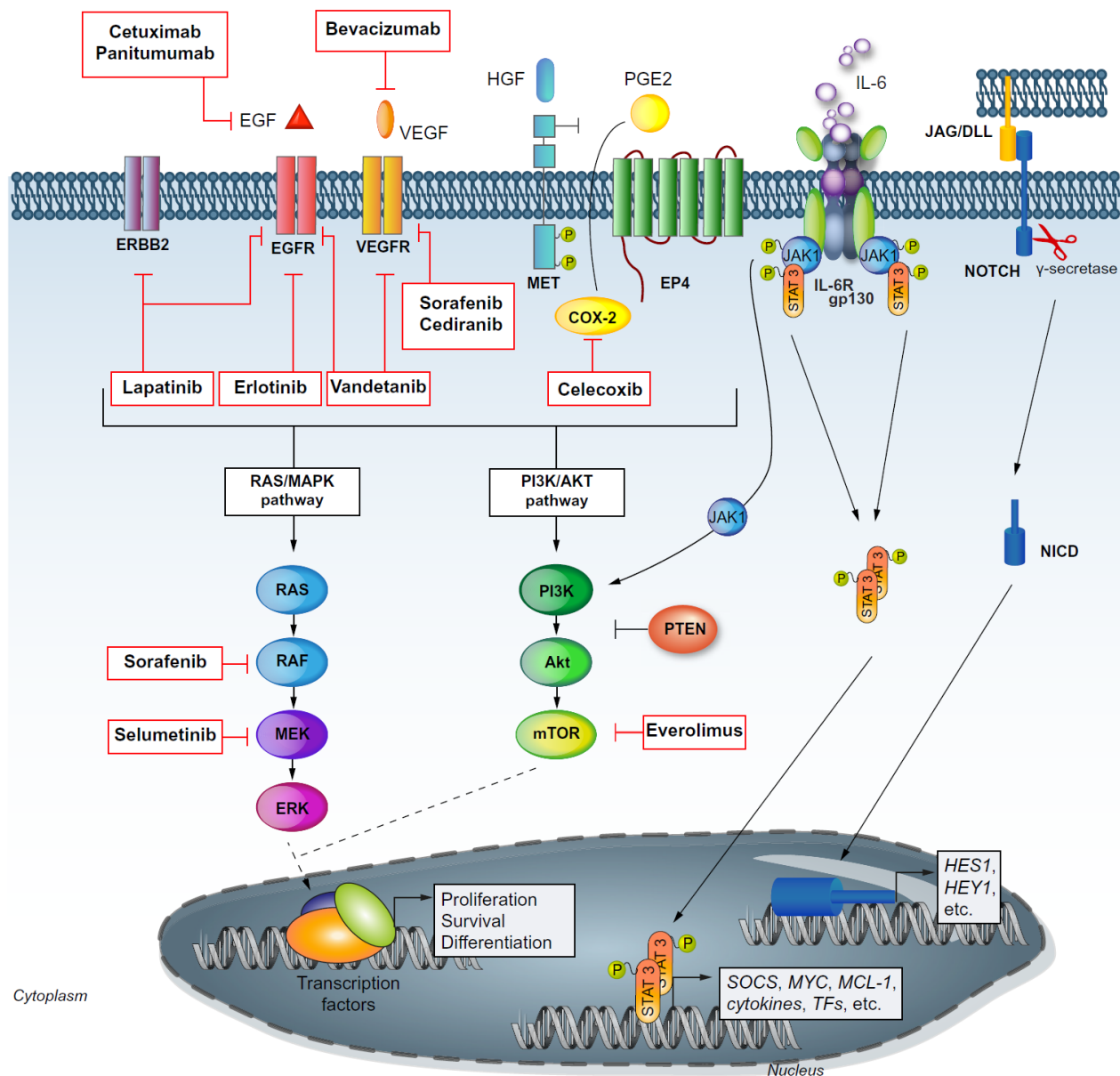


- Chronic liver disease
- Benign liver tumours
- **Malignant liver tumours**
 - HCC
 - **Cholangiocarcinoma**

Cell origins of Cholangiocarcinoma



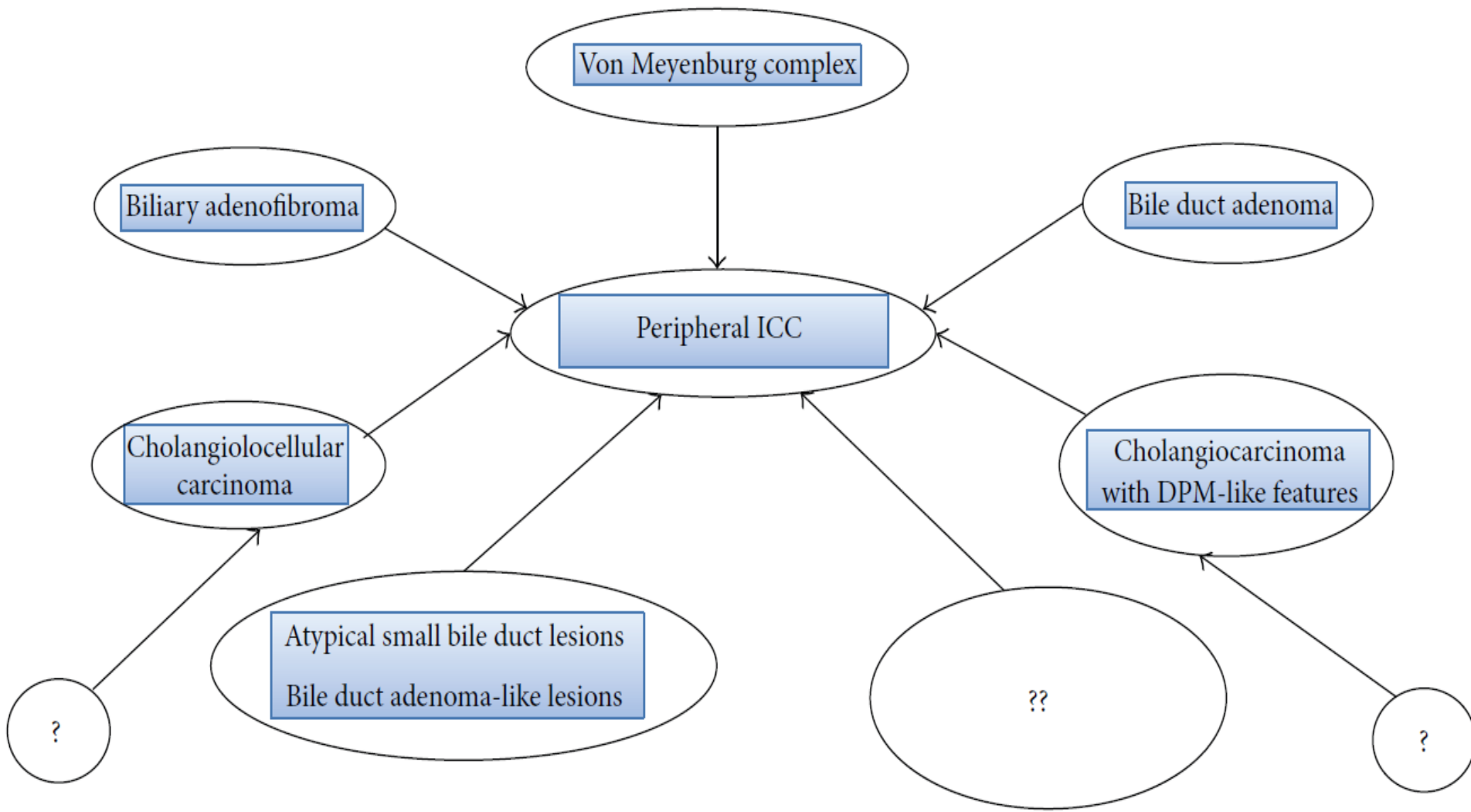
Targetable cholangiocarcinoma signalling pathways



What Are the Precursor and Early Lesions of Peripheral Intrahepatic Cholangiocarcinoma?

Int J Hepatol 2014, ID 805973

Yasuni Nakanuma.^{1,2} Akemi Tsutsui.¹ Xiang Shan Ren.¹ Kenichi Harada.¹



Hilar cholangiocarcinoma

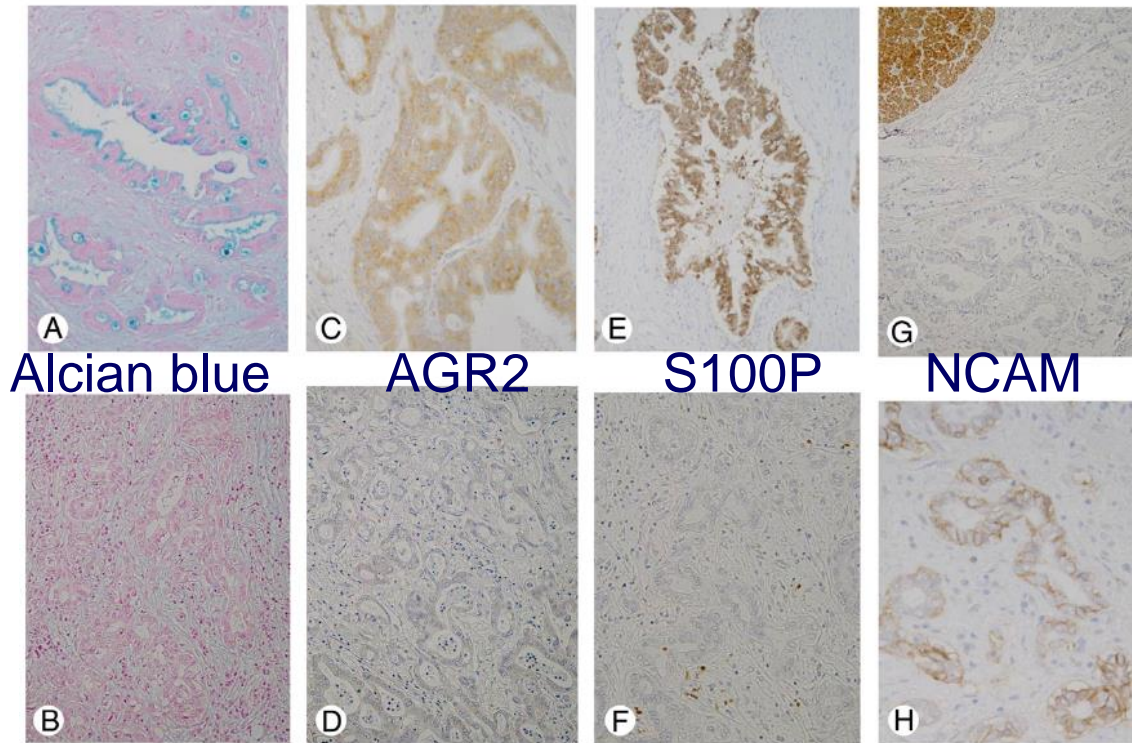
Human Pathology (2013) 44, 811–821

Hilar cholangiocarcinoma and pancreatic ductal adenocarcinoma share similar histopathologies, immunophenotypes, and development-related molecules ☆, ☆ ☆

Chihiro Gandou^a, Kenichi Harada^a, Yasunori Sato^a, Saya Igarashi^a, Motoko Sasaki^a, Hiroko Ikeda^b, Yasuni Nakanuma^{a,*}

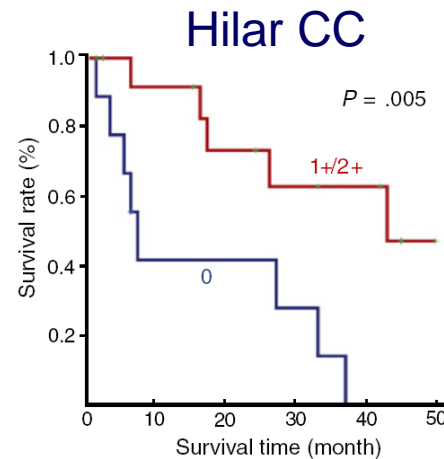
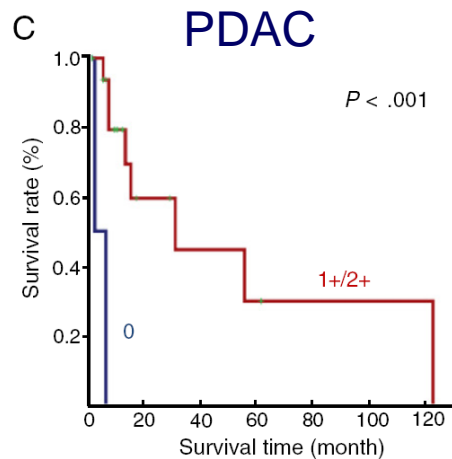
^a*Department of Human Pathology, Kanazawa University Graduate School of Medicine, 13-1 Takara-machi, Kanazawa 920-8640, Japan*

Hilar cholangiocarcinoma vs PDAC



Hilar CC
PDAC

ICC
cHC-CCC



Summary (1)

- **Histological sub-classification of cirrhosis becomes a reality**
- **Digital evaluation of fibrosis by image analysis is superior to histology for comparisons with HVG, evaluation of prognosis and correlations with noninvasive fibrosis methods**
- **qFibrosis is superior digital method for assessing fibrosis compared to the better known CPA**
- **Tissue angiogenesis is proposed to be included in histological assessment of CLD**



Summary (2)

- **DILI: - limited correlation between biochemical and pathological injury patterns**
 - **Severe or fatal injury is associated with**
 - ↑ necrosis, microvesicular steatosis, ductular reaction and fibrosis stage**
- **Perilipin, a lipid droplet associated protein, may be used for the differential diagnosis between chronic and acute steatosis**



Summary (3)

- **A new histological scoring system (SAF) and a classifier algorithm for NAFLD has been validated and helps decrease interobserver variability for NASH diagnosis**
- **Histological scoring systems with prognostic value have recently been developed for alcoholic hepatitis**
- **New histological staging and grading systems for PBC appear superior to classical staging systems**
- **FBI is simpler and has higher inter-observer agreement compared to the Japanese system**



Summary (4)

- **BSEP is a highly sensitive and specific new marker for HCC**
- **HCC that express “stemness”-related markers show more aggressive behaviour and poor prognosis**
- **Re-classification of primary liver carcinomas is the focus of intense research: a spectrum with carcinomas showing HC differentiation in one end and CC in the other**



Summary (5)

- **Different cell origin underlies the histological diversity of intrahepatic cholangiocarcinomas**
- **Precursor lesions of distal (peripheral) intrahepatic cholangiocarcinomas have been proposed**
- **The similarities between hilar cholangiocarcinomas and PDAC may reflect common pathogenesis based on embryology**



Drinking Coffee Burns Hepatic Fat by Inducing Lipophagy Coupled With Mitochondrial β -Oxidation

