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STOPAH

1053 patients were available for the primary end-point analysis.

“Pentoxifylline did not improve survival in patients with alcoholic hepatitis. Prednisolone was associated with a reduction in 28-day mortality that did not reach significance and with no improvement in outcomes at 90 days or 1 year.”

Prednisolone or pentoxifylline for alcoholic hepatitis
N Engl J Med. 2015 Apr 23;372(17):1619-28.

STOPAH Histology: Background

- In patients with severe alcoholic hepatitis, defined by a Maddrey's Discriminant Function ≥ 32 , examination of liver histology invariably implies that a transjugular biopsy be performed
- Facilities for transjugular biopsy are not ubiquitous so need to be sure that histology is useful.
- A recent review of clinical practice suggests that liver biopsy is rarely used in the management of patients with alcoholic hepatitis.

STOPAH Histology: Plan

- The purpose of this study was therefore to determine the utility of liver histology in patients presenting with a putative clinical diagnosis of severe alcoholic hepatitis by:
 1. estimating the proportion of patients in which the histology refutes the clinical diagnosis and
 2. assessing the prognostic information provided by histological analysis.

STOPAH Histology

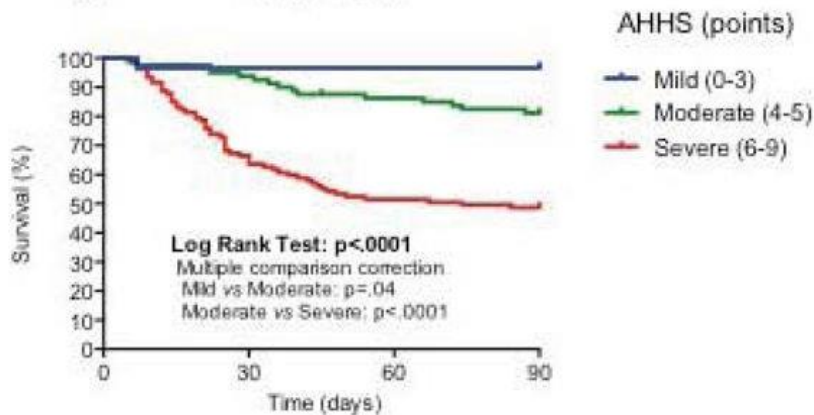
- Two pathologists blinded to the clinical details.
- Biopsies were considered adequate when there were at least 5 portal tracts.
- They were scored using:
 1. Alcoholic Hepatitis Histological Score
 2. NAFLD Activity Score and
 3. Laennec Fibrosis Score

Alcoholic Hepatitis Histological Score (AHHS) for Prognostic Stratification of Alcoholic Hepatitis

	Points	
Fibrosis stage		AHHS categories (0–9 points)
None Fibrosis or Portal fibrosis	0	Mild : 0–3
Expansive fibrosis	0	Intermediate: 4–5
Bridging fibrosis or Cirrhosis	+3	Severe: 6–9
Bilirubinostasis		
No	0	
Hepatocellular only	0	
Canalicular or ductular	+1	
Canalicular or ductular plus Hepatocellular	+2	
PMN infiltration		
No/Mild	+2	
Severe PMN Infiltration	0	
Megamitochondria		
No Megamitochondria	+2	
Megamitochondria	0	

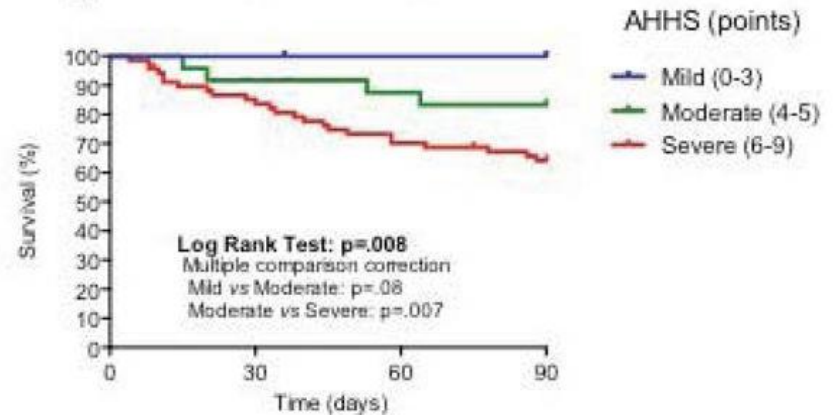
Gastroenterology. 2014 May; 146(5): 1231–1239.

a) Study Cohort



Mild (0-3)	30	29	29	29
Moderate (4-5)	80	75	68	65
Severe (6-9)	107	68	55	52

b) Validation Cohort



Mild (0-3)	17	17	17	17
Moderate (4-5)	24	22	21	20
Severe (6-9)	68	57	48	44

NAFLD Activity Score

Steatosis grade	Lobular inflammation	Hepatocellular ballooning
0: <5%	0: None	0: None
1: 5-33%	1:<2 foci/20x field	1: Mild, few
2: 34-66%	2: 2-4 foci/20x field	2: Moderate – marked,
3: >66%	3: >4 foci/20x field	many
NAFLD activity score (NAS): 0-8		
Steatosis (0-3) +	Lobular Inflammation (0-3)	+ Ballooning (0-2)

Stage:

Laennec Subclassification of Cirrhosis

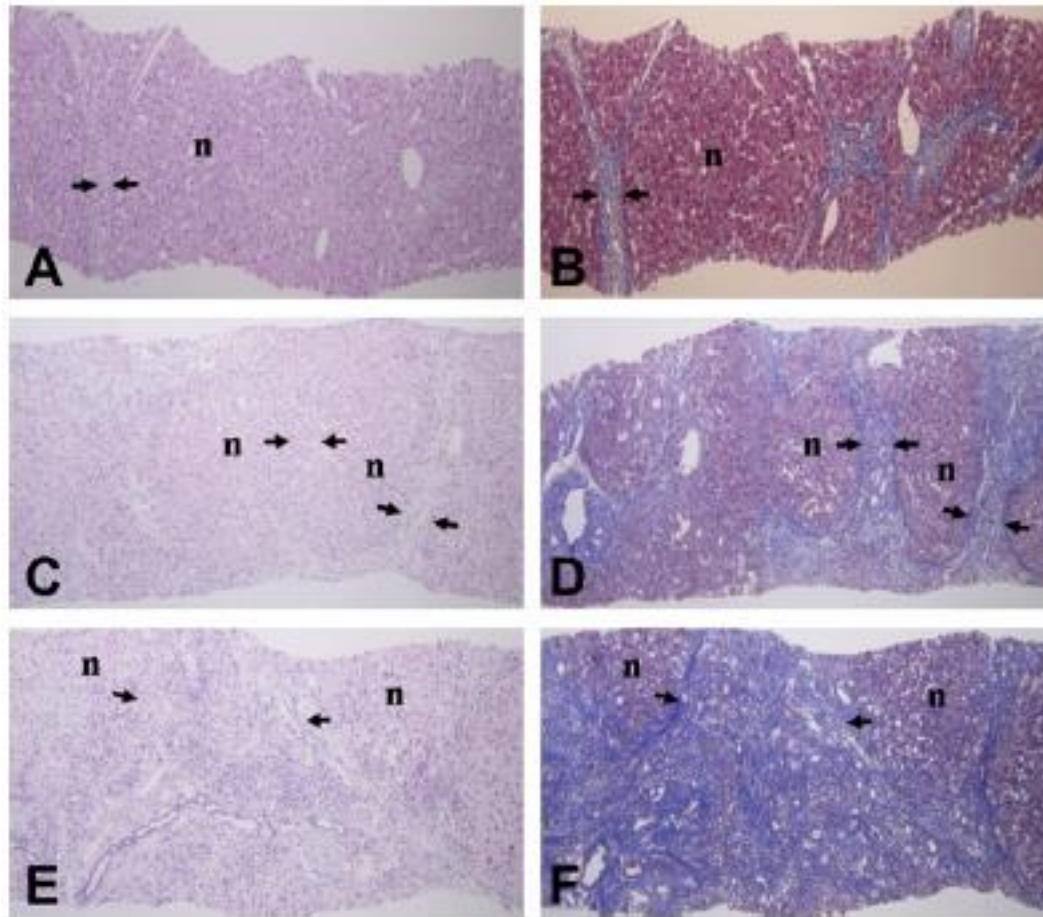
Table 1. Laennec stage for histological subclassification of cirrhosis

Stage	Name	Criteria
F0	No definite fibrosis	
F1	Minimal fibrosis	No septa or rare thin septum; may have portal expansion or mild sinusoidal fibrosis
F2	Mild fibrosis	Occasional thin septa; may have portal expansion or mild sinusoidal fibrosis
F3	Moderate fibrosis	Moderate thin septa; up to incomplete cirrhosis
F4A	Cirrhosis, mild, definite or probable	Marked septation with rounded contours or visible nodules. Most septa are thin (one broad septum allowed)
F4B	Moderate cirrhosis	At least two broad septa, but no very broad septa and less than half of biopsy length composed of minute nodules
F4C	Severe cirrhosis	At least one very broad septum or more than half of biopsy length composed of minute nodules (micronodular cirrhosis)

**The need for histological subclassification of cirrhosis:
a systematic review and meta-analysis.**

Liver Int. 2015 Jul 25.

Laennec Subclassification of Cirrhosis



STOPAH Histology: Prognostic information

- The histological scoring systems:

AHHS and NAS

were compared with

- clinical scoring systems:

DF, MELD, Lille and GAHS

for prognostic accuracy using area under the receiver operating characteristic analysis.

STOPAH Histology

- The STOPAH trial recruited 1103 patients with 1053 available for primary endpoint (28 day mortality) analysis.
- Biopsies were taken from 188/1103 (17%) patients during the trial enrolment admission
- Of these, 25/188 (13%) were inadequate for histological assessment, leaving 163 cases for further evaluation.

STOPAH Histology:

Diagnosis of Alcoholic Hepatitis

- Overall a diagnosis of alcoholic hepatitis was confirmed in 142 of 163 cases (87%).
- Delay in obtaining a liver biopsy resulted in a numerical reduction in the rate of diagnostic confirmation:

91% for biopsies obtained days 0-2 vs.

84% for biopsies obtained days 7-28 (n.s.)

STOPAH Histology Prognostic Accuracy

Prognostic score	28 day mortality		
	n	AUC	95% CI
DF	95	0.776	0.632, 0.921
GAHS	86	0.608	0.409, 0.807
MELD	96	0.597	0.409, 0.784
Lille	73	0.812	0.664, 0.961
AHHS	96	0.693	0.548, 0.838
NAS	96	0.473	0.315, 0.630

The Alcoholic Hepatitis Histology Score Performs Poorly in a Cohort of Severe Alcoholic Hepatitis in the US

“The AHHS model performed poorly in predicting 90-day mortality or LT in a real-world cohort of severe AH patients in the United States.”

Histological and laboratory correlations

In the 100 selected liver biopsies we sought correlations between haematological and biochemical values at baseline with baseline histological characteristics.

There were strong correlations between:

- serum bilirubin and bilirubinostasis
- prothrombin time and Laennec classification of fibrosis
- serum white blood and neutrophil counts correlated with lobular inflammation

STOPAH Histology

- Liver histology remains a useful tool in patients presenting with features of alcoholic hepatitis but with diagnostic uncertainty.
- Where the diagnosis is made clinically with confidence histology will identify 13 % of patients with alternative diagnoses, predominantly that of inactive cirrhosis.
- Provides independent validation of the AHSS

Elevated leukocyte count combined
with radiologic evidence
of a nodular liver surface in
uninfected patients
strongly predicts histologic alcoholic
hepatitis, obviating
the need for liver biopsy

- The combination of an elevated leukocyte count and a nodular liver surface in the absence of infection retrospectively identified patients with a high likelihood of having histologic AH and suggests that a liver biopsy may not be necessary in this subset.
- For patients with suspected severe AH who do not fulfill these criteria, liver biopsy remains important, as 23% of these patients have no histologic AH.

Limitations: Clinical

- The utility of histology will be greater outside the context of a clinical trial.

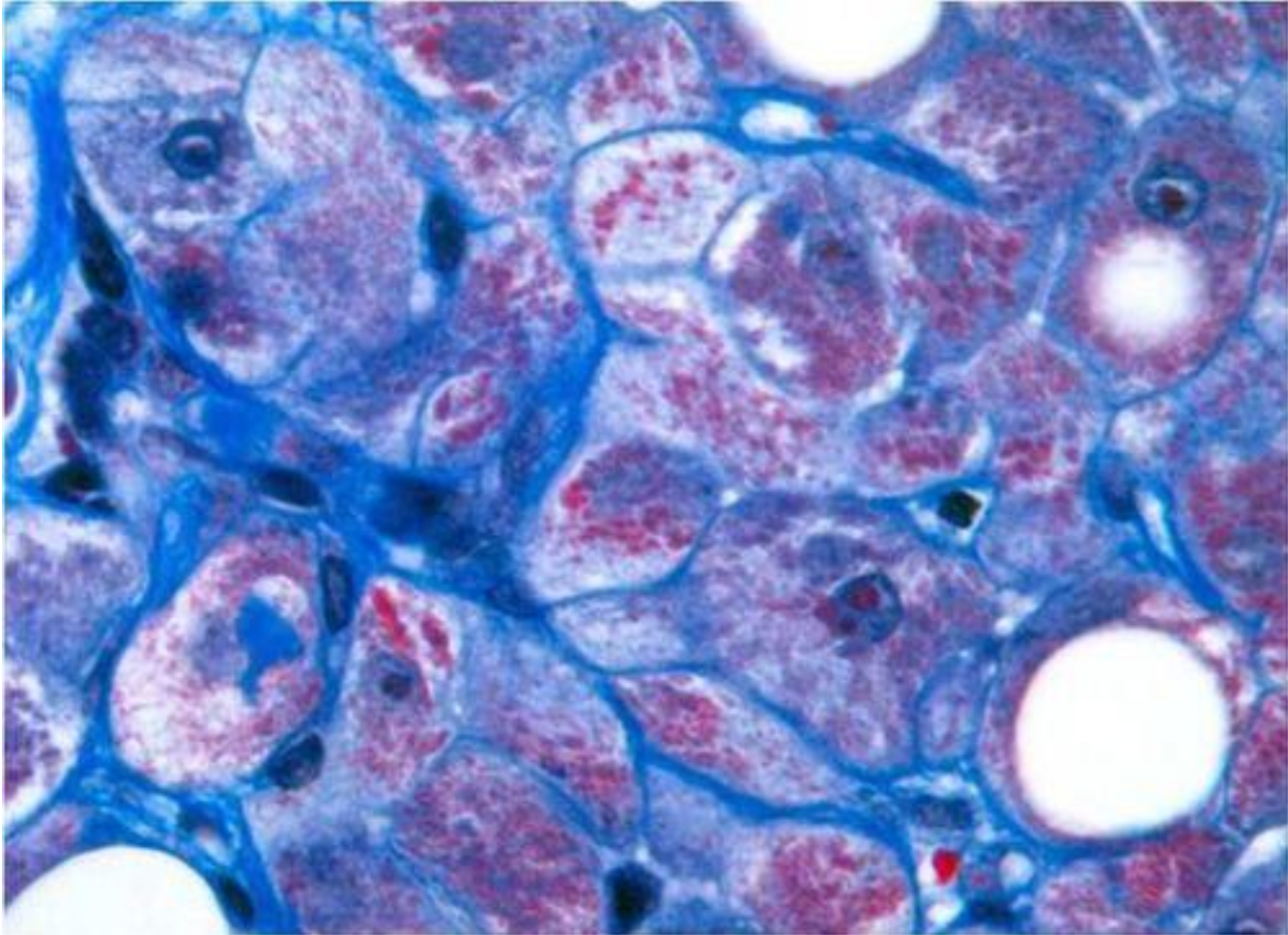
Limitations: Pathological

- Number of cases
- Number of stains

What next?

- Complete image analysis
- Put the digitised images up on the web and invite you to score them!

Megamitochondria



Megamitochondria

- Normal, increase with age
- Increased in ALD and may correlate with the amount of alcohol drunk
- May correlate with milder disease.

Significance of megamitochondria in alcoholic liver disease.

Gastroenterology. 1986 Jun;90(6):1858-64.

Histopathological agreement

0.65 for fibrosis

0.86 for bilirubinostasis

0.60 for neutrophil infiltration and

0.46 for megamitochondria



Let me know if you are
interested:

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AASLD
THE LIVER MEETING®
2015 SAN FRANCISCO



“PBC”

- The disease previously known as:
‘Primary Biliary Cirrhosis’

will now be called:

“Primary Biliary Cholangitis”

Fibrosis in PBC

- Absent / few septa 44%
- Numerous septa 31%
- Cirrhosis 25%

Liver International. 2004;24(3)

Primary biliary cholangitis

- **Cons:**

Tautological

Sounds too much like “primary sclerosing cholangitis”

- **Pros:**

Inaccurate

Stigma

Am J Gastroenterol 2015; 110:1536–1538

Extending the Ballooning Score
Beyond 2:
A Proposal
for a New Balloon Score

NAFLD Activity Score

Steatosis grade	Lobular inflammation	Hepatocellular ballooning
0: <5%	0: None	0: None
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NAFLD activity score (NAS): 0-8		
Steatosis (0-3) +	Lobular Inflammation (0-3)	+ Ballooning (0-2)

- A criticism of the NAFLD Activity Score (NAS) has been that it gives less weight to ballooning than to steatosis or lobular inflammation.
- Beginning in April, 2010 we prospectively classified all biopsies with ballooning as
classical (CB: distinct, enlarged, with clumped cytoplasm) or
non-classical (NCB: cytoplasmic changes without distinctive cytomegaly).
- **Severe** ballooning was defined as clusters of CB cells visible at low magnification.
- The NASH CRN new balloon score was created by combining the old balloon score and these new characteristics with a final range from 0 to 4.

NASH CRN New Balloon Score

Score	0	1	2	3	4	
Ballooning	None	NCB only	CB, few	CB, many	Severe	p for trend
N	410	194	178	261	188	
Mean Age (yr)	48.7	50.1	51.4	52.6	52.4	<0.0001
% Female	52.9	53.6	62.4	74.7	82.4	<0.0001
Mean BMI (kg/m ²)	33.1	34.2	34.7	35.2	36.1	<0.0001
% Diabetes	28.0	35.6	47.2	59.4	62.2	<0.0001
% Metabolic Syndrome	66.1	81.4	80.9	83.5	87.8	<0.0001
Mean ALT (U/L)	56.1	59.9	68.7	83.0	85.8	<0.0001
Mean Glucose (mg/dL)	103	105	114	119	127	<0.0001
Mean Insulin (mcU/mL)	19.3	23.5	22.0	34.0	34.6	<0.0001
Mean HOMA-IR	5.1	6.3	6.3	10.6	11.6	<0.0001

- Compared to cases without ballooning, NCB cases had more severe histology
- Compared to NCB cases, CB cases had more severe histology
- Severe ballooning cases differed from non-severe ballooning in that they had more severe histology

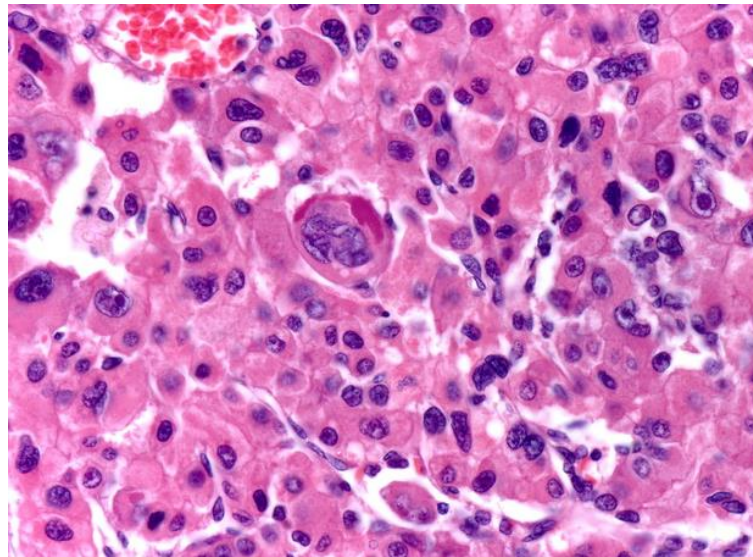
Renal Biopsy Histopathological
Features in Patients with
Cirrhosis:
Post Mortem Study of 27 Patients

- Acute tubular necrosis and bile cast formation was semiquantitatively graded as per recent report. (Kidney Int 2013;84:192-97) .
- 3+ (numerous bile casts) were considered bile cast nephropathy. Less than 5 casts were not considered significant

Renal histopathology	Total Bilirubin (mg/dL)	S. Creatinine (mg/dL)	Maddrey Discriminant Function	INR
ATN (Acute tubular necrosis)	18.2	1.9	91	3.2
ATN+BCN (Bile cast nephropathy)	27	3.3	83	2.2
Normal	4.7	1.4	79	2.5

Impact of Hepatic p62
Overexpression on Survival of
Patients with Hepatocellular
Carcinoma

- p62 is an adaptor or a scaffolding substrate between the ubiquitin–proteasome and the autophagy–lysosome pathways



- The results of the current study indicated that overexpression of p62 was closely associated with overall survival

Differences between radiology and
histopathology in
HCC transplanted patients:
are we judging wrong?

Discrepancy between pathological and radiological findings regarding the number of nodules was found in 103/184(56%):

78 were underestimated and 25 overestimated by radiology.

Considering the diameter of the biggest nodule on explant, discordance was observed in 158/181(87%):

93 were underestimated and 65 overestimated by radiology.

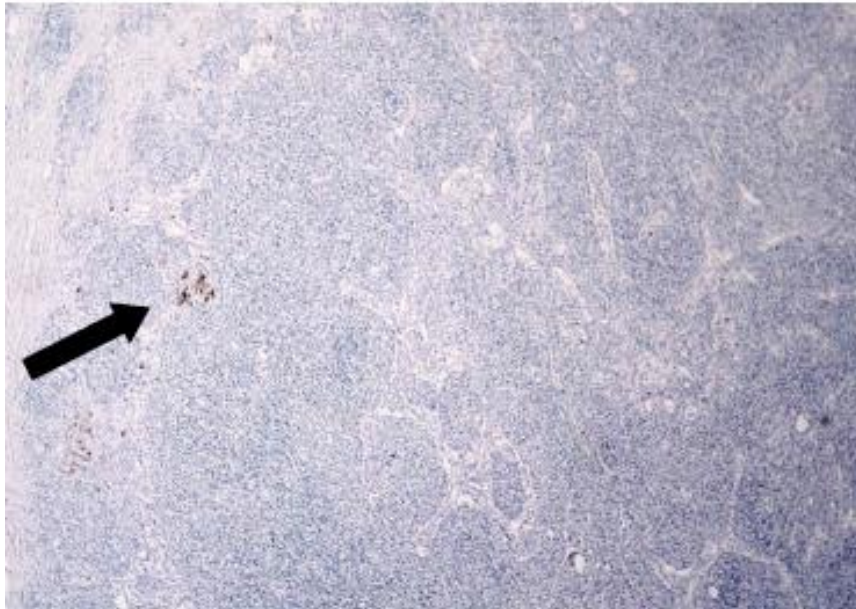
The Clinical-Pathological Spectrum
and Outcomes of
Liver Injury due to Drugs and
Botanicals Associated with
Loss of Bile Ducts.

- Out of 461 patients, paucity of intra-lobular bile ducts was found in 6% and was categorized as either:
mild/moderate [25-50% loss] or
severe [$> 50\%$ loss].
- The likelihood of dying or requiring liver transplantation within 6 months of onset was greater in those with severe bile duct loss

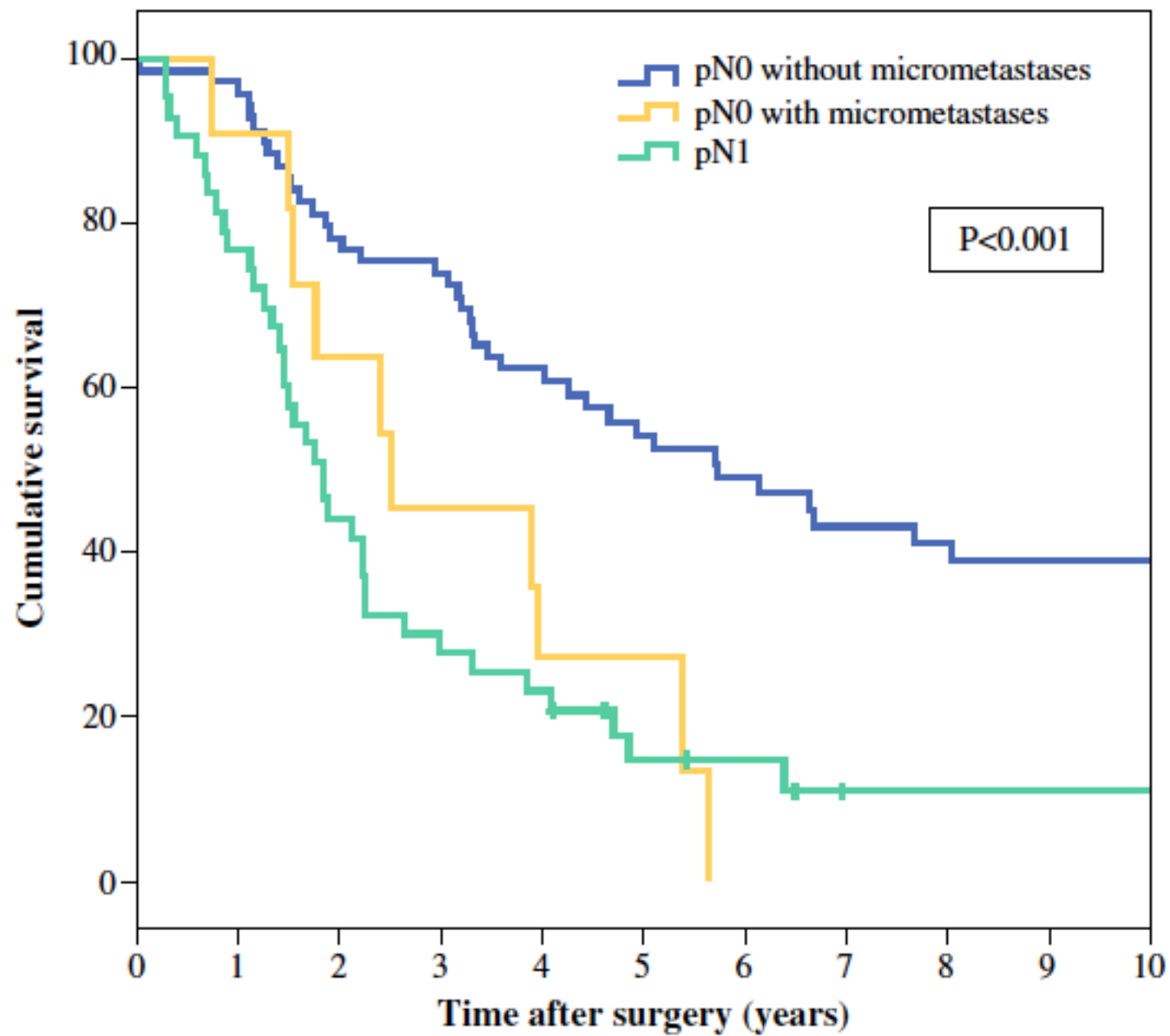
- Cases were attributed to 20 different agents:
 - 3 to amoxicillin/clavulanic acid;
 - 3 to temozolomide;
 - 3 to botanicals[Cactus nopal; Artemisia annua; unknown];
 - 2 to azithromycin; and
 - 1 each due to cefalexin, cefazolin, levofloxacin, moxifloxacin, allopurinol, enalapril, hydralazine, infliximab, lenalidomide, thalidomide, montelukast, olanzapine, quetiapine, lansoprazole, omeprazole, metoclopramide and mesalazine.

Lymph Node Micrometastases are
Associated with Worse
Survival in Patients with Otherwise
Node-Negative Hilar
Cholangiocarcinoma

- “To this end, we applied rigorous multiple sectioning of the lymph node tissue blocks to achieve deeper levels, investigated several levels of each lymph node, and increased the sensitivity of tumor cell identification by K19 immunolabeling. “

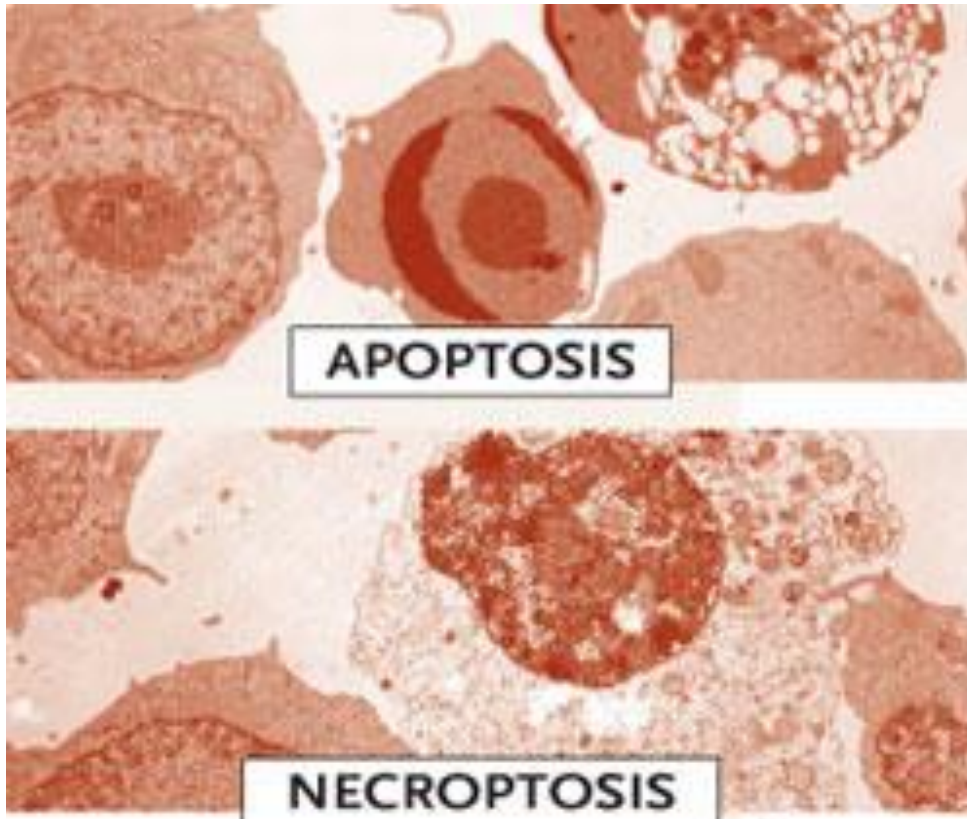


- Using this technique, micrometastases were detected in 5 % of the collected lymph nodes, which related to 12 % of the 91 patients who were initially characterized as pN0 on the basis of conventional histologic examination of the surgical resection specimen with H&E staining



RIP3-dependent hepatocyte
necroptosis in human and
experimental non-alcoholic
steatohepatitis

But now there is another type of programmed cell death!



- In chronic liver disease patients, RIP3 levels were significantly increased and correlated with steatohepatitis histological severity.
- Necroptosis is increased in the liver of NAFLD patients (and in experimental models of NASH).

Histology predicts the need for liver
transplantation in
patients with acute severe
autoimmune hepatitis

- In patients with severe acute autoimmune hepatitis histological assessment has a key prognostic role as the absence of chronic hepatitis predicts the need of liver transplantation, despite steroids therapy.

Long term Effects of Bariatric
Surgery In Patients with
Nonalcoholic Fatty Liver Disease:
A Literature Review
and Meta-Analysis

- Our search identified 2588 citations with 5 trials, having 4399 patients, meeting our eligibility criteria.
- We identified 29 of uncontrolled trials reporting changes in histology after bariatric surgery.

- 20 studies reported a decrease in the prevalence of hepatic steatosis (from 84.5% to 36.1%),
- 6 studied reported a decrease in the prevalence of NASH (from 51.45% to 9.76%),
- 9 reported a change in fibrosis score.

- In this meta-analysis, patients with NAFLD who underwent bariatric surgery showed significant reduction of all-cause mortality, weight loss, fibrosis score and ALT.

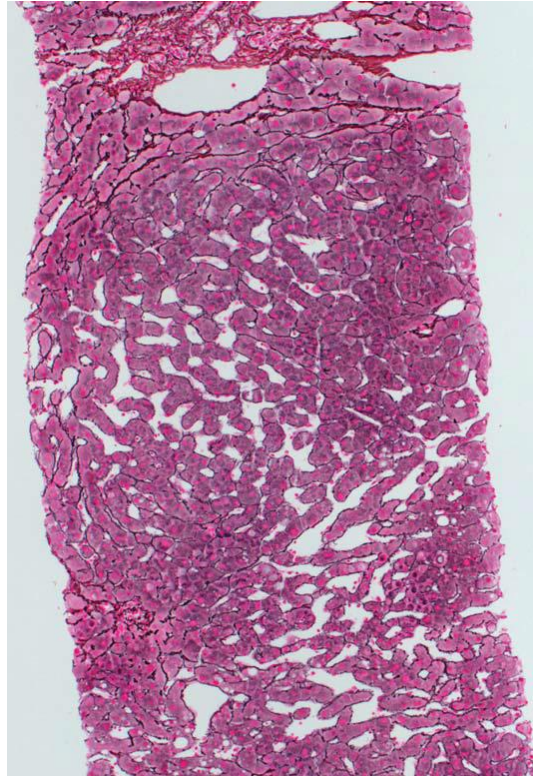
Concomitant Non-Alcoholic Fatty
Liver Disease Drives
Progression of Overall Liver Disease
More Than Chronic
Hepatitis B Alone in Chinese-
Americans

- Despite the proven efficacy of current antiviral therapy for chronic hepatitis B (CHB), up to 20% of patients on long term oral antiviral treatment who have complete HBV suppression have persistently elevated serum alanine transferase levels.
- It has been previously shown that non-alcoholic fatty liver disease (NAFLD) is a likely culprit. .
- Asians may be especially affected given endemic CHB and significant prevalence of metabolic syndrome and NAFLD despite lower body mass index and rate of obesity compared to other ethnicities

- Of the 148 patients, 41 were NAFLD+:
38 with steatosis,
18 with steatohepatitis,
13 with steatofibrosis

- There is a significantly higher combined necro-inflammatory activity and overall combined staging in patients in the NAFLD+ group.
- Clinically, alanine transaminase, body mass index, and weight in pounds are significantly higher in the NAFLD+ group.

Systemic Disease Associated With Noncirrhotic Portal Hypertension



Clinical Liver Disease, Vol 6, No 4, October 2015

Pathophysiological Mechanisms Leading to NCPH in Systemic Diseases

- **Sinusoidal compression** (e.g. sarcoidosis)
- **Sinusoidal occlusion/infiltration** (e.g. metastatic disease)
- **Vascular remodeling in nodular regenerative hyperplasia** (e.g. systemic lupus erythematosus)
- **Defenestration of sinusoidal lining** (e.g. early alcoholic disease)
- **Arterio-portal shunting** (e.g. hereditary hemorrhagic telangiectasia)

Diagnostic Criteria for Idiopathic Noncirrhotic Portal Hypertension

1) **Clinical signs of portal hypertension**

e.g. Splenomegaly/hypersplenism

2) **Exclusion of cirrhosis on liver biopsy**

3) **Exclusion of chronic liver disease**

e.g. chronic viral hepatitis

4) **Exclusion of conditions causing other forms of noncirrhotic portal hypertension**

e.g. Congenital liver fibrosis, Sarcoidosis, Schistosomiasis

5) **Patent portal and hepatic veins** (Doppler ultrasound or computed tomography scanning)

*All five criteria must be fulfilled to diagnose idiopathic noncirrhotic

Repeated biopsies within 23 years showed increased frequency of HCV infections and suggested a 3-year median monitoring to allocate fibrosis progressions

- Fibrosis progression rate becomes important for low fibrosis groups, since they are non-prioritized for the new direct acting retrovirals in most countries.
- Therefore, to target a strategy of fibrosis monitoring within low fibrosis population, based on studied intervals is needed.

- Fibrosis progression in the absence of SVR significantly affects the long-term natural history of this process even in low fibrosis groups
- Median monitoring intervals of 3 years is suggested to allocate fibrosis and is crucial in non-SVR & non-transplant patients with F0-F2.

Integrator complex subunit 6
(INTS6) is a prognostic
marker for hepatocellular carcinoma

- Integrator complex subunit 6 (INTS6), previously known as the gene encoding deleted in cancer cells 1 (DICE1) was found to play a tumor suppressive role in certain types of solid tumors just like prostate cancer and cervical cancer.

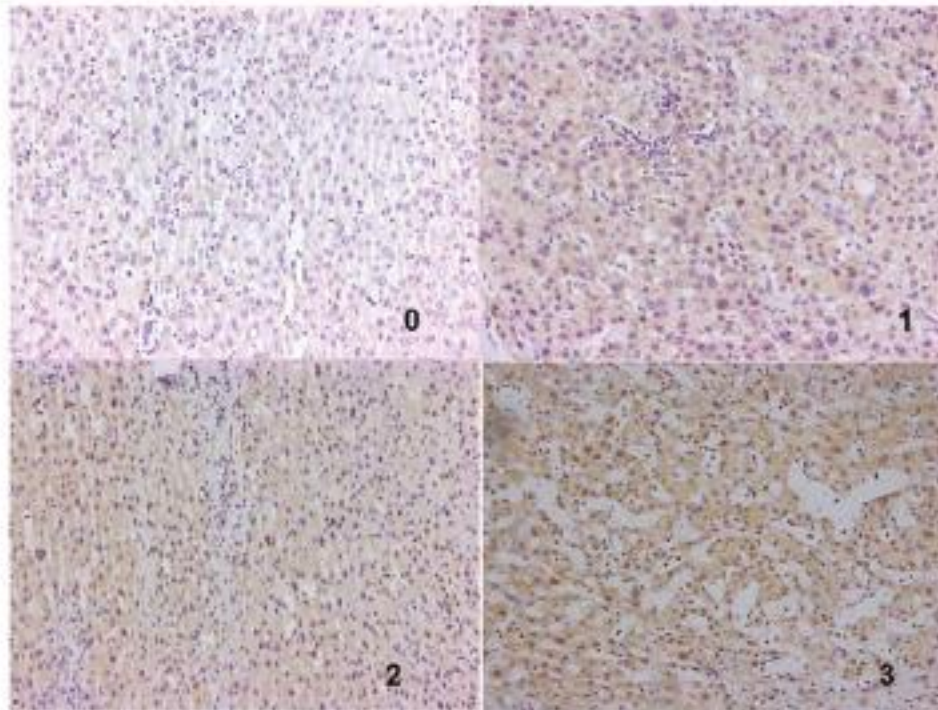


Image.1 Immunohistochemical staining of INTS6 in HCC. INTS6 protein expression localized mainly to the nuclei of cancer cells. Different INTS6 staining intensities [negative 0, weak 1, moderate 2, and strong 3, respectively] are indicated in micrographs

- The results of our study showed that down-regulated INTS6 expression was associated with poorer prognosis in HCC patients.

Intraductal papillary neoplasm of
bile duct is a heterogeneous
disease with respect to its
histopathologic
similarities to pancreatic intraductal
papillary mucinous
neoplasm

- Intraductal papillary neoplasm of bile duct (IPNB) is characterized by papillary tumor covered by well-differentiated neoplastic epithelium with fine fibrovascular cores in the dilated bile ducts.
- IPNB reportedly resembles intraductal papillary mucinous neoplasm (IPMN) of the pancreas

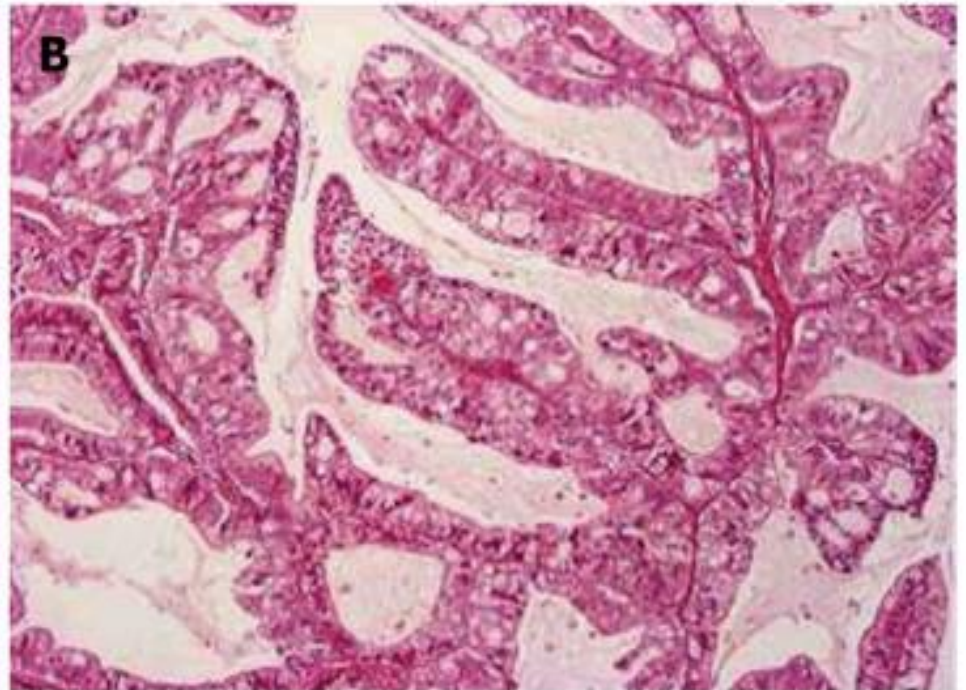
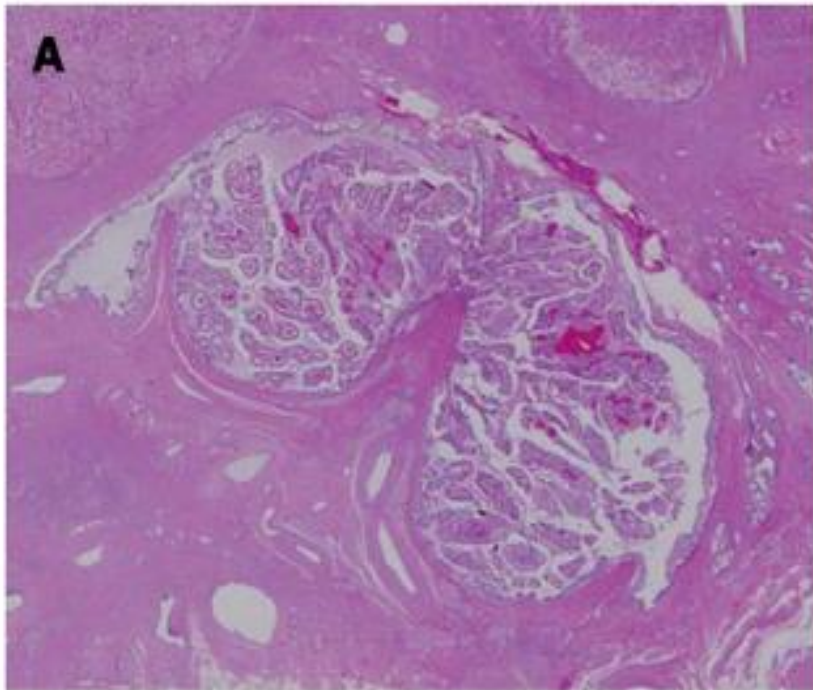
- IPNB cases were classifiable into four groups with their histopathological similarities to IPMN:

group A (identical to IPMN)

group B (similar but a little different from IPMN),

group C (focally or vaguely similar to IPMN) and

group D (different from IPMN, 10 cases).



World J Gastroenterol. Apr 14, 2011; 17(14): 1923-1926

Liver Fibrosis is Present in One-Third
of Adults with
Alpha-1 Antitrypsin Deficiency
Without Overt Liver Disease

- The primary aim of this study is to define the prevalence and histologic spectrum of liver disease in adults with AATD.
- Adults with confirmed AATD Pi*ZZ and other rare AATD alleles
- Clinically significant liver fibrosis defined by Ishak fibrosis score ≥ 2 .

In this cross section of older AATD subjects, over one-third had clinically significant liver fibrosis confirmed by biopsy.

This is much higher than our previously reported prevalence of 7.9%.

We also confirmed our previous finding that ALT and GGT for affected subjects fall within normal range, which limits clinical utility.

The histologic spectrum was varied both in fibrosis and qualitative presence of AATD globules.



That's all Folks!