Is it still a place for liver biopsy in chronic viral hepatitis ?

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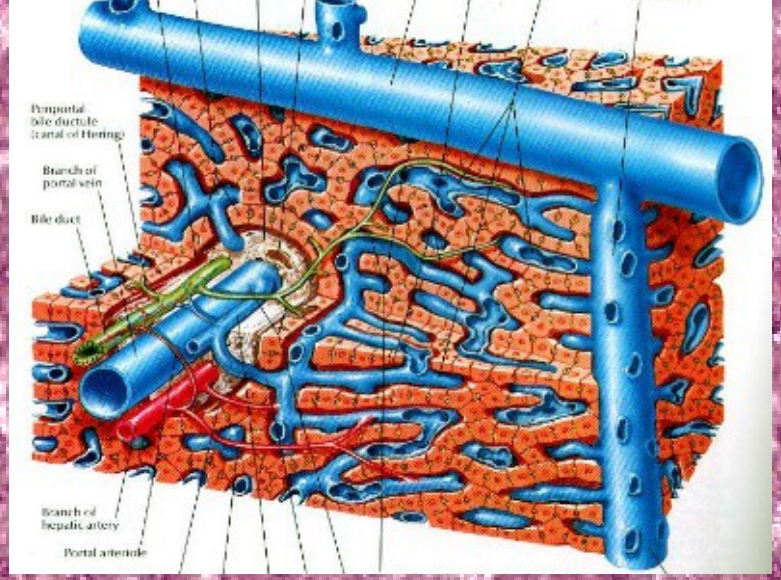
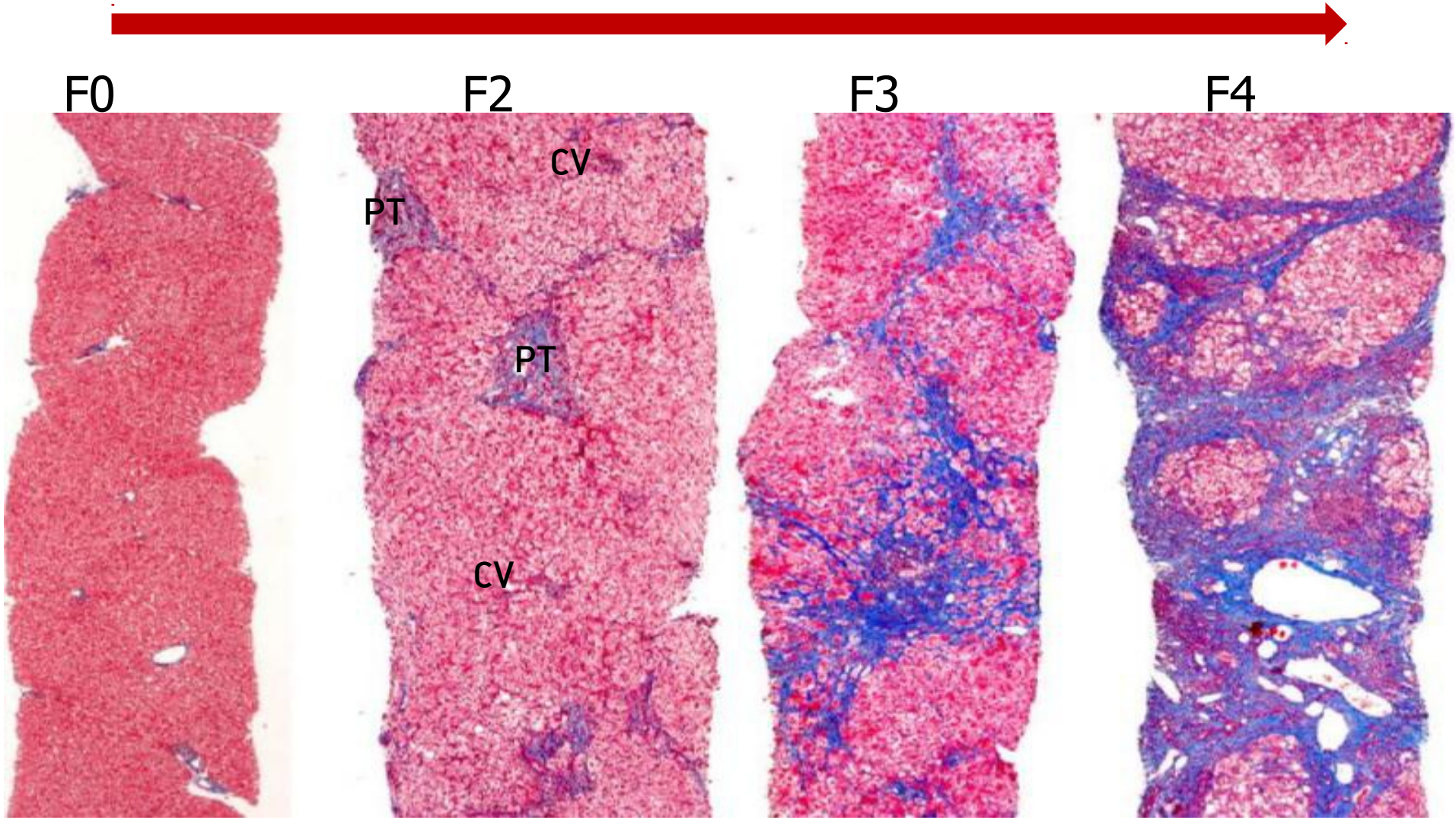
Outlines

- Is there remaining indications for liver biopsy in Hepatitis C ?
- Liver biopsy in Hepatitis B
- Liver biopsy in NAFLD



Normal liver

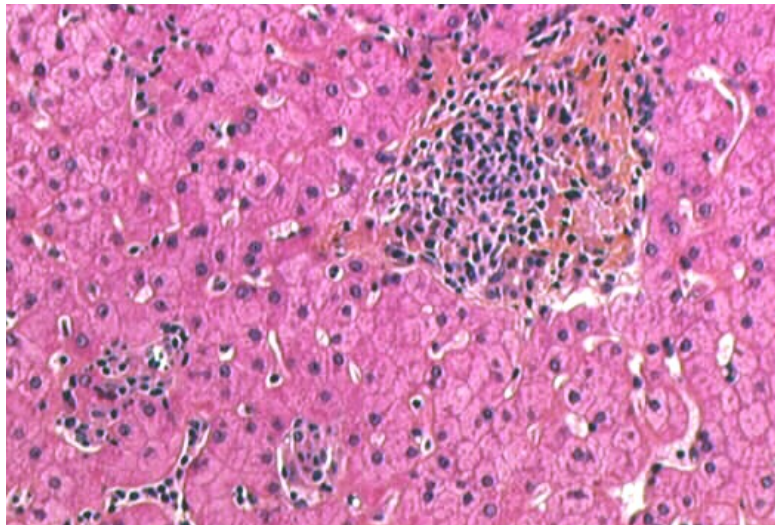
FIBROSIS IN CHRONIC HEPATITIS



Histological scoring in viral hepatitis
Grading and Staging

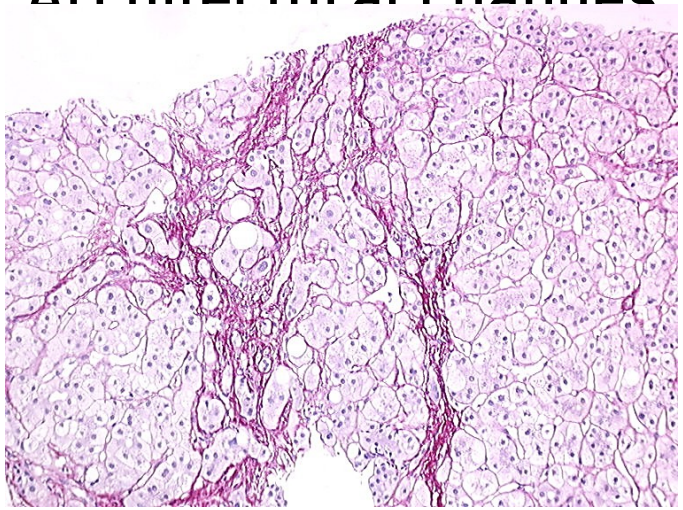
Grade

- Disease activity
- Inflammation and necrosis
- // ↑ALT, ↑AST
- Predictor of fibrosis ?



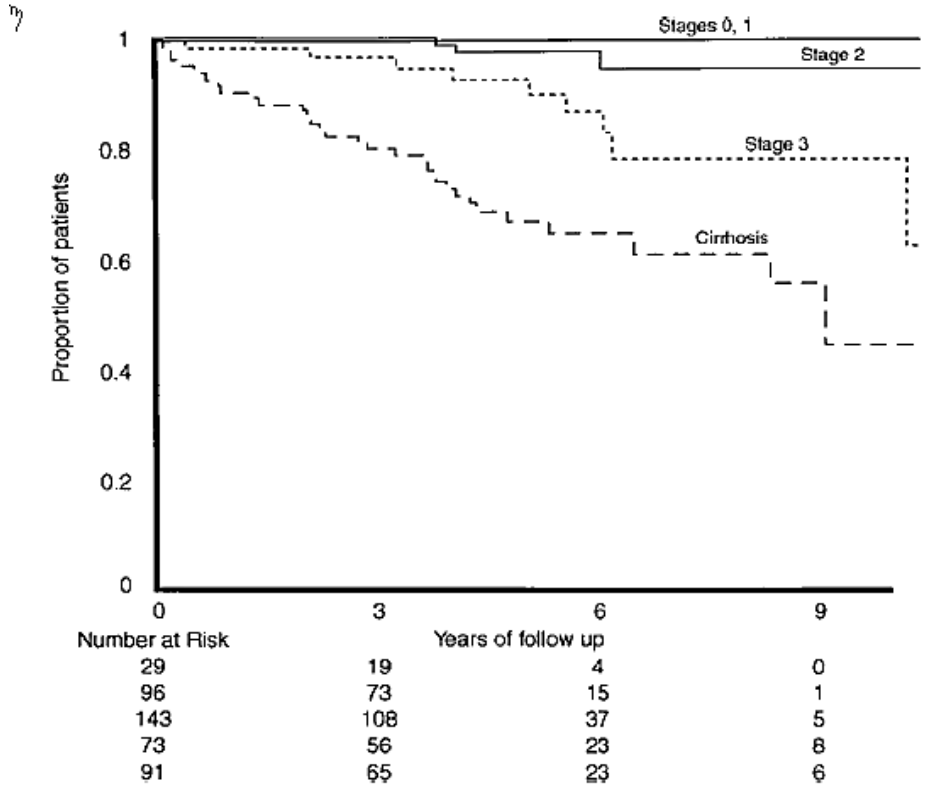
Stage

- Long term prognosis
- Amount of fibrosis
- Location of fibrosis
- Architectural changes



Fibrosis : The histological prognostic factor

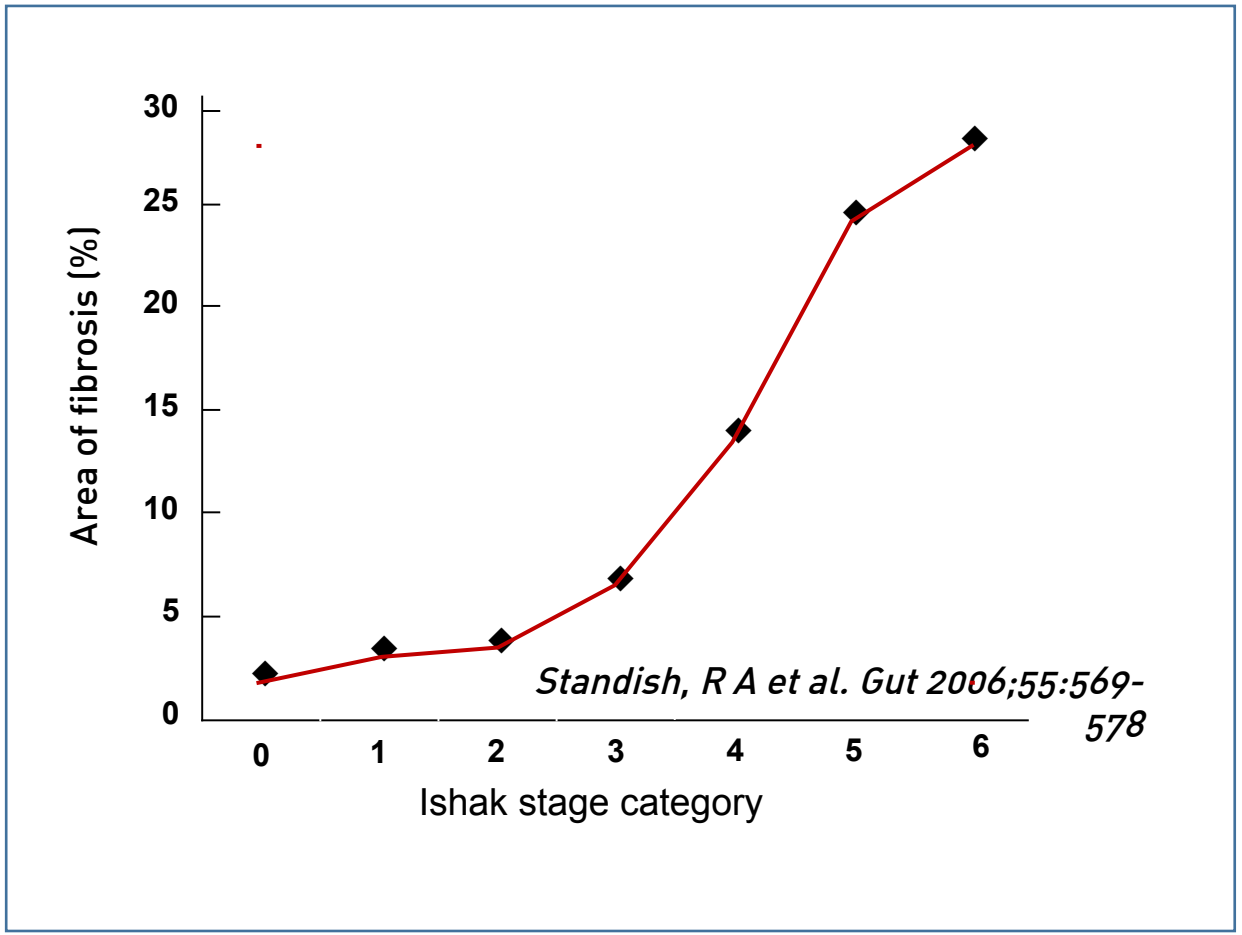
Survival to liver-related complications
according to liver fibrosis stage on initial biopsy in Hepatitis C



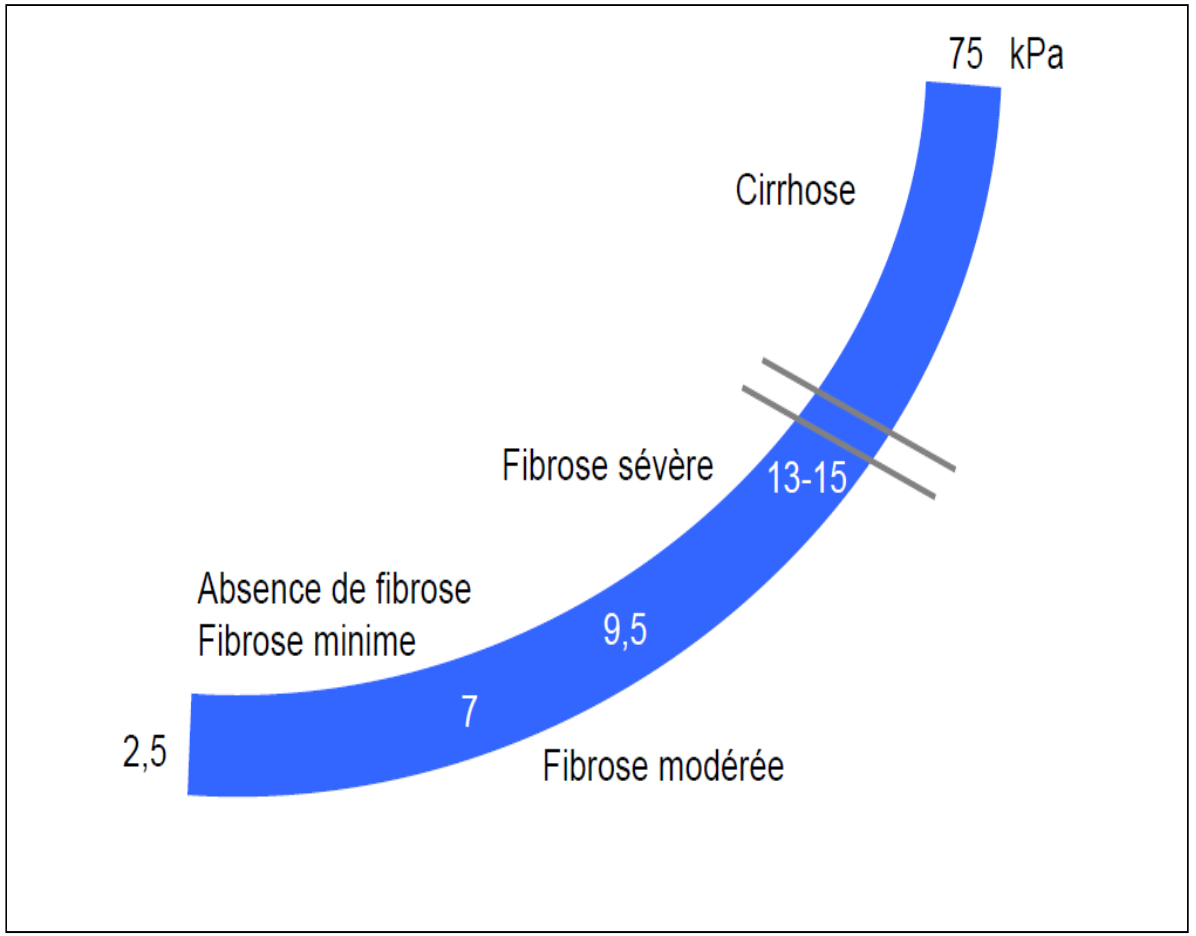
MH. Khan et al. **Which patients with hepatitis C develop liver complications?** Hepatology 2000; 31:513-520

AMOUNT OF FIBROSIS, STIFFNESS AND STAGE OF FIBROSIS

Amount of fibrosis (morphometry) and histological stage

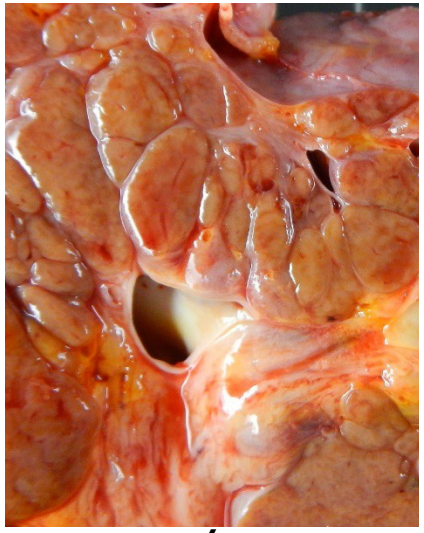


liver stiffness and stage of fibrosis



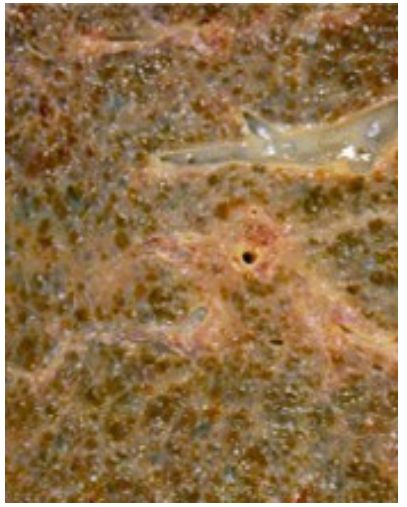
All Cirrhosis are not alike : a disease with a wide spectrum

Histological	F1-F3		F4 (Cirrhosis)	
Clinical	***Non-cirrhotic***	***Compensated***	***Compensated***	***Decompensated***
Symptoms	None	None (no varices)	None (varices present)	Ascites, VH, Encephalopathy
Sub-stage	-	Stage 1	Stage 2	Stages 3 and 4
Hemodynamic (HVPG, mmHg)	>6	>10	>12	



4a

4b

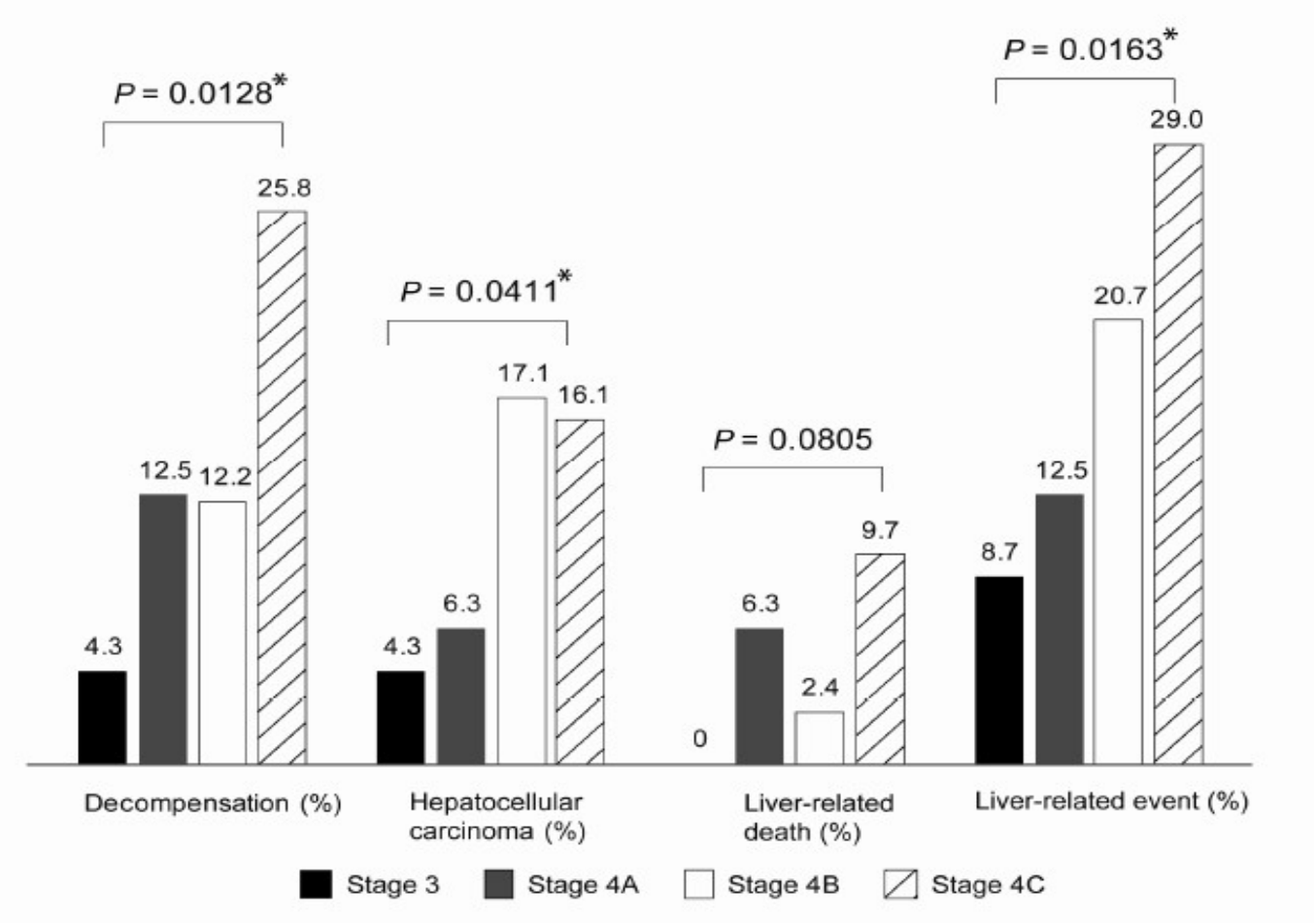


4c

Garcia-Tsao G, et al. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. Hepatology 2010; 51: 1445–9

SU Kim, et al. The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis. J Hepatol 2012

Clinical relevance of scoring cirrhosis

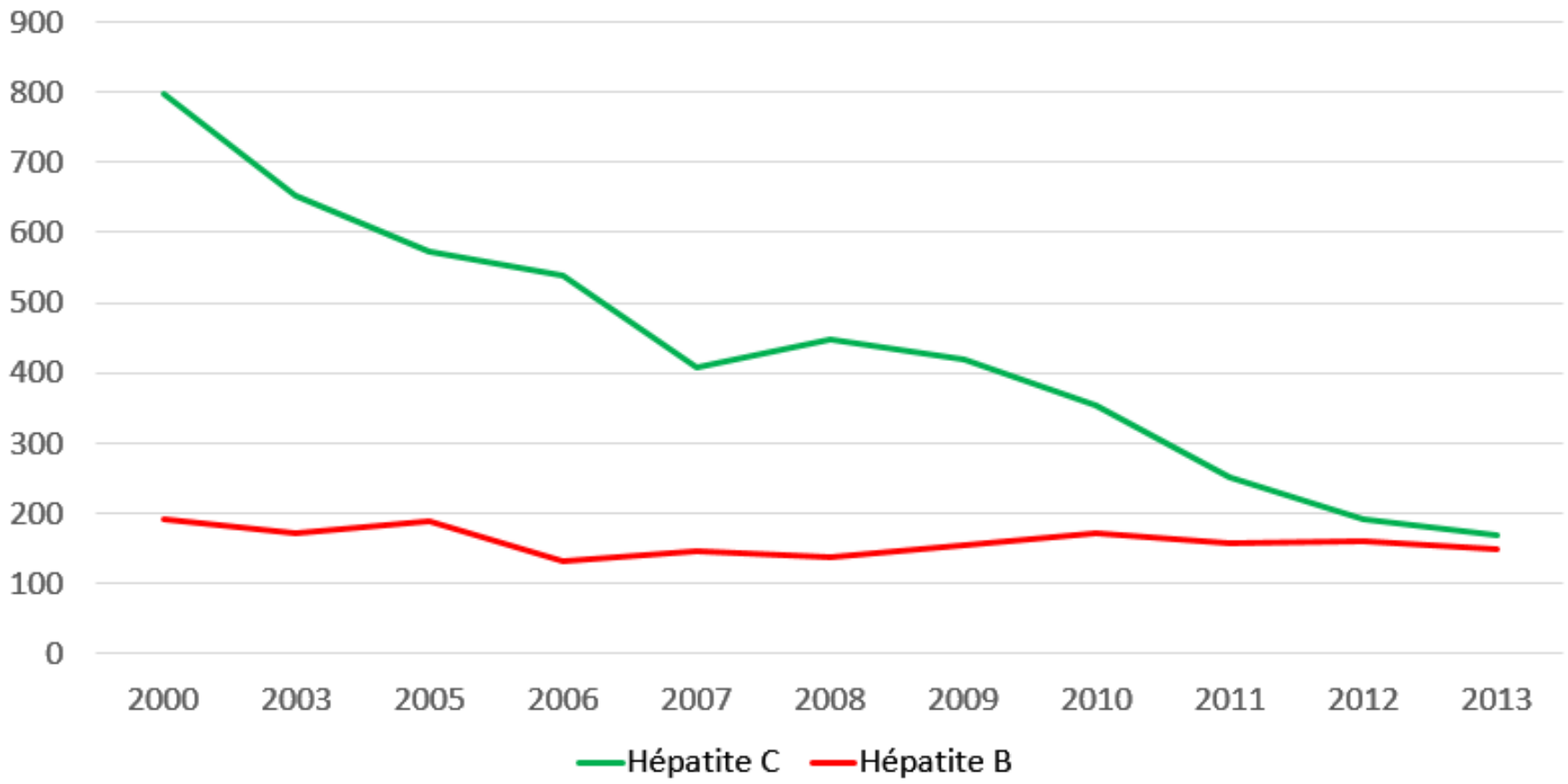


The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis SU Kim, HJ Oh, IR. Wanless, S Lee, YN Park, J Hepatol 2012

Outlines

- Is there remaining indications for liver biopsy in hepatitis C ?
- Liver biopsy in hepatitis B
- Liver biopsy in NAFLD

Number of liver biopsy per year from 2000 to 2013 for chronic viral hepatitis in Beaujon hospital



Is there remaining indications of liver biopsy in hepatitis C ?

No more indication of liver biopsy in Hepatitis C

- Major progress of antiviral treatment in Hep C :
  - Highly efficient
  - short duration
  - Adverse events limited

- Clinically relevant questions :
  - No/mild vs advanced fibrosis / cirrhosis → Treatment vs no treatment
  - Cirrhosis vs non cirrhosis → Prevention of HCC

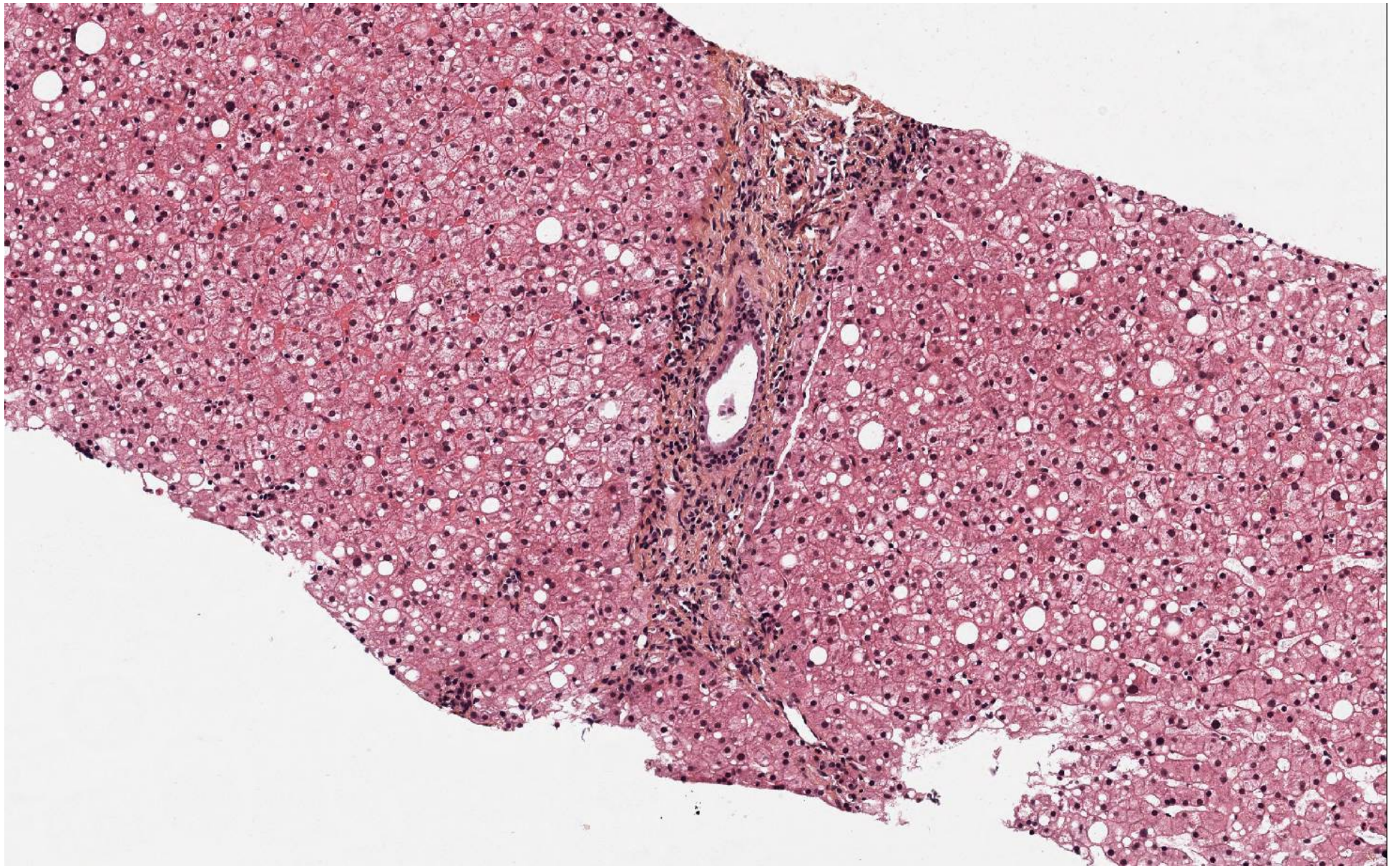
→ non invasive markers

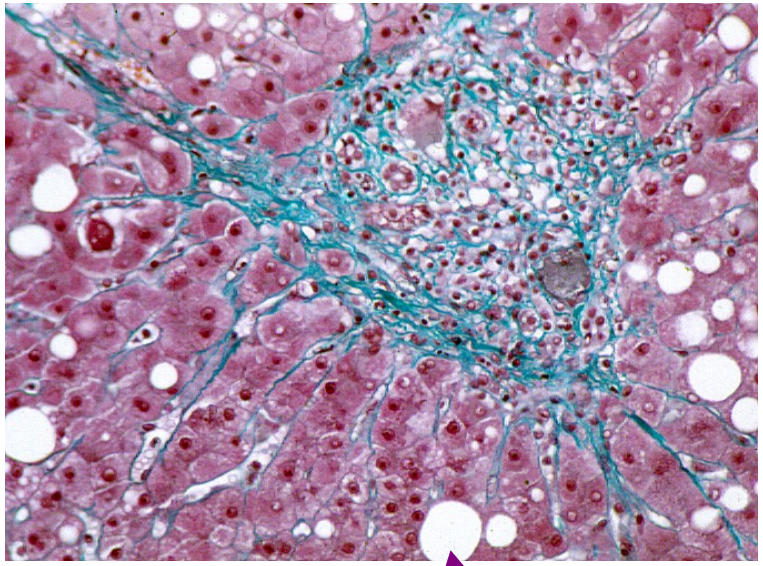
Is there remaining indications of liver biopsy in hepatitis C ?

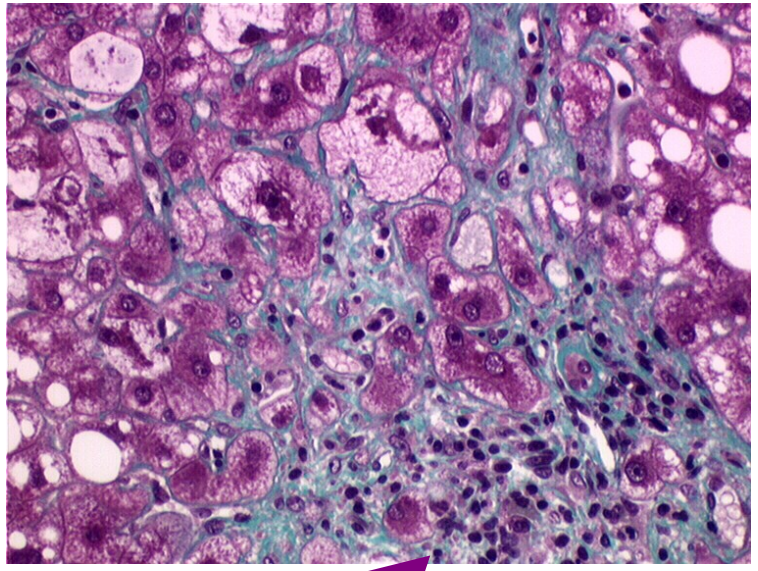
When to perform still a liver biopsy in hepatitis C :

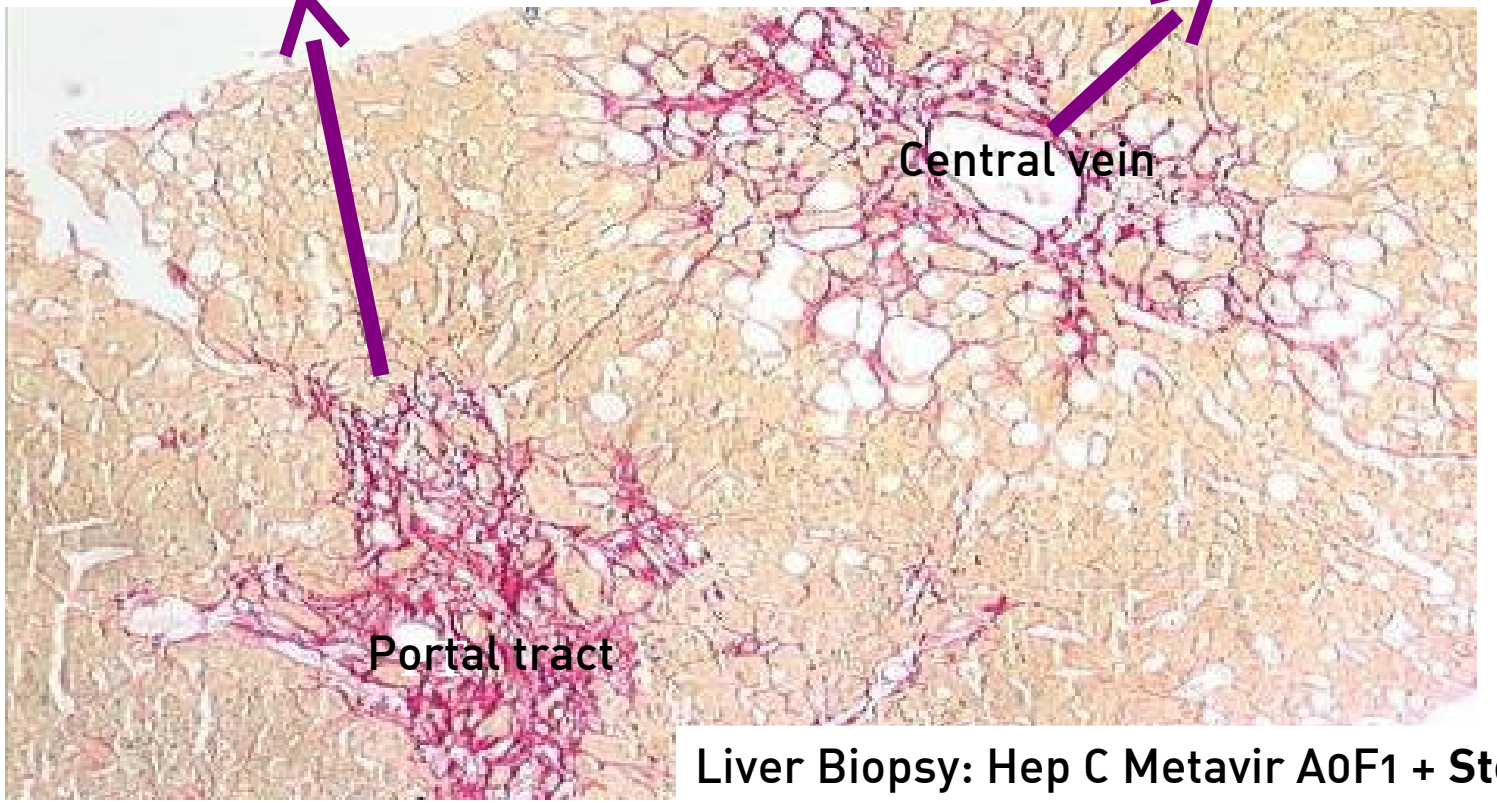
- Clinical evidence of comorbidities
  - Respective role of HCV and comorbidity in abnormalities of LFT and in the mechanism of fibrosis
  - Relevance for treatment

Chronic hepatitis C + metabolic syndrom (T2D). Naïve patient, genotype 1b
Mild increase in AST/ALT and GGT - Fibrotest = F4, Fibroscan = 12 kpA



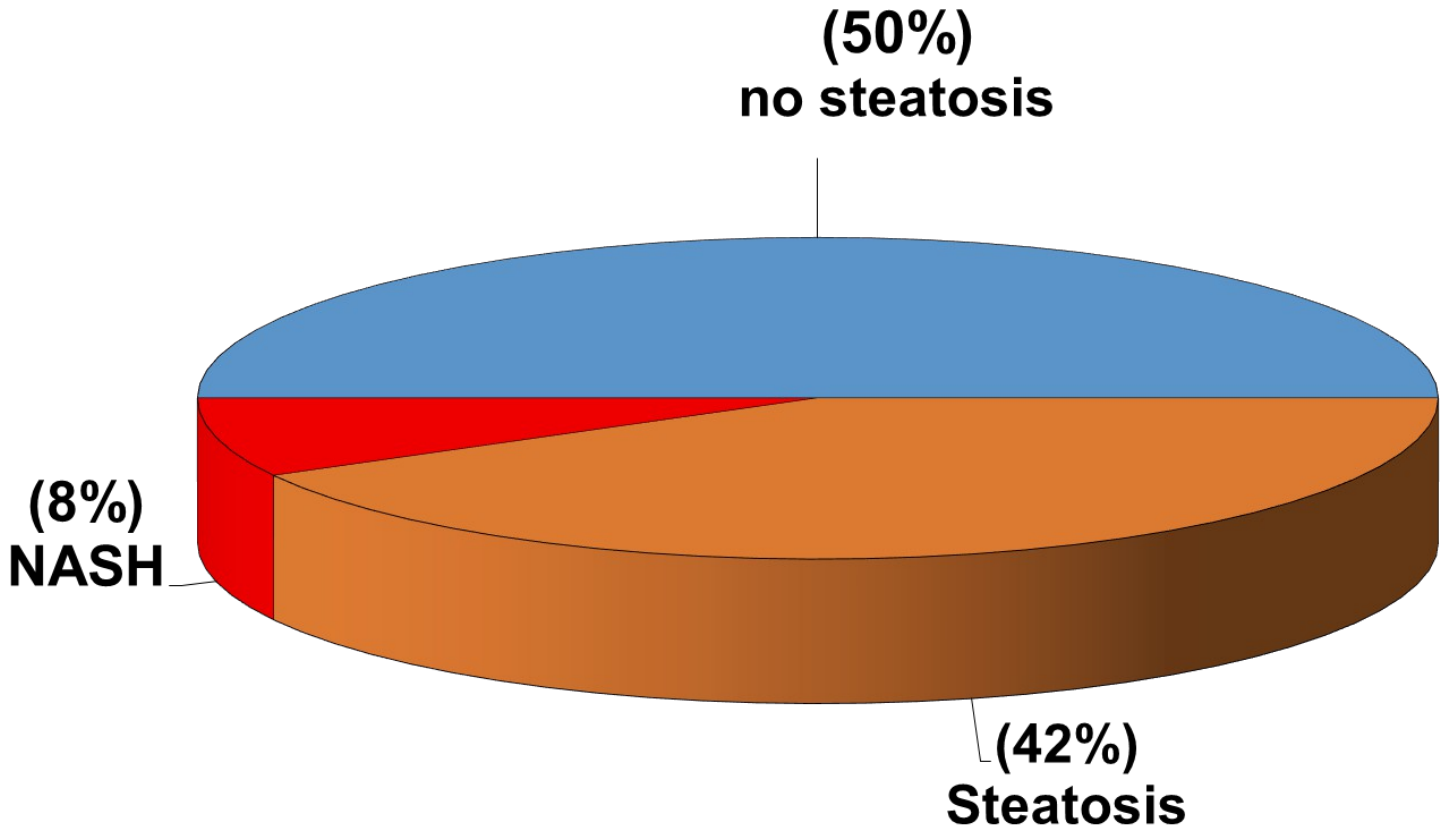






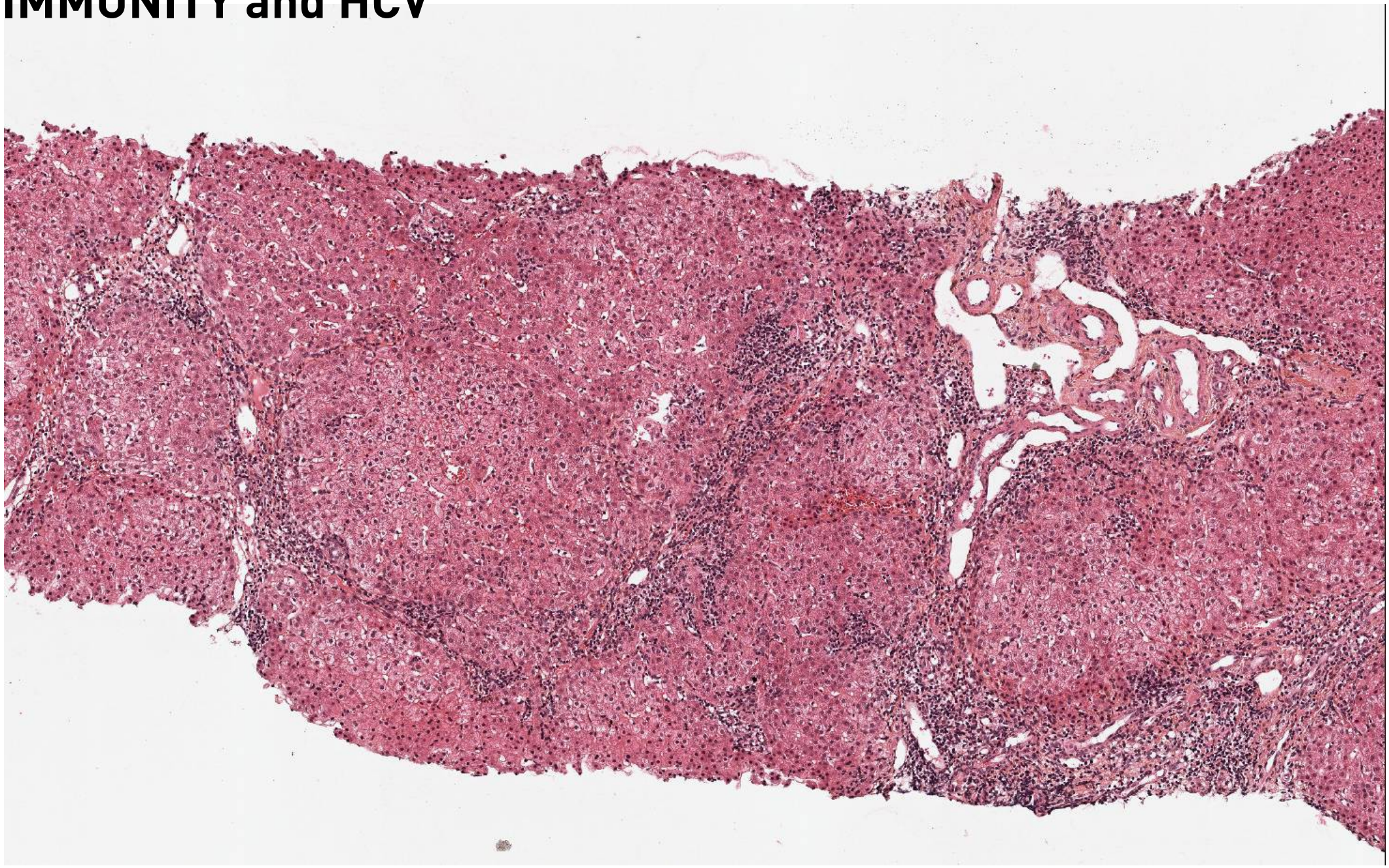
Liver Biopsy: Hep C Metavir A0F1 + **Steatohepatitis**

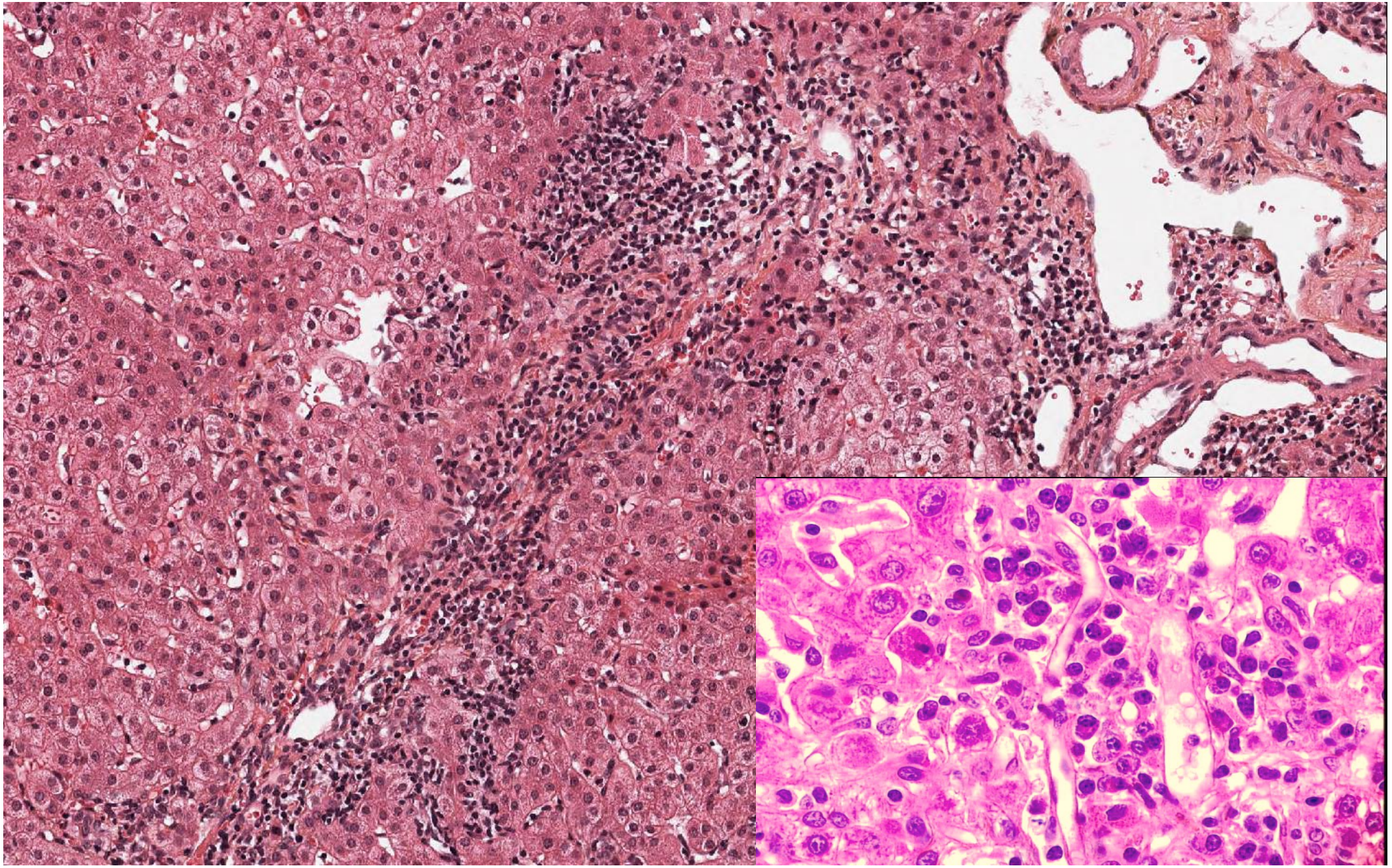
NAFLD AND HEPATITIS C



Evidence for a role of nonalcoholic steatohepatitis in hepatitis C: a prospective study. Bedossa P, Moucari R, Chelbi E, Asselah T, Paradis V, Vidaud M, Cazals-Hatem D, Boyer N, Valla D, Marcellin P. ***Hepatology****. 2007*

AUTOIMMUNITY and HCV





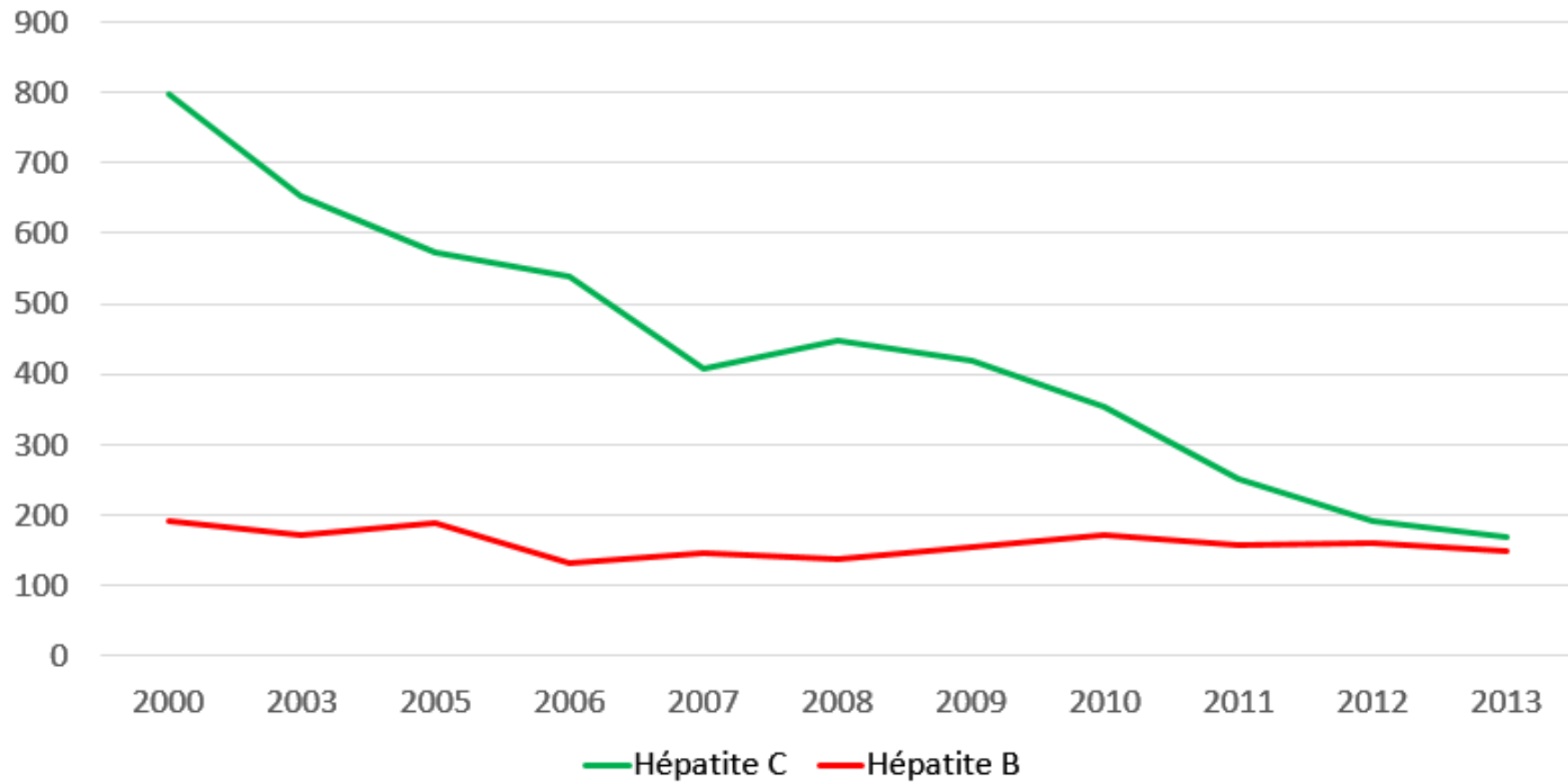
Is there remaining indications of liver biopsy in hepatitis C ?

When to perform still a liver biopsy in hepatitis C :

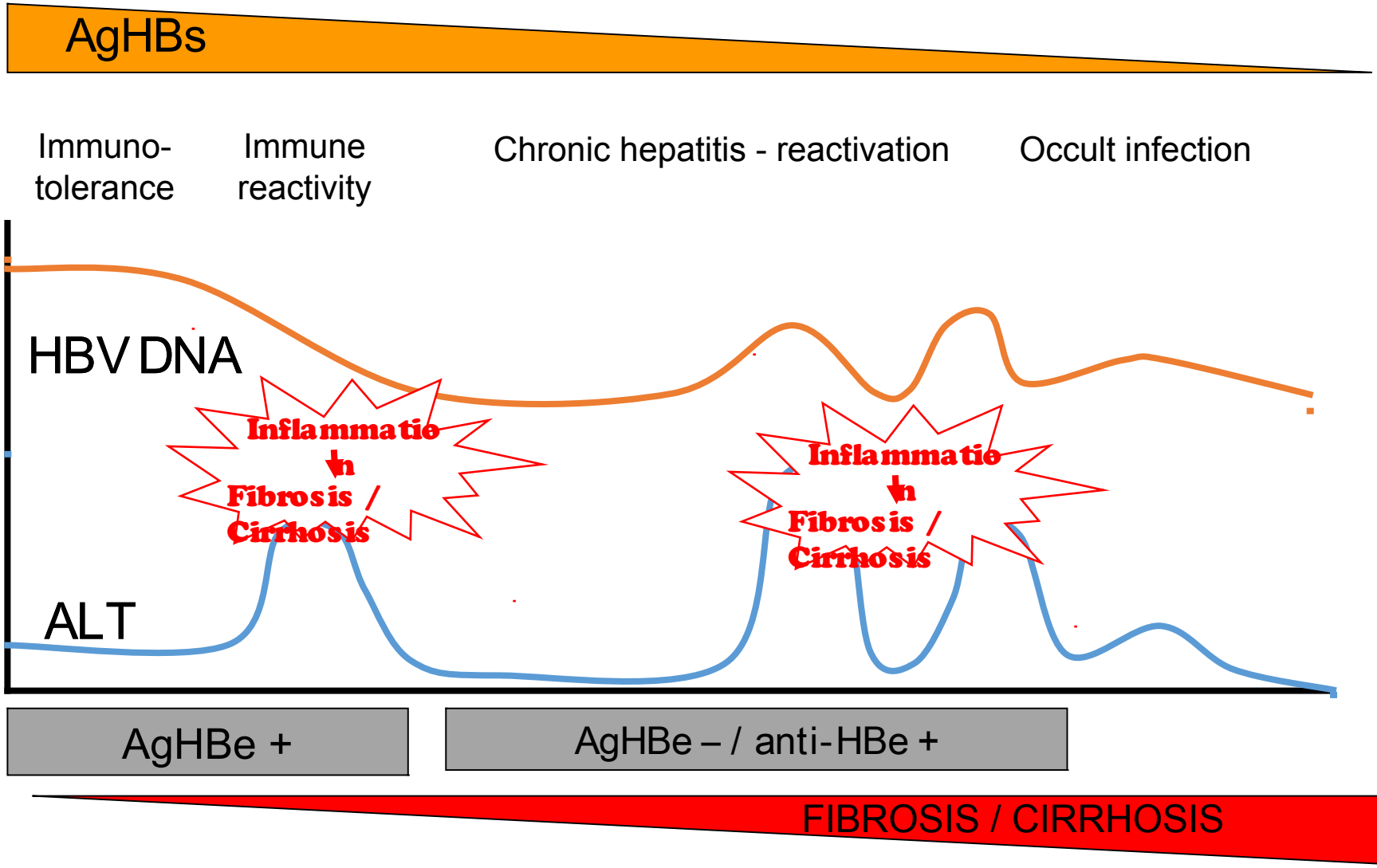
- Evidence of comorbidities
  - Others: drug interaction, iron, granulomatous disease.....
- Discordances between non invasive markers (serum vs Fibroscan)
- Discordance between non invasive markers and symptoms
- Patients difficult to treat, retreatment, any complex situation
- Follow-up of transplanted patients for cirrhosis C

Remaining indication of liver biopsy in Hep C : 10 – 20% of Hep C patients in tertiary care hospital

Number of liver biopsy per year from 2000 to 2013 for chronic viral hepatitis in Beaujon hospial



Hepatitis B : natural history is more complex



Neither DNA quantification, HBs Ag, transaminases or HBeAg, alone or in combination,

Liver biopsy in hepatitis B

- Different context :
  - Non invasive markers not validated as well in HBV as in HCV
  - Viral Suppression not eradication
  - Long-term treatment → Cost, observance
  - Adverse events after long-time use ?

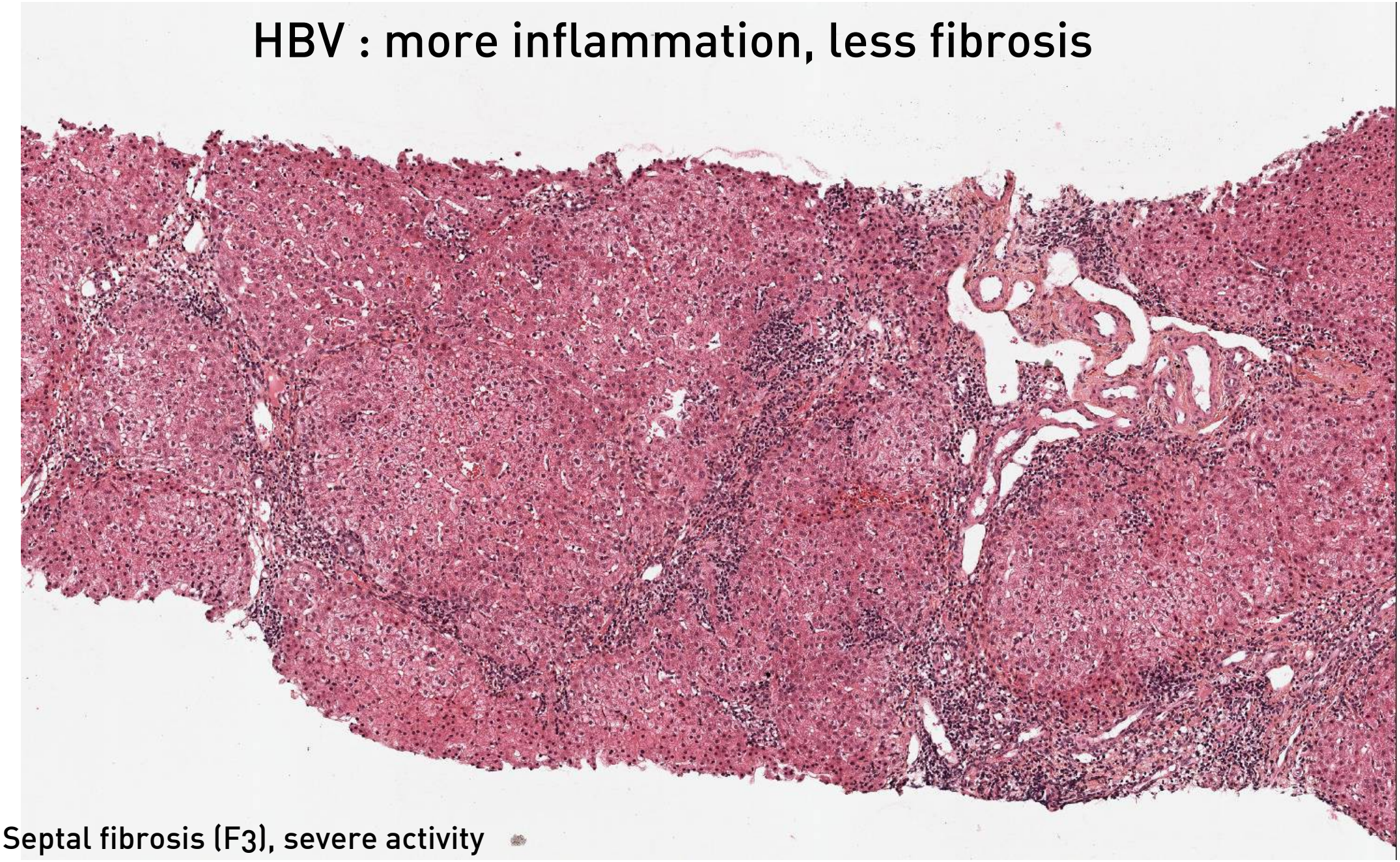
  → Biopsy helpful to decide the best timing for starting treatment : not too early – not too late (in addition to viral makers and transaminases)

Liver biopsy in Hepatitis B

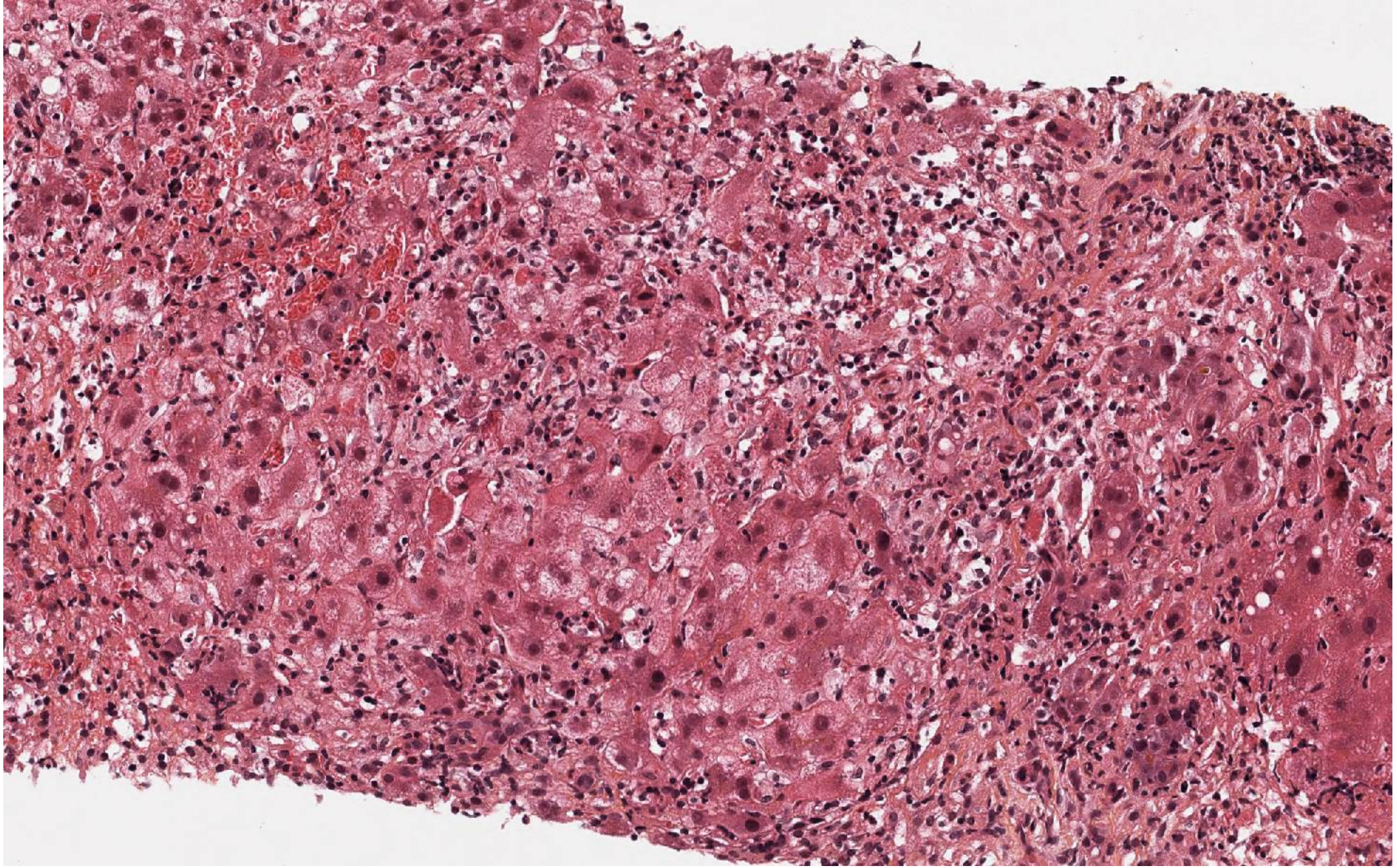
Liver biopsy should be considered in pre-treatment evaluation of HEP B (EASL guidelines 2012)

- CON
  - Invasive
  - Acceptability
  - Accessibility
  - Cost
  - Sampling error
- PRO
  - Gold Standard
  - Fibrosis ….but not only
  - NI markers risk of errors:
    - Histological confounding patterns

HBV : more inflammation, less fibrosis

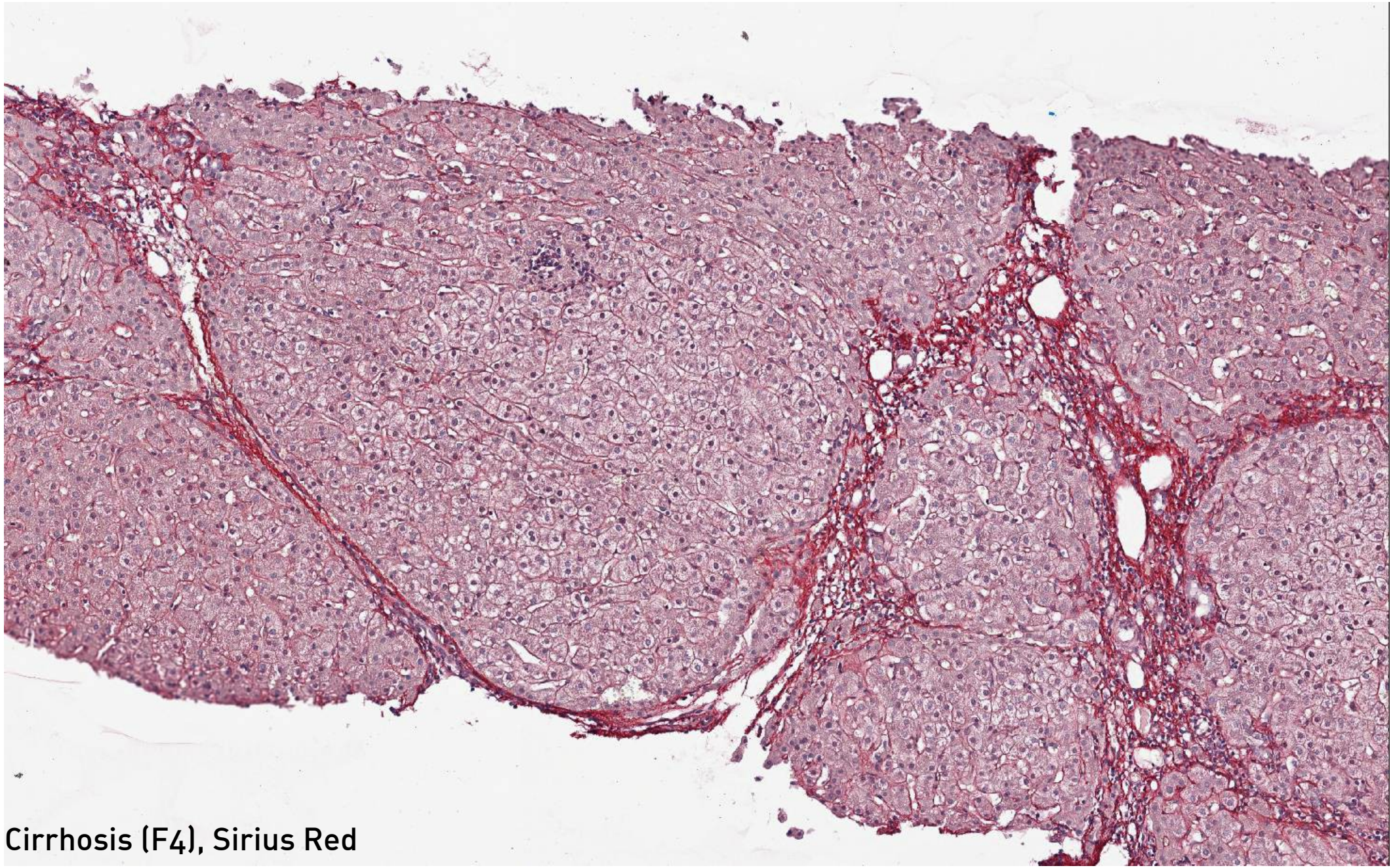


Septal fibrosis (F3), severe activity



Viral reactivation : Fibroscan = 25 Kpa, Fibrosis F2

HBV : more inflammation, less fibrosis

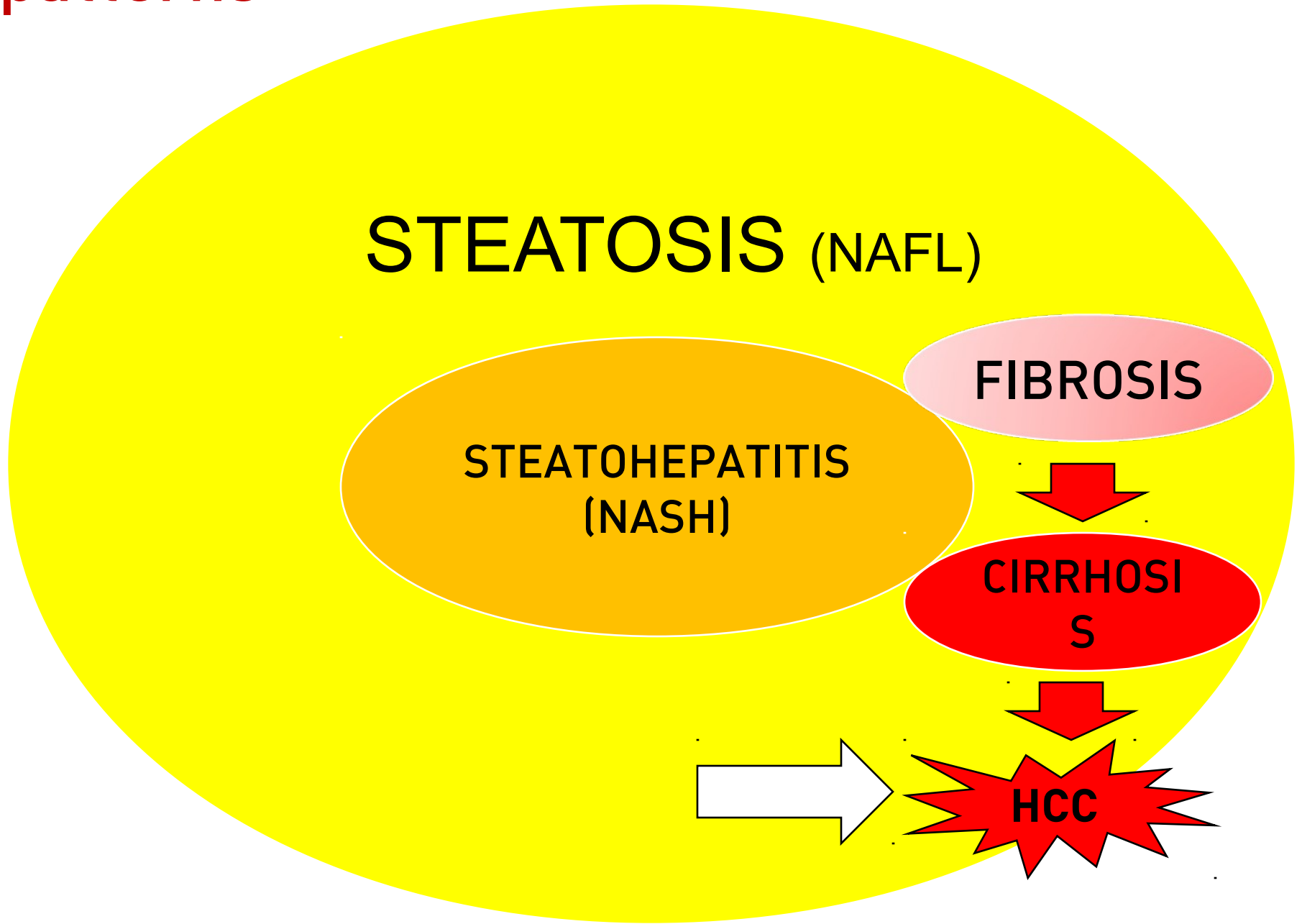


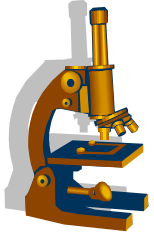
Cirrhosis (F4), Sirius Red

Issues to be discussed

- Is there remaining indications of liver biopsy in hepatitis C ?
- Liver biopsy in hepatitis B
- Liver biopsy in NAFLD

NAFLD : a spectrum of histological patterns





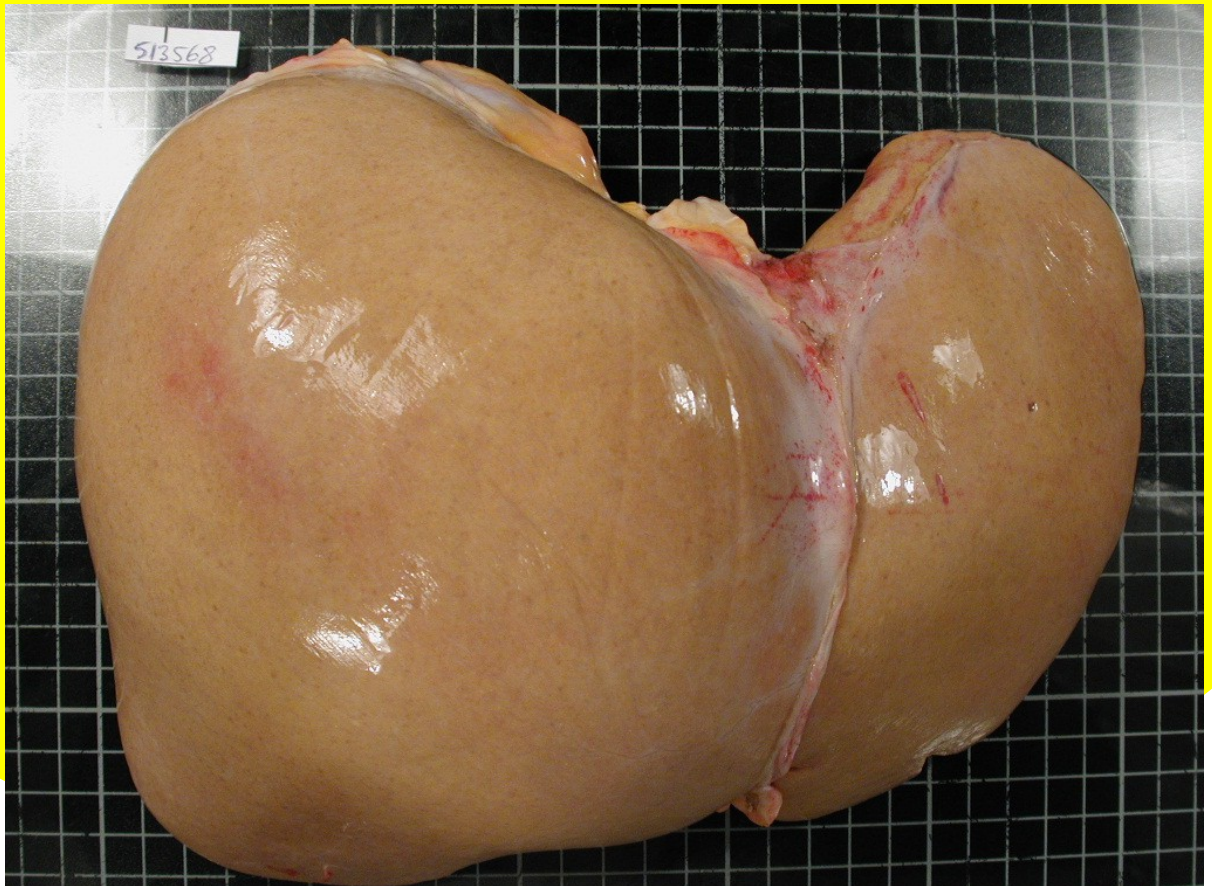
Liver biopsy in NAFLD

- Liver biopsy in NAFLD : focused indication
  - Non invasive tools (Ultrasound, serum makers, NAFLD fibrosis score)
  - Therapeutic options still limited
- Pathology is the gold standard in NAFLD :
  - Criteria for classification in NAFLD subtypes are solely based on histology
- Liver biopsy for :
  - Diagnosis: distinction between steatosis and NASH
  - Prognosis: grade and stage NAFLD

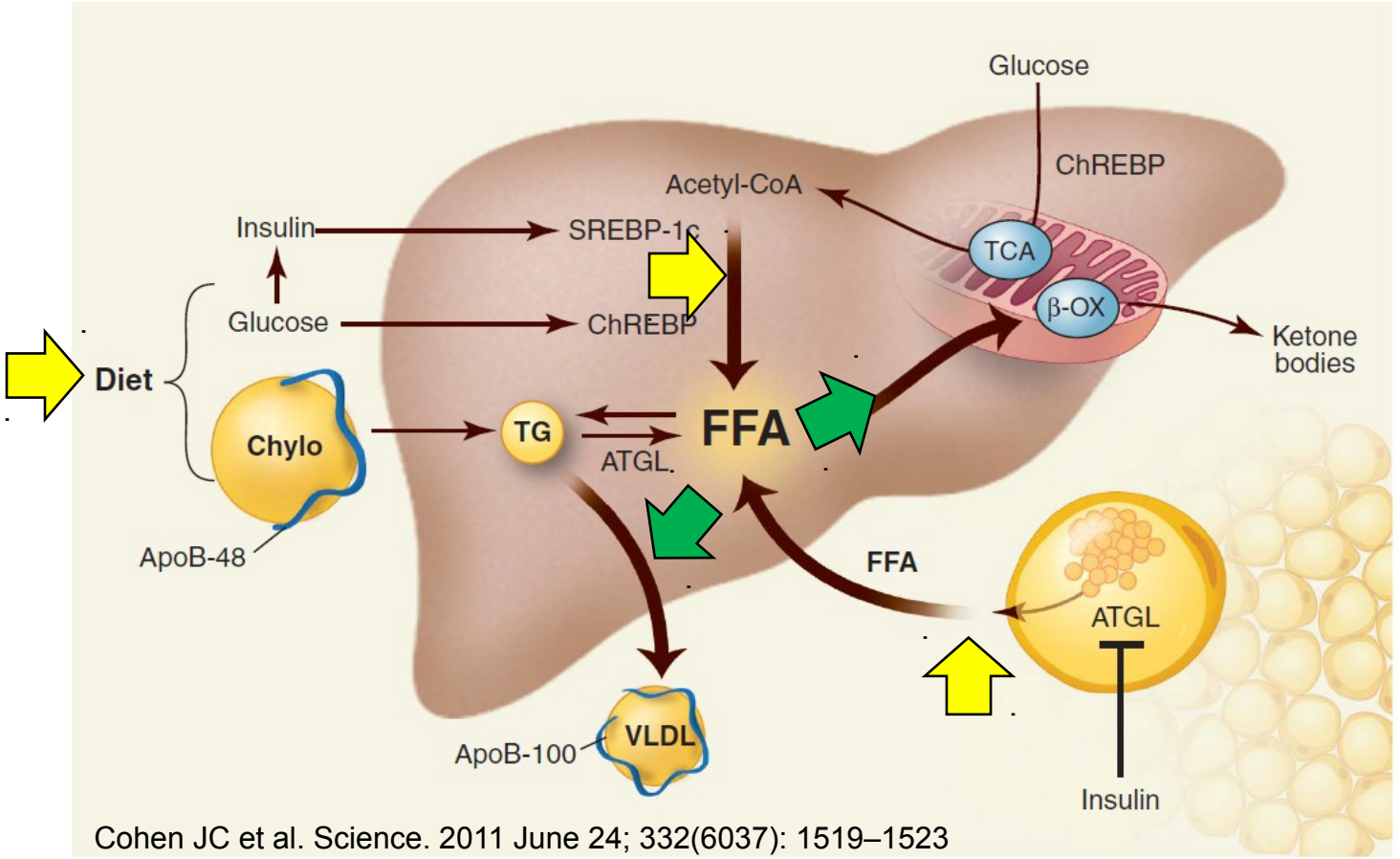
NAFLD : a spectrum of histologic patterns

STEATOSIS

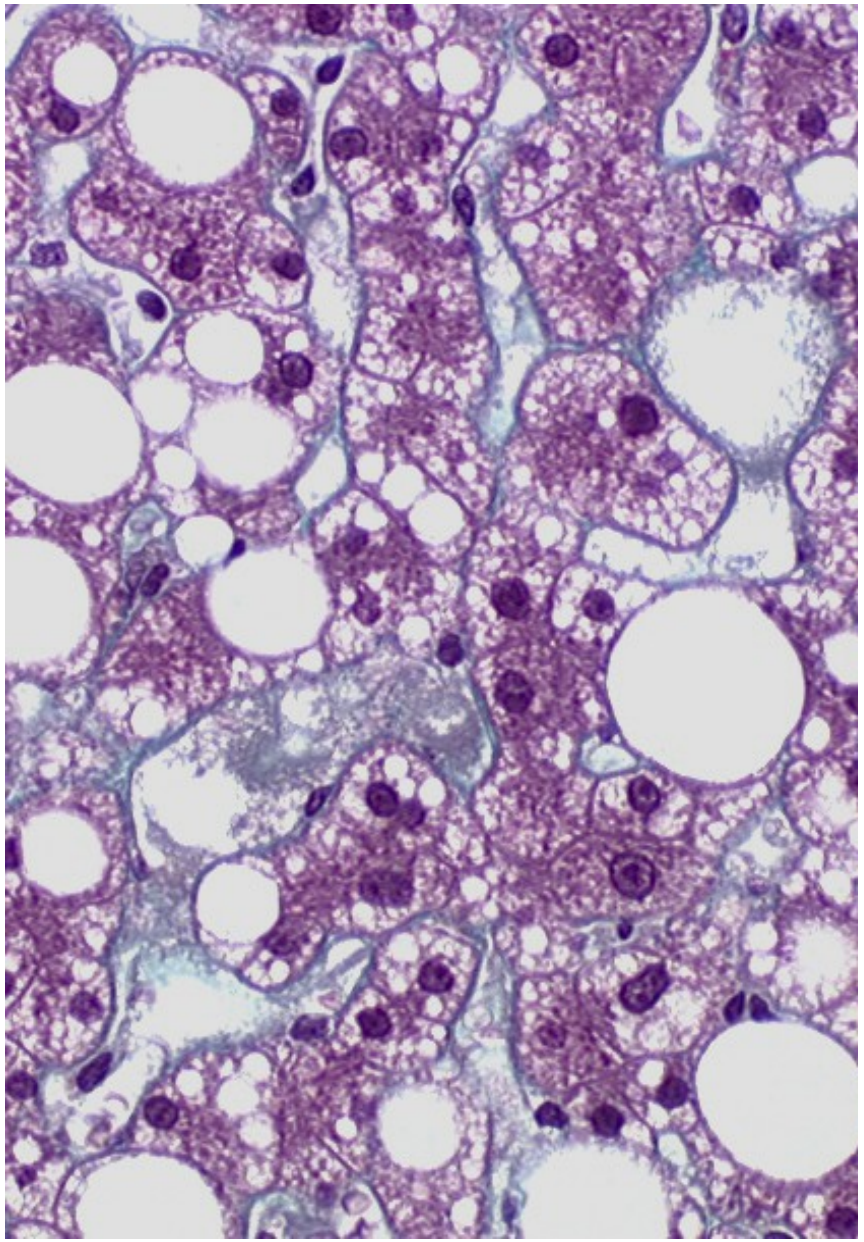
(NAFL, Fatty Liver)

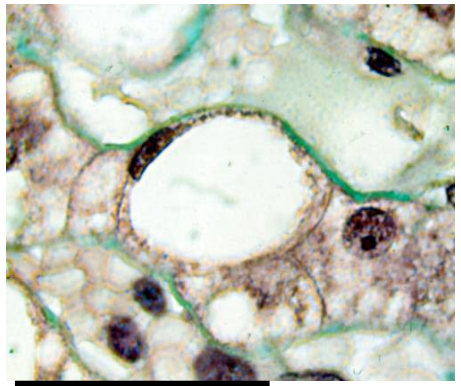


Hepatic metabolism of Free Fatty Acid

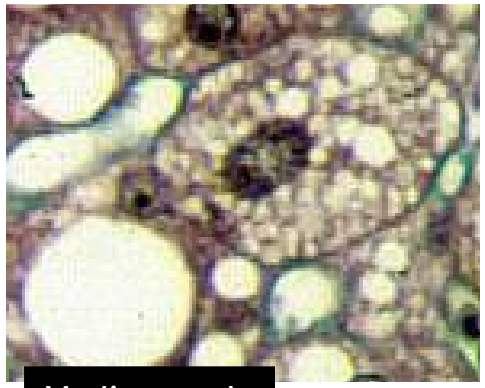


Cohen JC et al. Science. 2011 June 24; 332(6037): 1519–1523

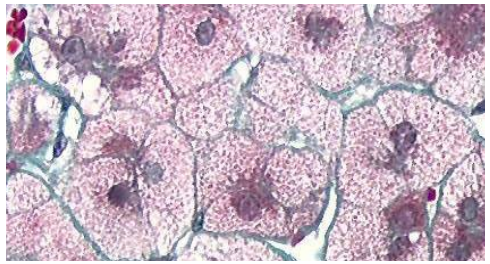




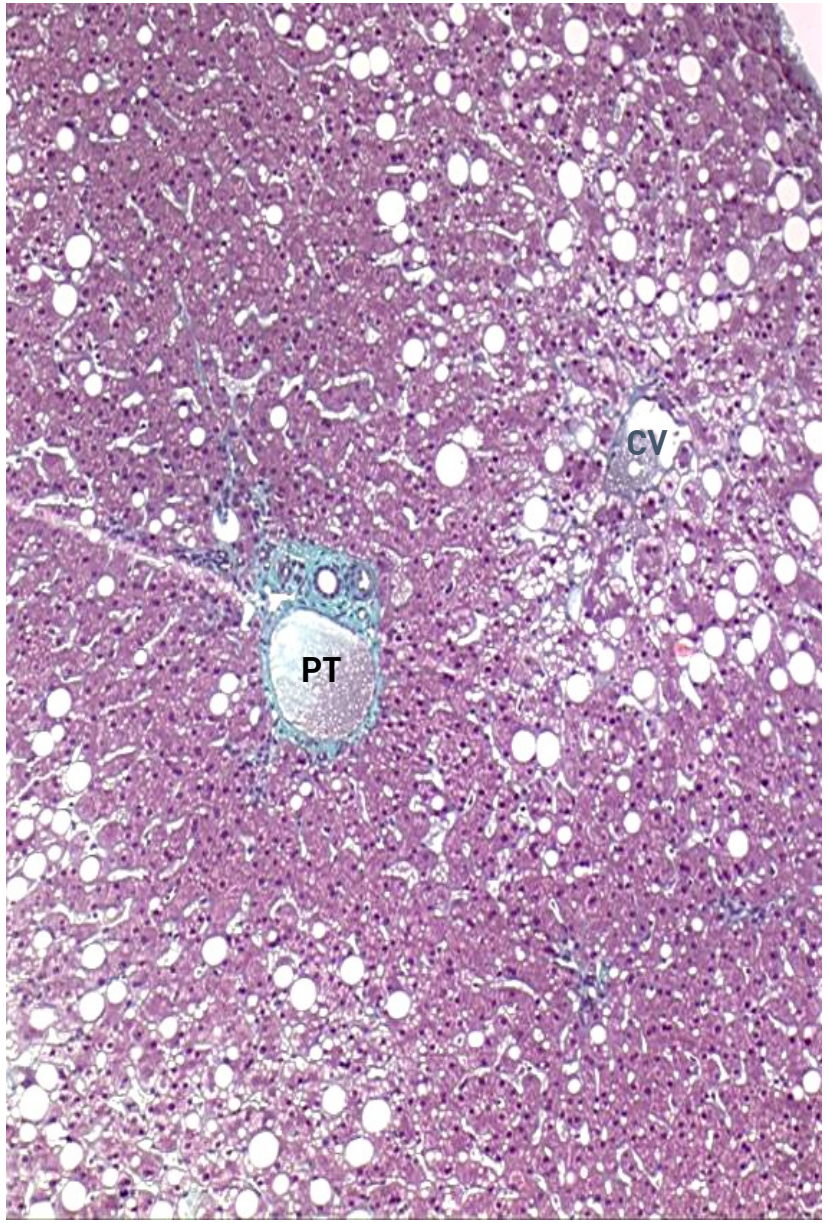
Macrovacuole

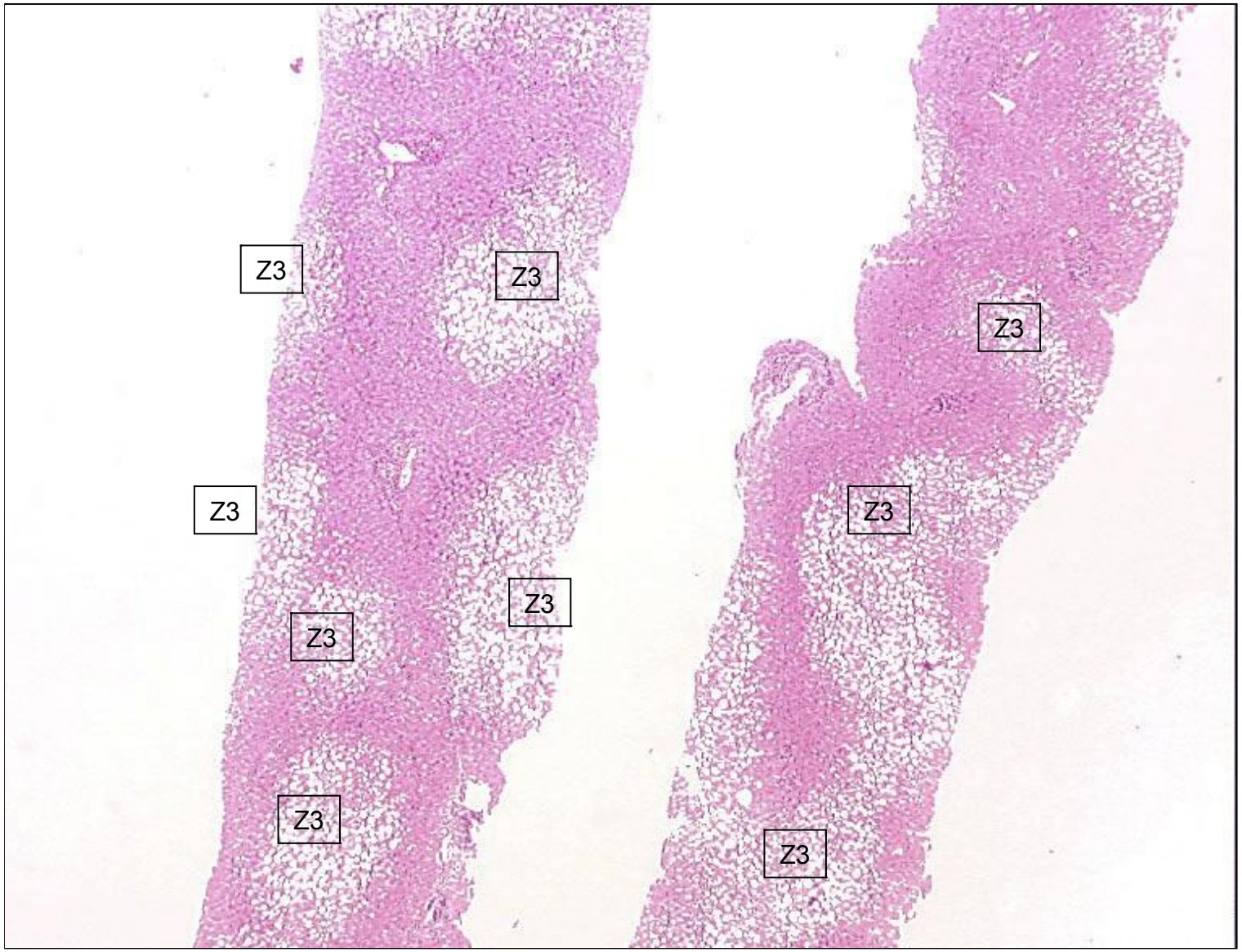


Mediovacuole



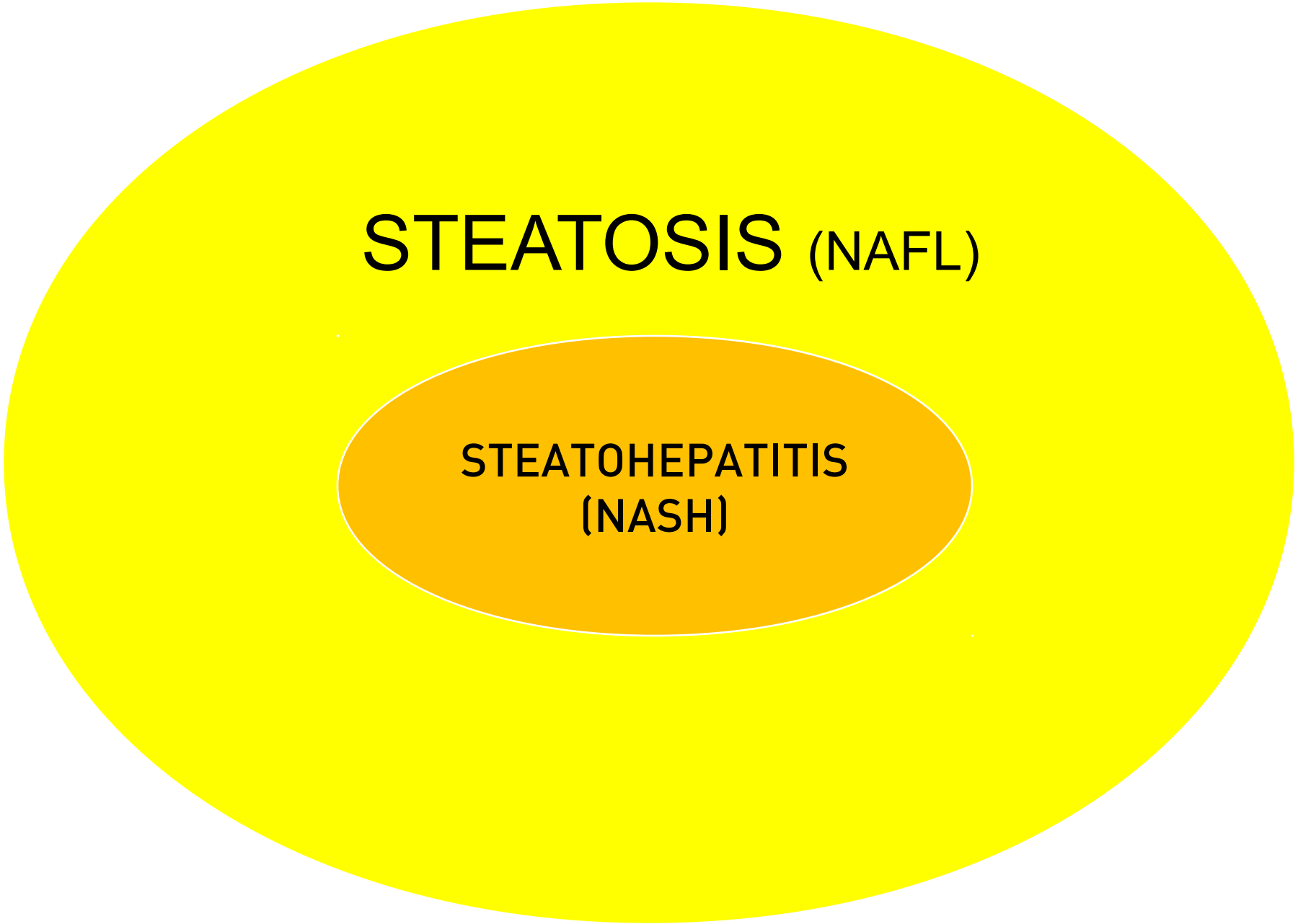
Microvacuole (rare)



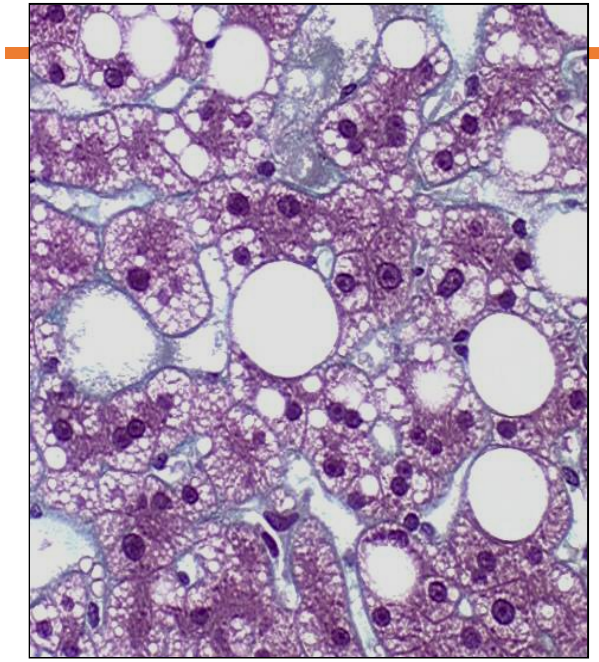


Homogeneous distribution of steatosis in zone 3 of the lobule

NAFLD : a spectrum of histologic patterns



Non Alcoholic Steatohepatitis (NASH)



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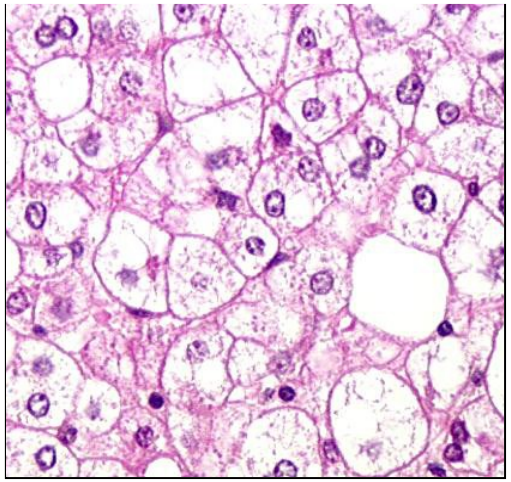
Ballonisation/clarification



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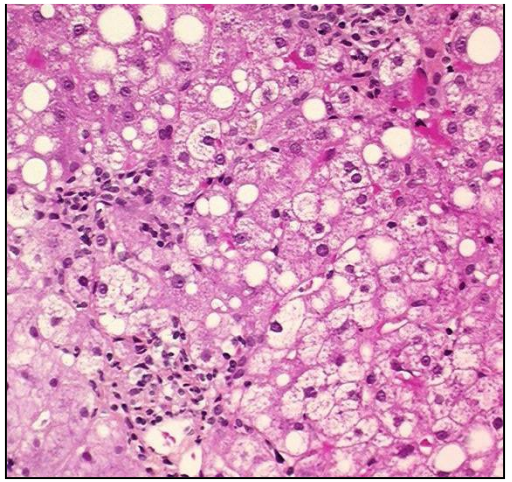
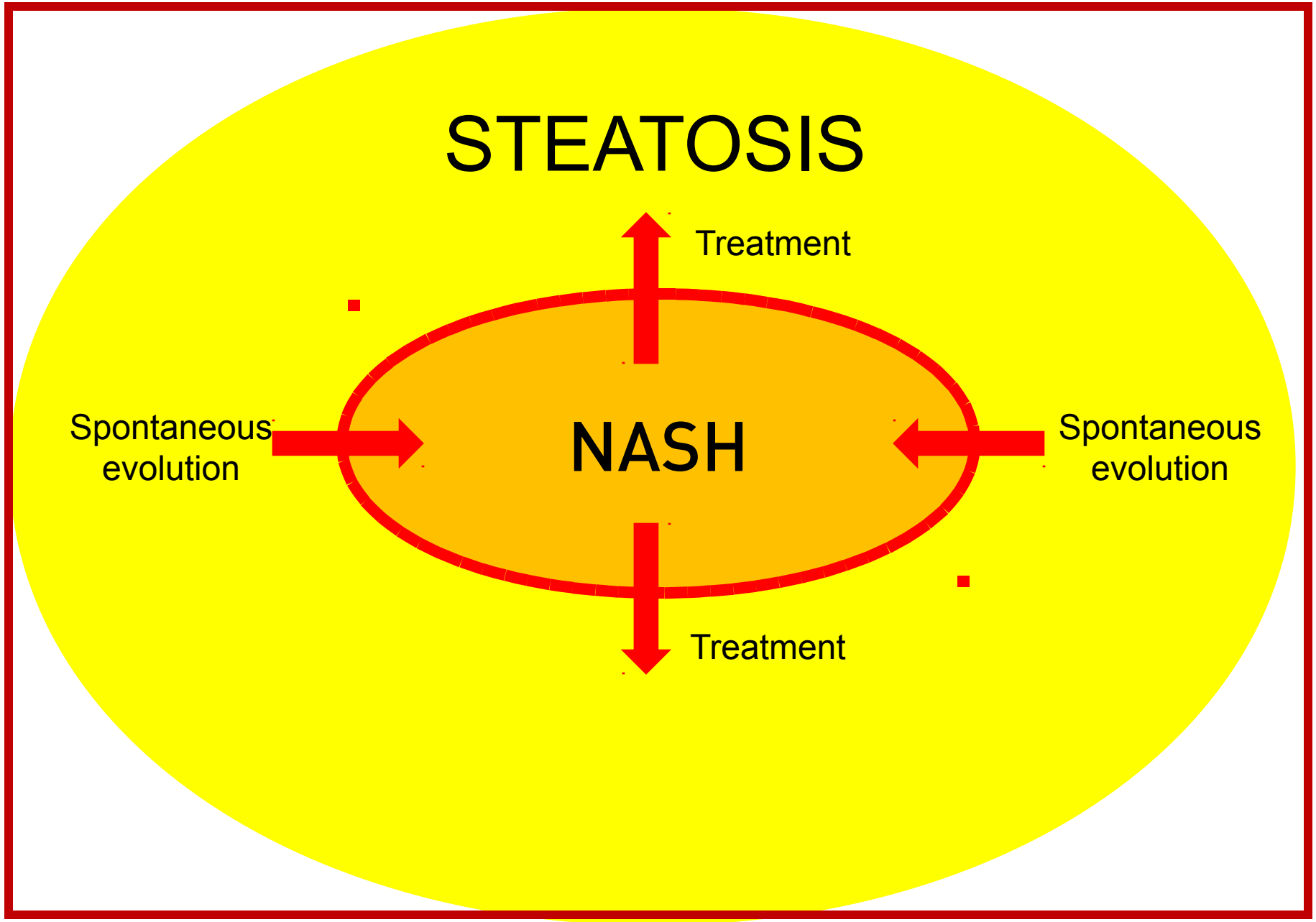
Inflammation lobulaire



> 5% steatosis (≥ grade 1)
> + Lobular inflammation of any degree (≥ grade 1)
> + Liver cell ballooning of any amount (≥ grade 1)

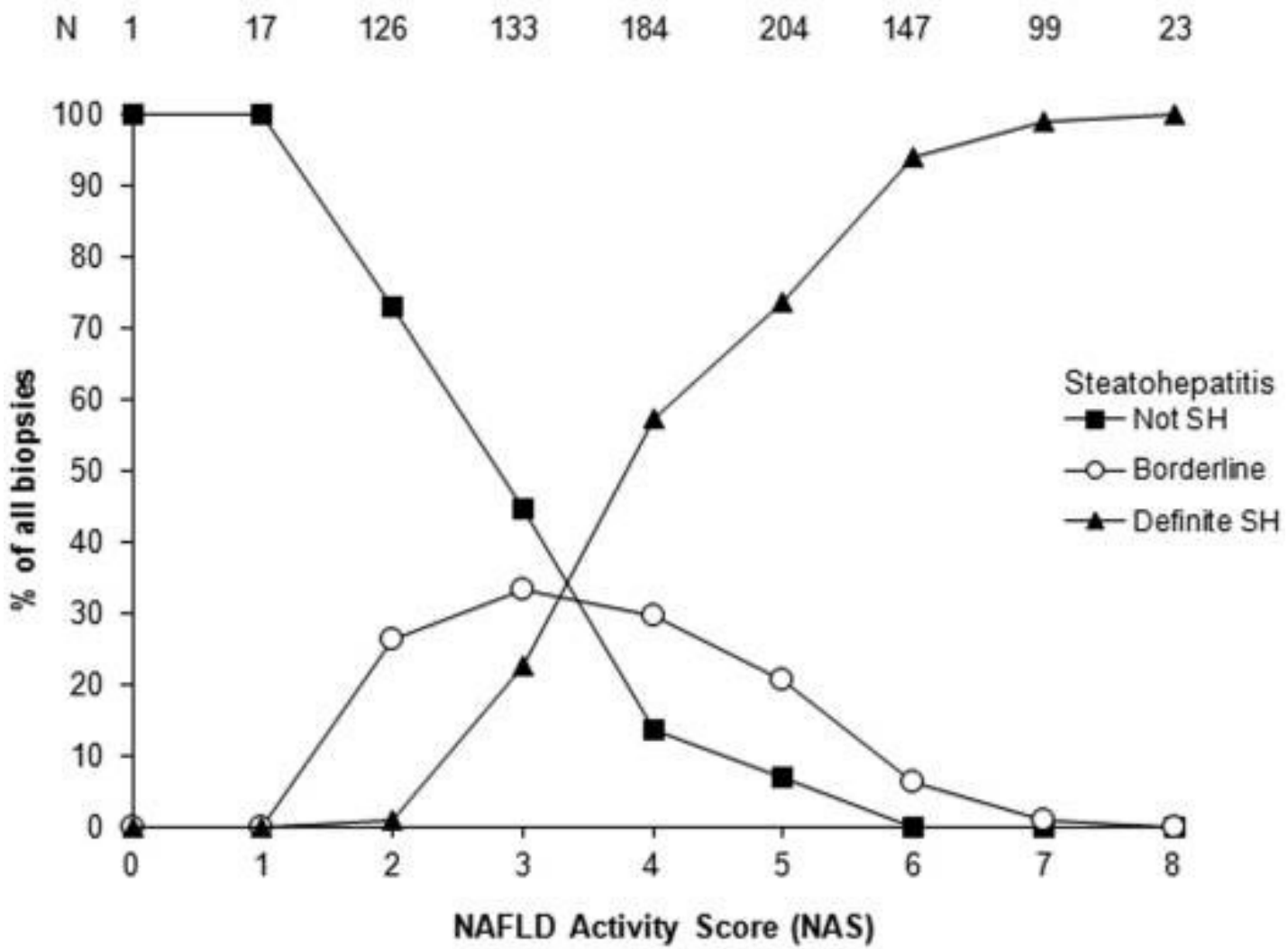
"Endpoints and Clinical Trial Design for Nonalcoholic Steatohepatitis."
AJ. Sanyal, EM. Brunt, DE. Kleiner, KV. Kowdley, N. Chalasani, JE. Lavine, V. Ratziu, A.McCullough.
HEPATOLOGY 2011;54:344-353

The limit of dichotomizing Steatosis alone / NASH



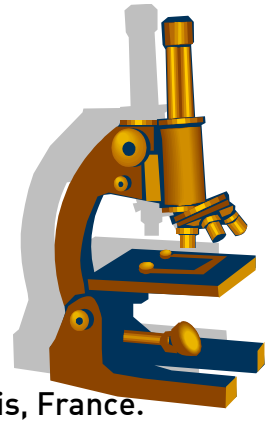
The NAFLD activity score

Item	Definition	Score
Steatosis	Low- to medium-power evaluation of parenchymal involvement by steatosis	
Grade	<5%	0
	5~33%	1
	>33~66%	2
	>66%	3
Lobular inflammation	Overall assessment of all inflammatory foci	
	No foci	0
	<2 foci per 200x field	1
	2-4 foci per 200x field	2
	>4 foci per 200x field	3
Ballooning	None	0
	Few balloon cells	1
	Many cells/prominent ballooning	2
NAS	Not NASH	0~2
	Borderline	3, 4
	NASH	5~8



Brunt et al. Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. Hepatology. 2011 Mar;53(3):810-20

The FLIP pathologist consortium



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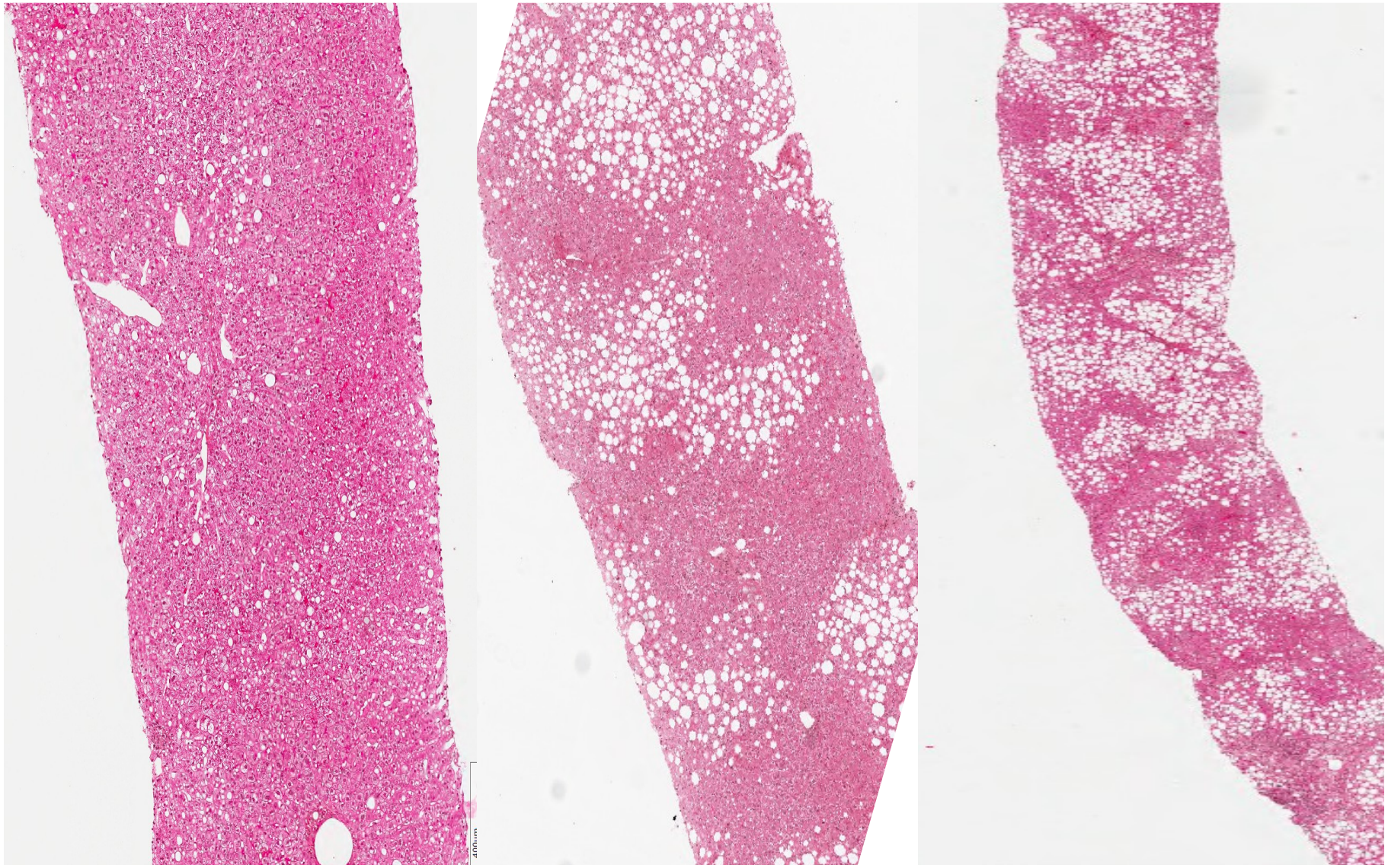
The S.A.F. score

- **S**teatosis (0-3) 0 = ↓5%, 1 = 5-33%, 2 = 34-66%, 3 = ↑66%
- **A**ctivity (0-4) : Ballooning (0-2) + Lobular inflammation (0-2)
- **F**ibrosis (0 – 4) 1a,b,c = perisinusoidal or periportal fibrosis, 2 = both perisinusoidal and periportal fibrosis, 3 = bridging fibrosis, 4 = cirrhosis

Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Bedossa P, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, Tordjman J, Clement K. Hepatology. 2012 Nov;56(5):1751-9

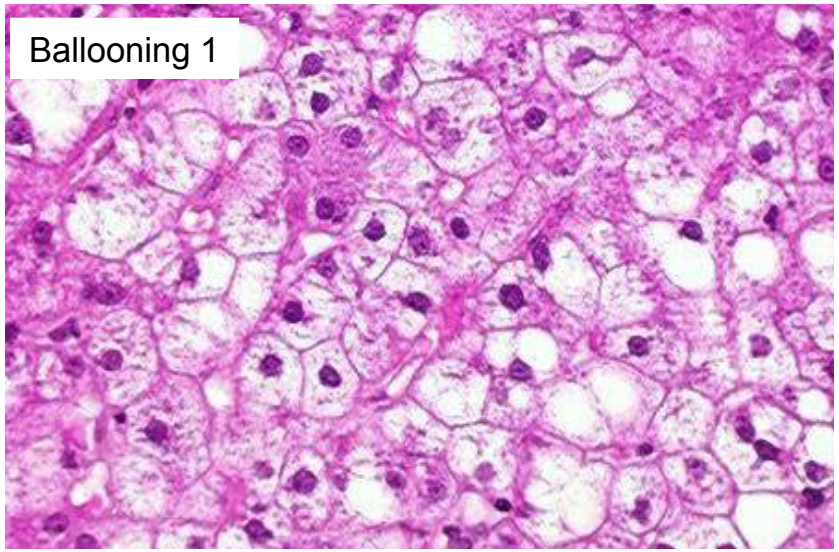
$S_{0-3}A_{0-4}F_{0-4}$

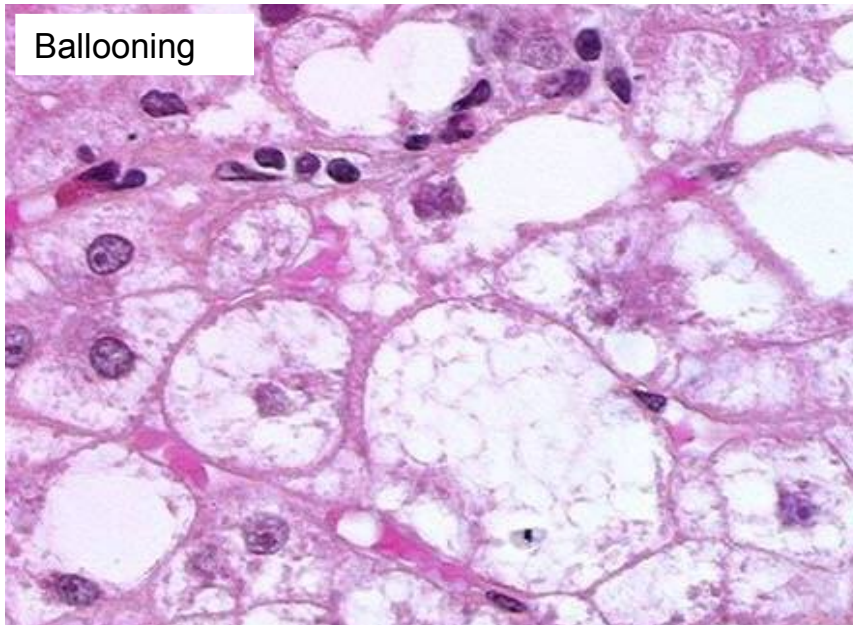
- **S**teatosis (0-3) 0 = <5%, 1 = 5-33%, 2 = 34-66%, 3 = >66%



S1 S2 S3

•Activity (0-4) : Ballooning (0-2) + Lobular inflammation (0-2)





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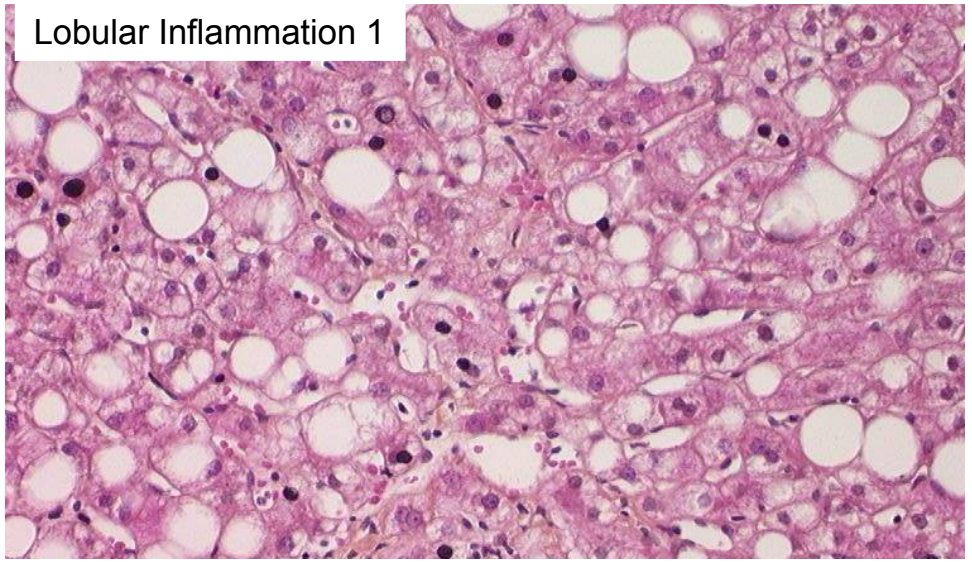
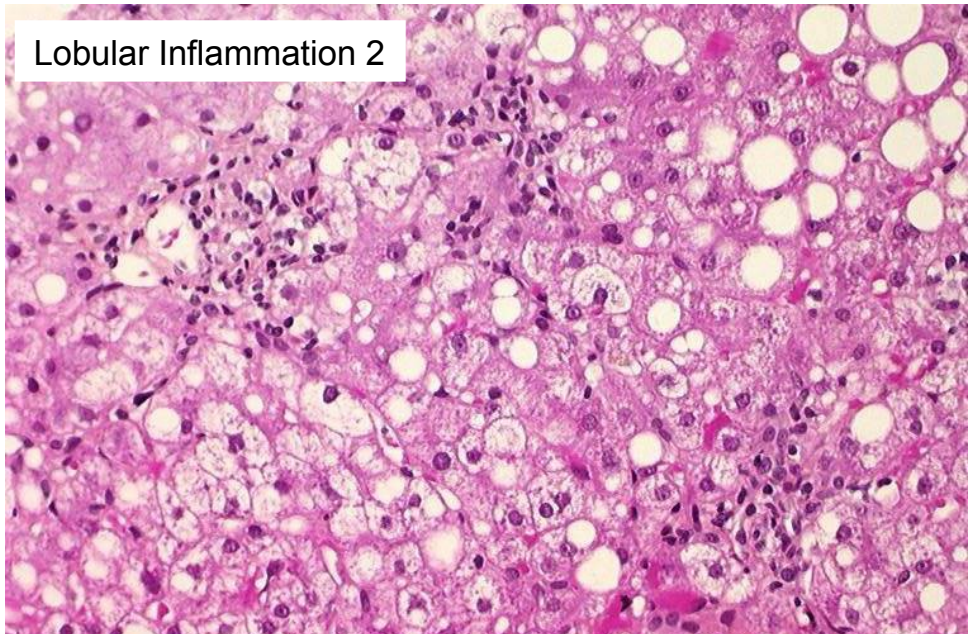
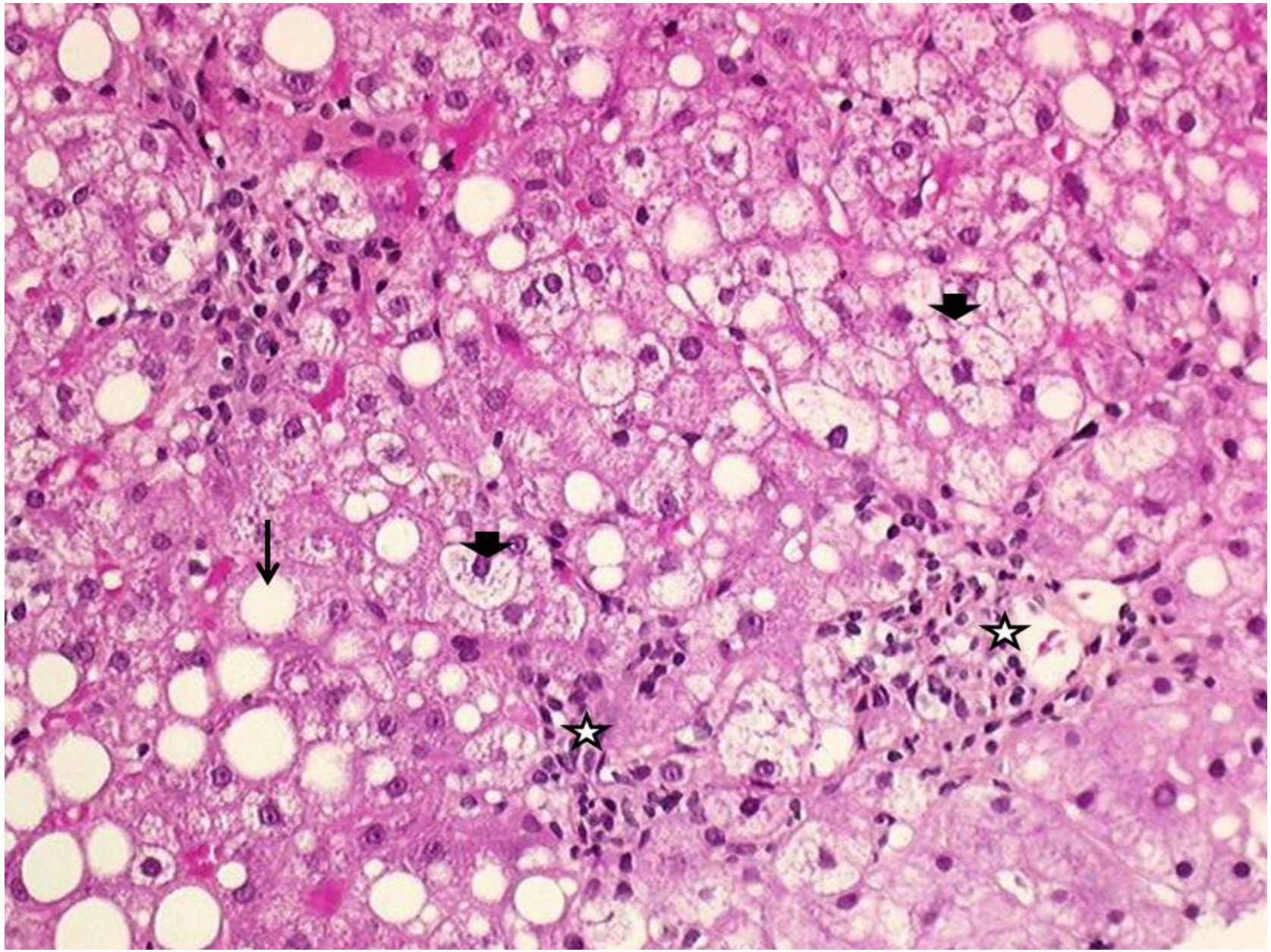




Activity A4 : Balooning = 2 + Inflammation = 2



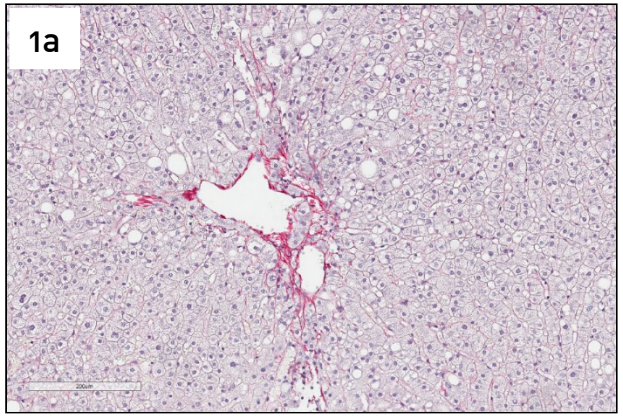
Fibrosis in NAFLD/NASH

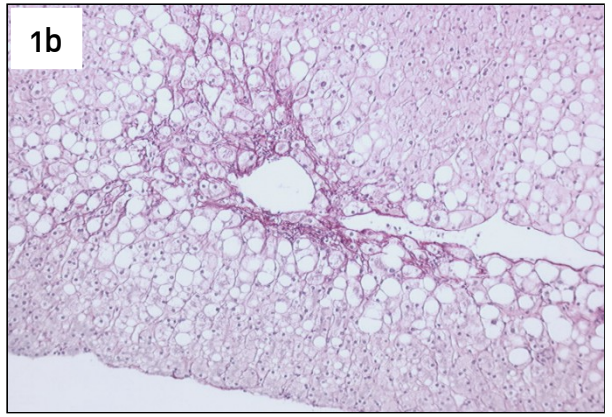
- Patterns of fibrosis in NAFLD :
  - Extending from central zone of the lobule (zone 3)
  - Developing along the sinusoidal wall (perisinusoidal)
  - Typical « Chicken-wire » pattern
  - Strongly associated with diabetes
  - Periportal fibrosis : pediatric, obesity

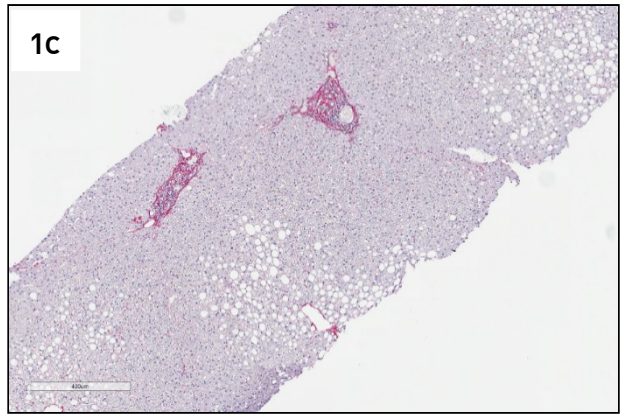
- Avanced fibrosis in NAFLD :
  - Septal fibrosis
  - cirrhosis

•Fibrosis (0 – 4) 1a,b,c = perisinusoidal or periportal fibrosis, 2 = both perisinusoidal and periportal fibrosis, 3 = bridging fibrosis, 4 = cirrhosis

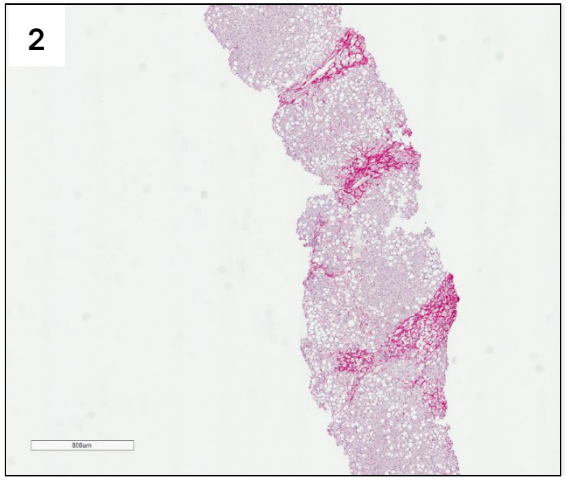
MILD FIBROSIS

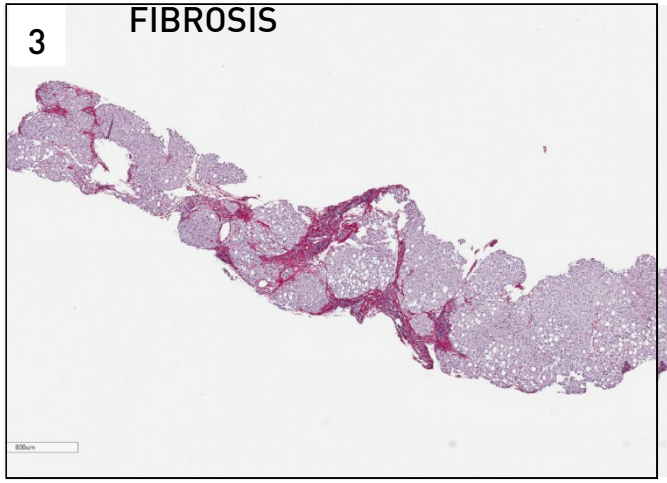


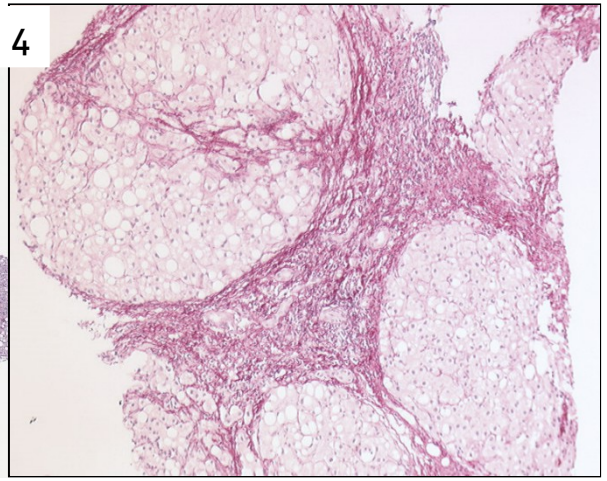




SIGNIFICANT FIBROSIS

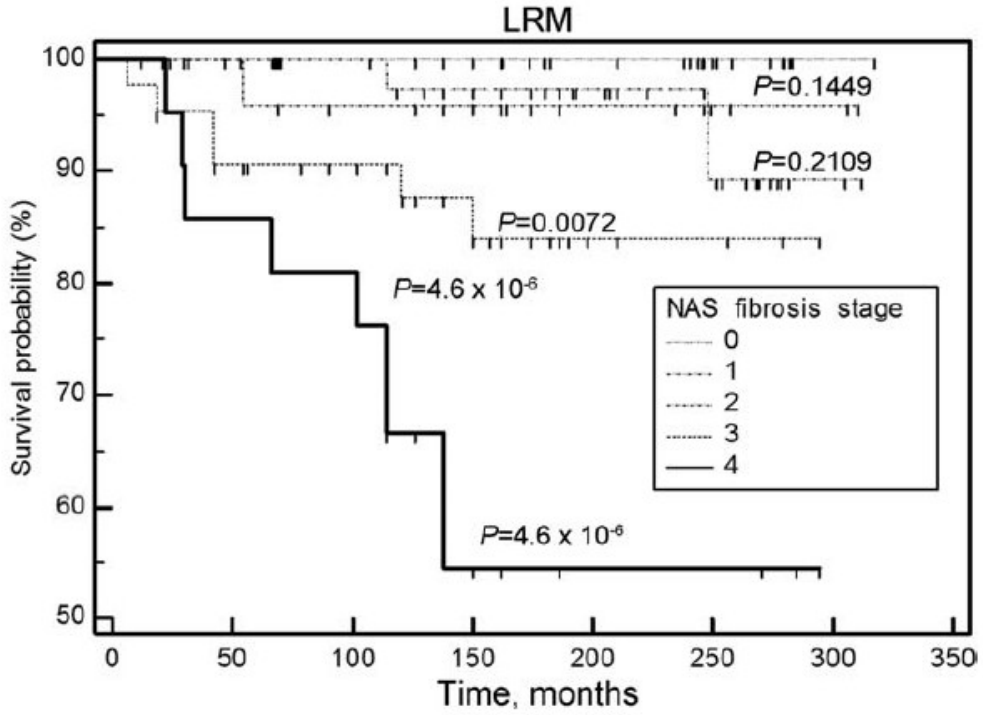






Clinical relevance of fibrosis assessment (staging) in NAFLD

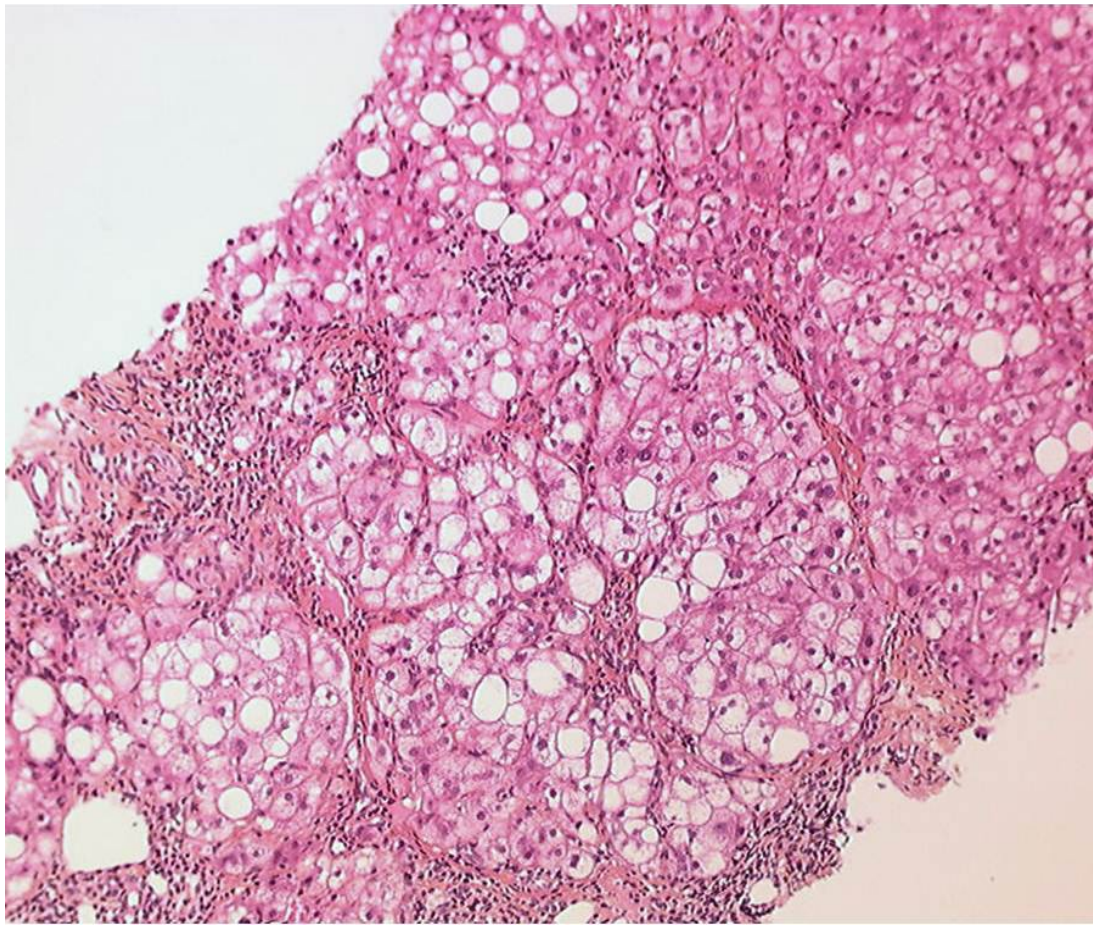
Histological stage of fibrosis predict survival in NASH



Cumulative liver-related mortality according to stage of fibrosis in index liver biopsy

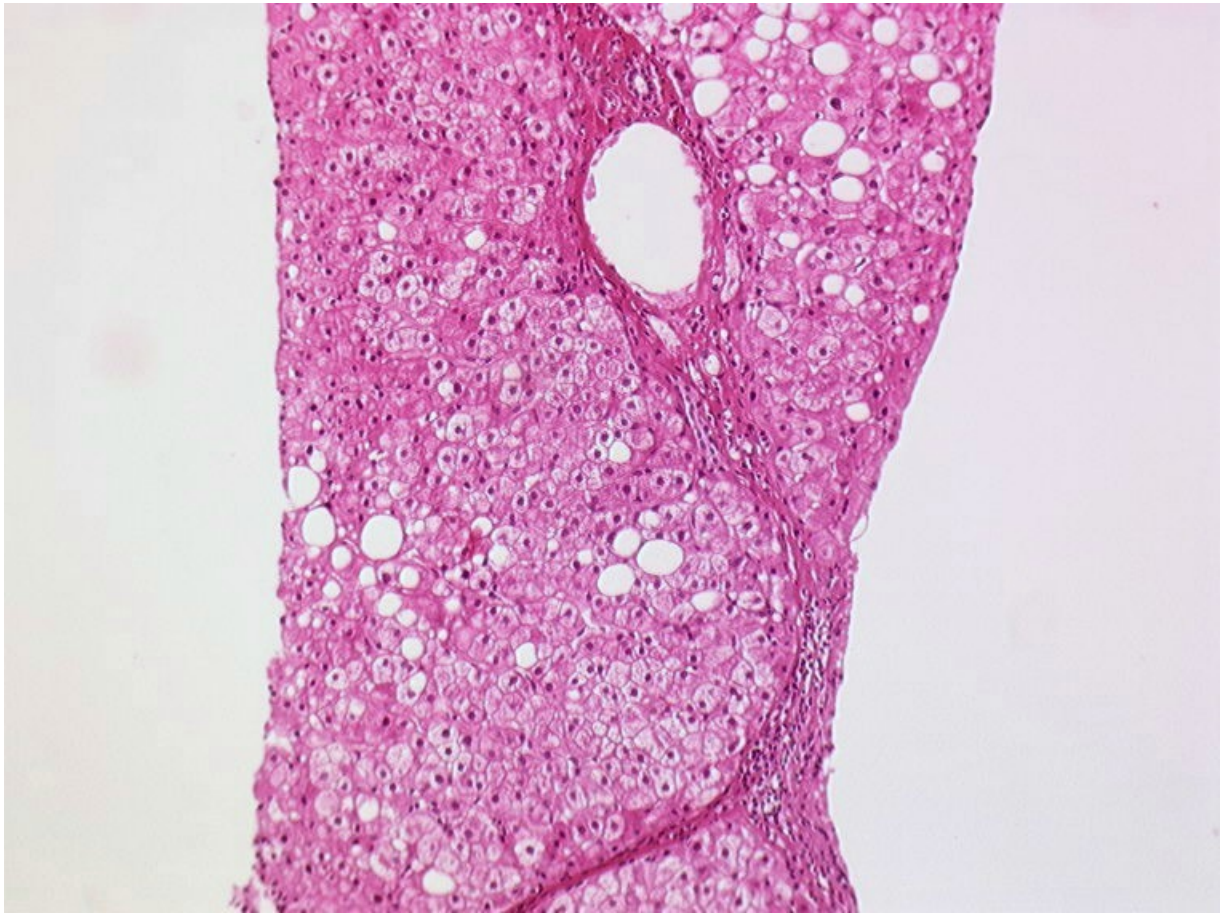
Younossi ZM, Stepanova M, Rafiq N, et al.. Hepatology 2011

S.A.F.



$S_2A_{4(2+2)}F_4$

S.A.F.



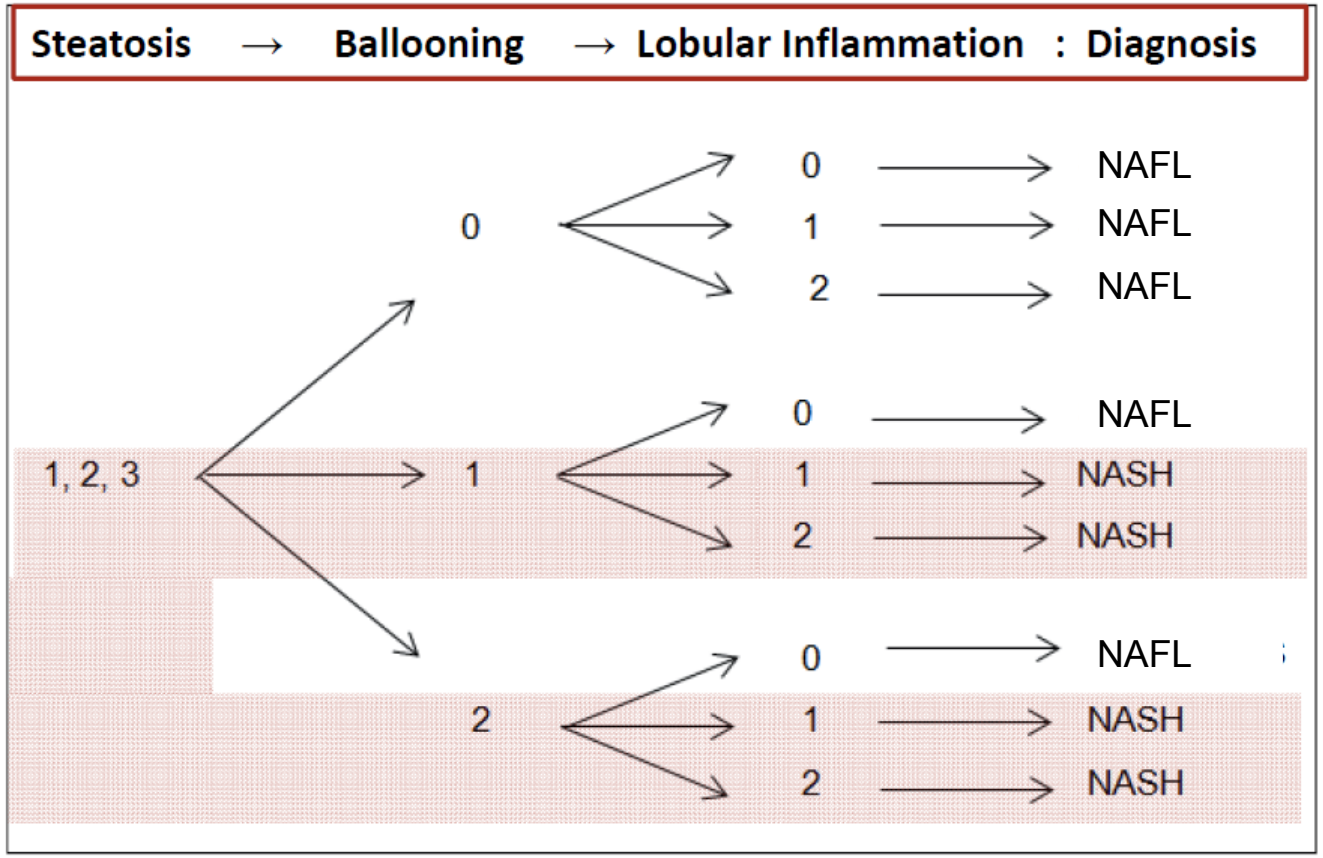
$S_1A_1F_3$

SAF score reproductibility

	κ score	
Steatosis	κ = 0.61	Substantial
Activity Ballooning Lob. Infl	κ = 0.75 κ = 0.8 κ = 0.72	Substantial
Fibrosis (1a,b,c-2-3-4)	κ = 0.53.	Moderate
Fibrosis (1-2-3-4)	κ = 0.83	Perfect

SAF score : highly reproducible semiquantitative features

An algorithm for the categorization of liver diseases in NAFLD
The FLIP algorithm



Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Bedossa P, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, Tordjman J, Clement K. Hepatology. 2012 Nov;56(5):1751-9

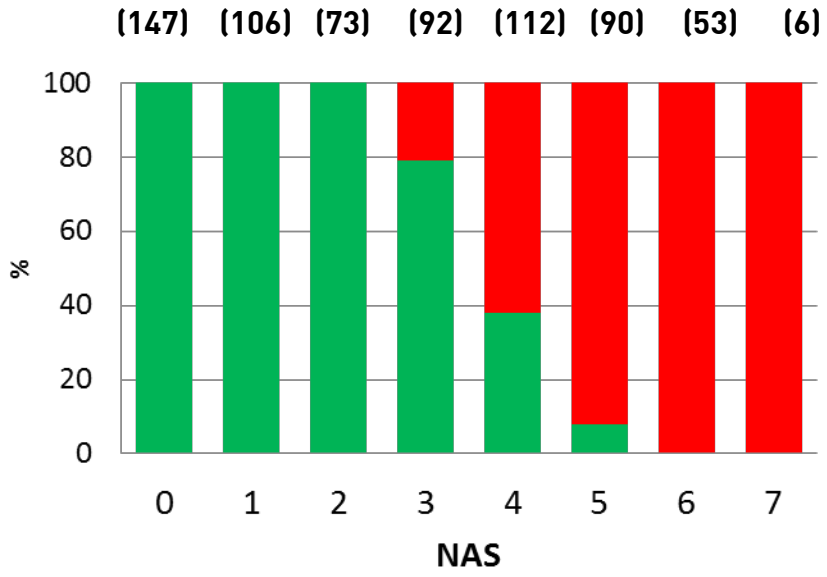
Results : Diagnosis of NASH with classifier

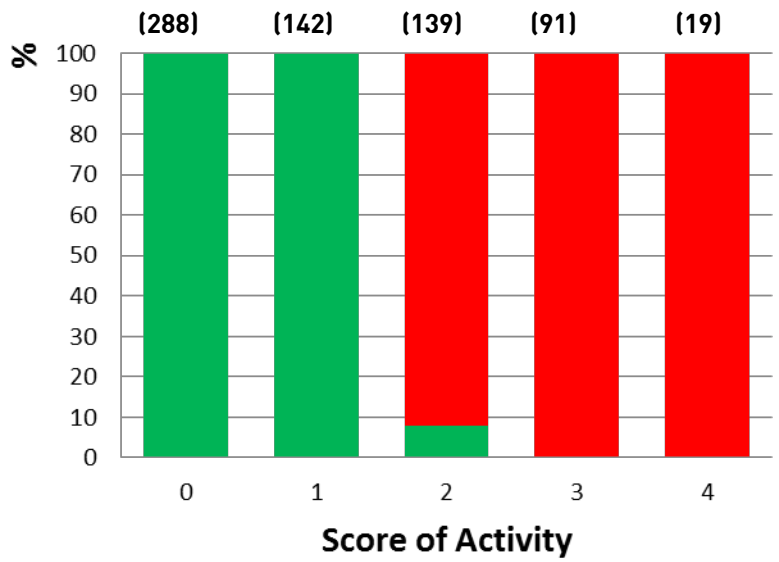
40 biopsies (Steatosis, NASH)	1st session (unsupervised)	2nd session (with classifier)
Expert liver Pathologists (n=6)		
• κ score	0.54 (moderate)	0.66 (substantial)
• % with global agreement	77 %	83 %
• Nbr of biopsies with full agreement	26/40 (65 %)	34/40 (85 %)
General Pathologists (n=10)		
• κ score	0.35 (fair)	0.70 (substantial)
• % with global agreement	55 %	75 %
• Nbr of biopsies with full agreement	18/40 (45 %)	34/40 (85 %)

- The use of algorithm for histological classification of NAFLDs increase the reproducibility of histological diagnosis between pathologists and raises the level of general pathologists to expert liver pathologists

From NAS to SAF

- Morbidly obese patients (n=600) with liver biopsy at bariatric surgery
- Distribution of NAS and activity according to SAF according to presence of NASH (algorithmic definition) (In green, % of cases without NASH, in red, % of cases with NASH)





The S.A.F. scoring system

- Allows a comprehensive, complete and simple overview of the main liver lesions in NAFLDs
- Easy to understand, simple to use
- Mirror the continuous spectrum of the histopathologic features in NAFLD
- The dynamic scale of the SAF score is adapted to clinical trials