Liver Biopsy: Best Practices for Increasing Reliability

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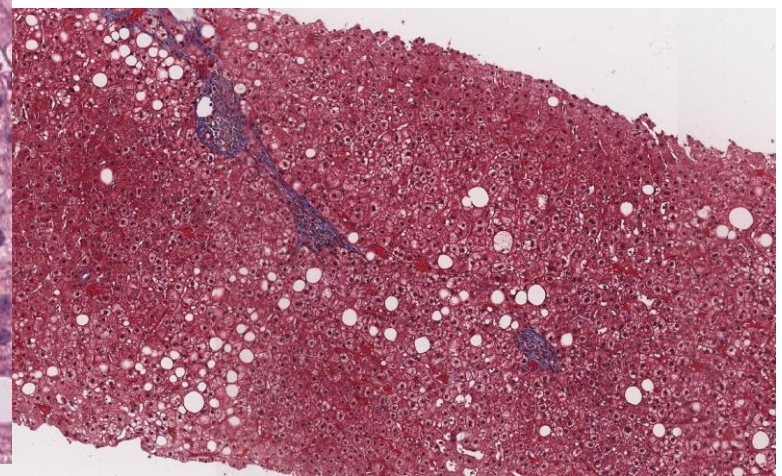
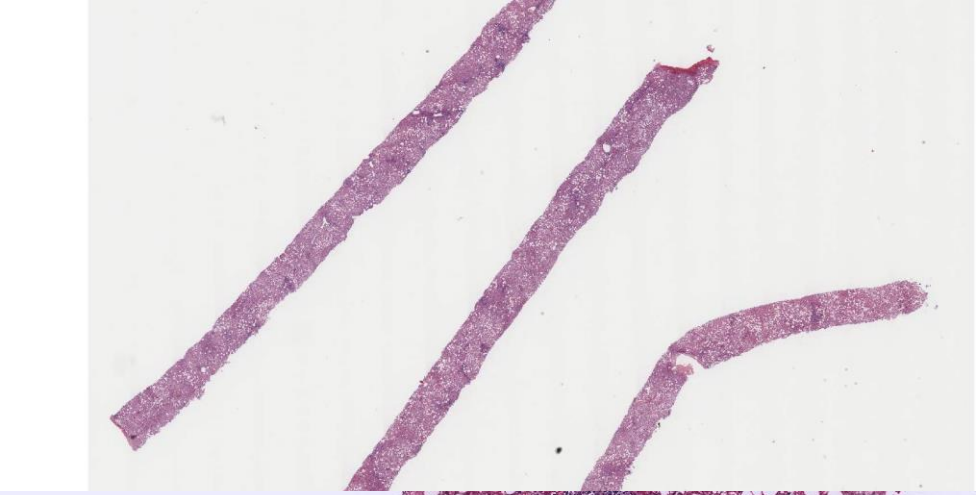
Background

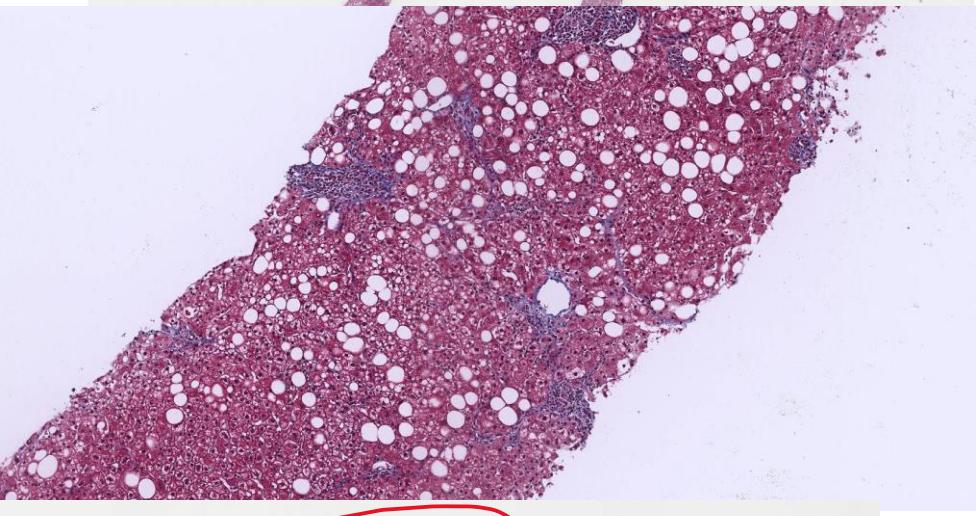
- The level of discordance between pathologists, and the differences in operationalizing liver biopsy collection in trial protocols have been frequently raised as major issues and areas of concern for NASH clinical trials.
- The goal of this session will be to discuss the different approaches regarding how biopsies are read (i.e., 1 reader vs. 2 readers vs. a panel of readers); when they are read; and how training standards can be implemented

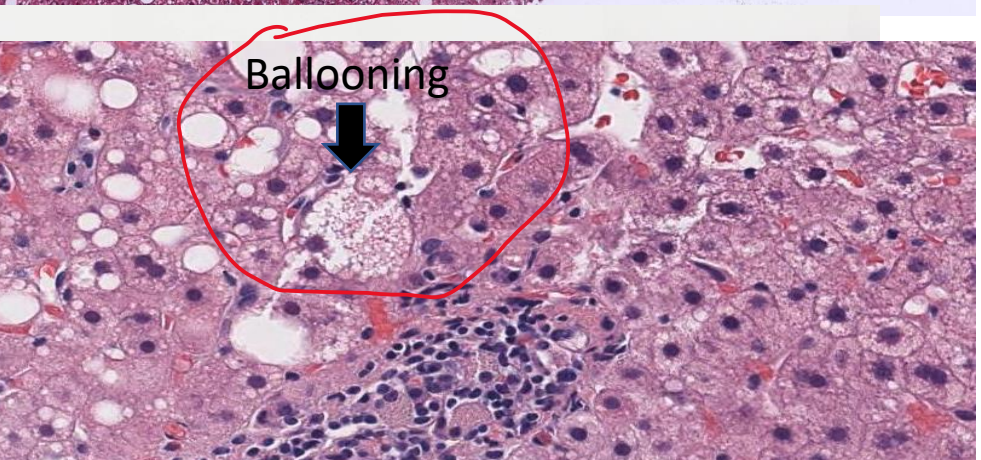


NASH Study Patient #1

- Tale of 2 path interpretations
- Pathologist 1:
  - NAS: 4 (Steatosis 1, Ballooning 1, Lobular Inflammation 2)
  - Fibrosis: 3
- Pathologist 2
  - NAS: 3 (Steatosis 1, Ballooning 0, Lobular Inflammation 2)
  - Fibrosis: 2

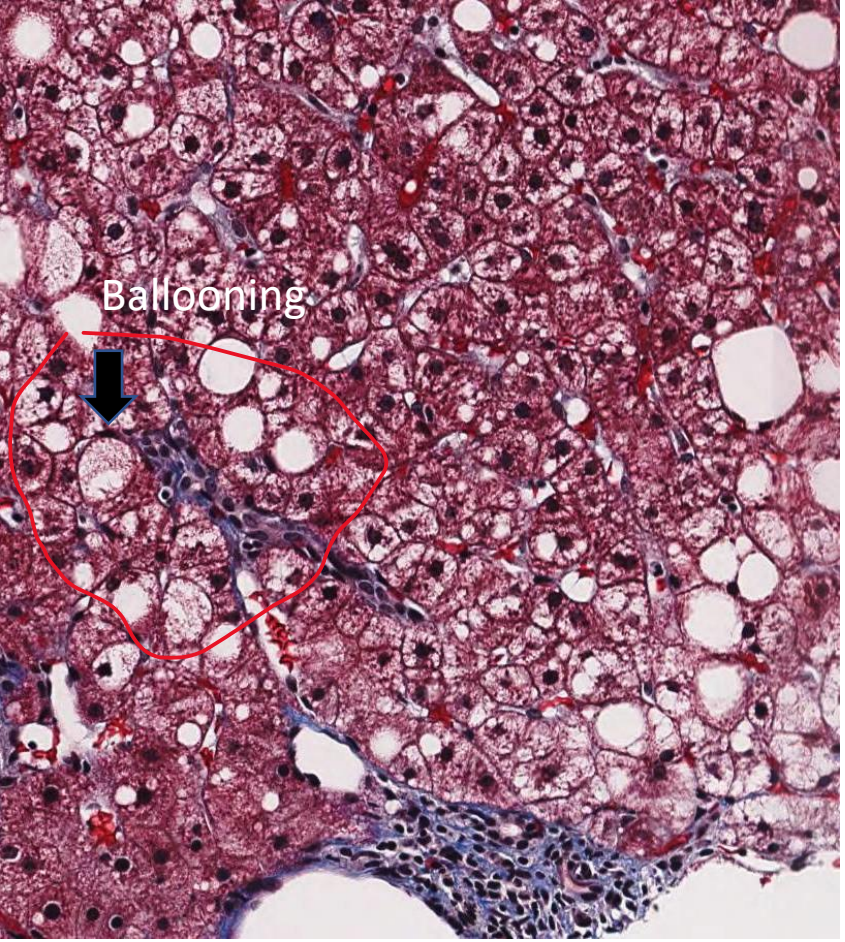


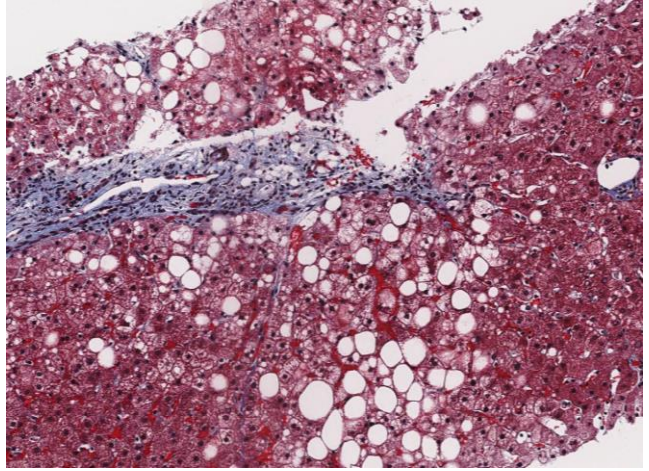


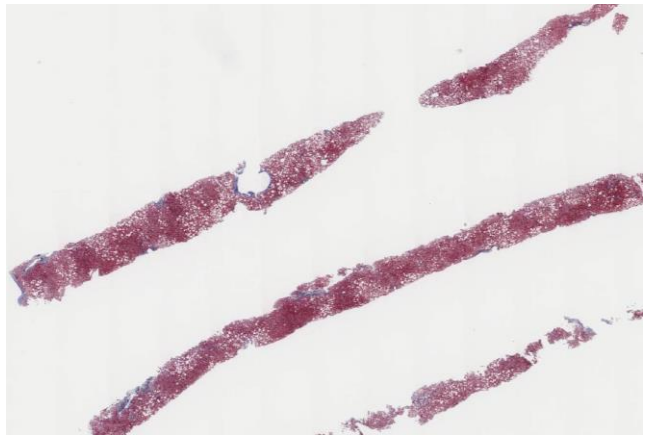


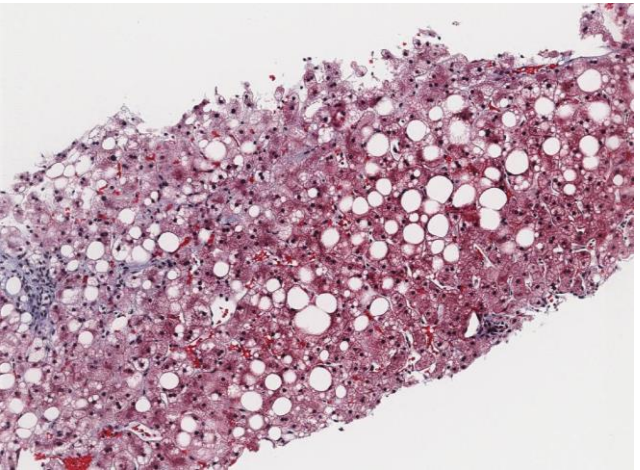
NASH Study Patient #2

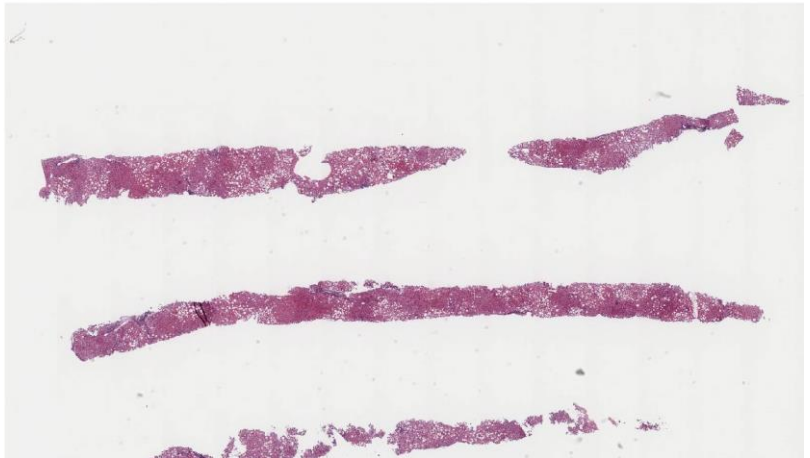
- Tale of 2 path interpretations
- Pathologist 1:
  - NAS: 5 (Steatosis 2, Ballooning 1, Lobular inflammation 2)
  - Fibrosis stage: 2
- Pathologist 2
  - NAS: 4 (Steatosis 2, Ballooning 0, Lobular inflammation 2)
  - Fibrosis: 2











NASH Study Patient #3

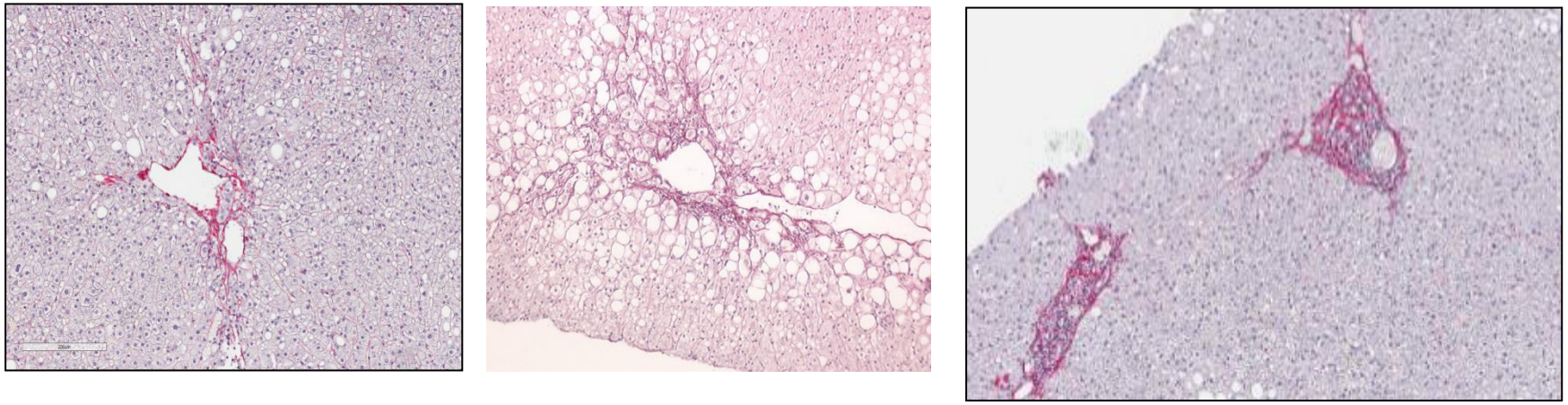
- Tale of 2 path interpretations
- Pathologist 1:
  - NAS: 4 (Steatosis 2, Ballooning 1, Lobular Inflammation 1)
  - Fibrosis: 2
- Pathologist 2
  - NAS: 3 (Steatosis 2, Ballooning 0, Lobular Inflammation 1)
  - Fibrosis: 0

Currently Acceptable Surrogate Endpoints for Regulatory Approval

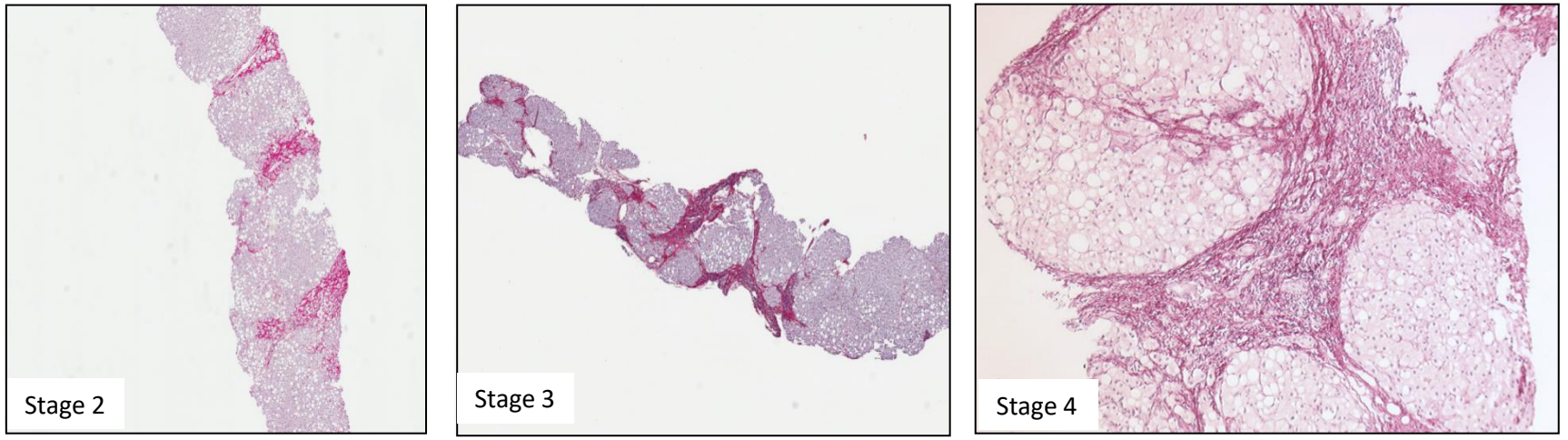
1. Resolution of NASH without worsening of fibrosis
2. Improvement in fibrosis by ≥ 1 stage without worsening of NASH

Example of fibrosis staging (NASH)

MILD FIBROSIS (Stage 1)



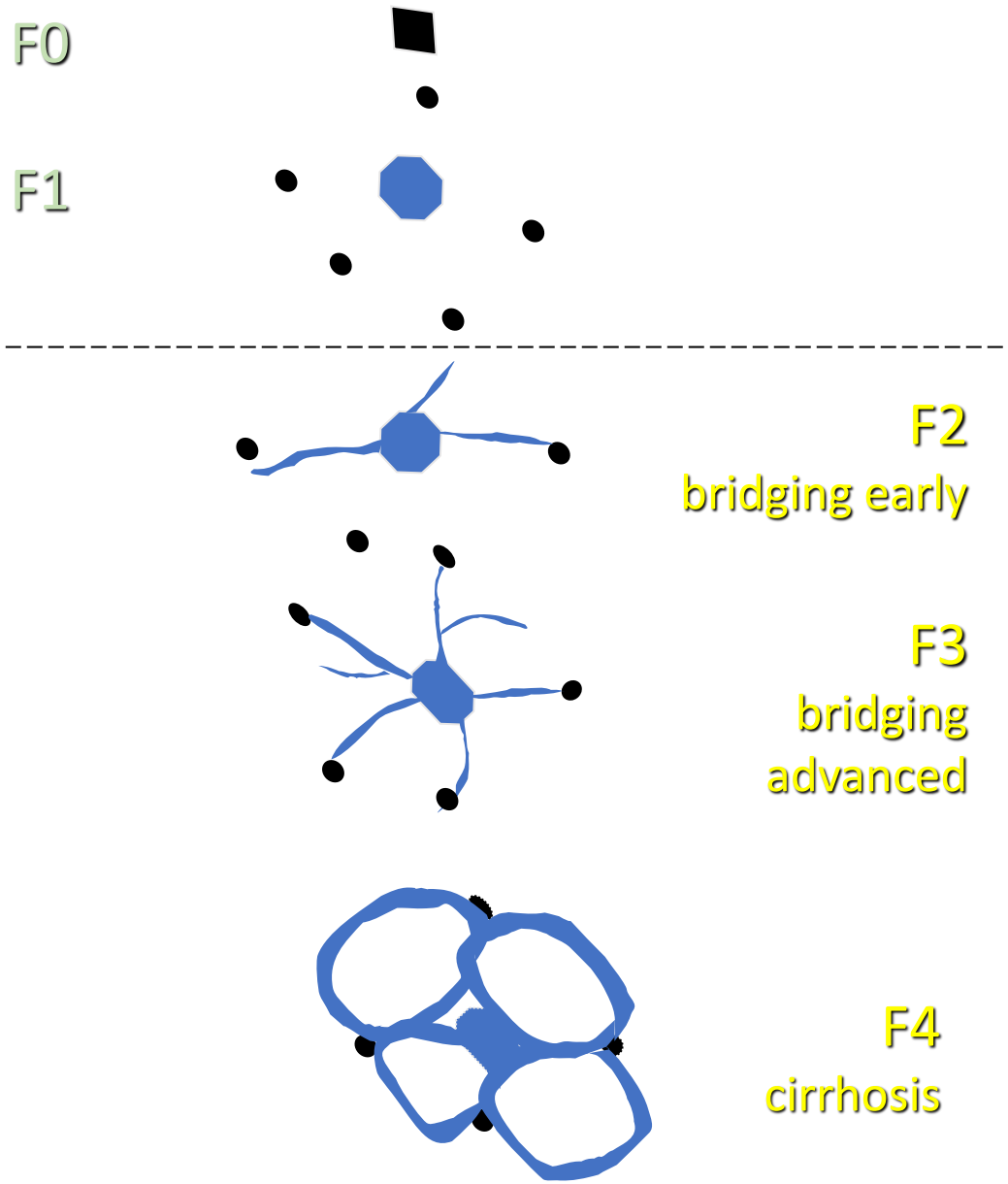
SIGNIFICANT FIBROSIS



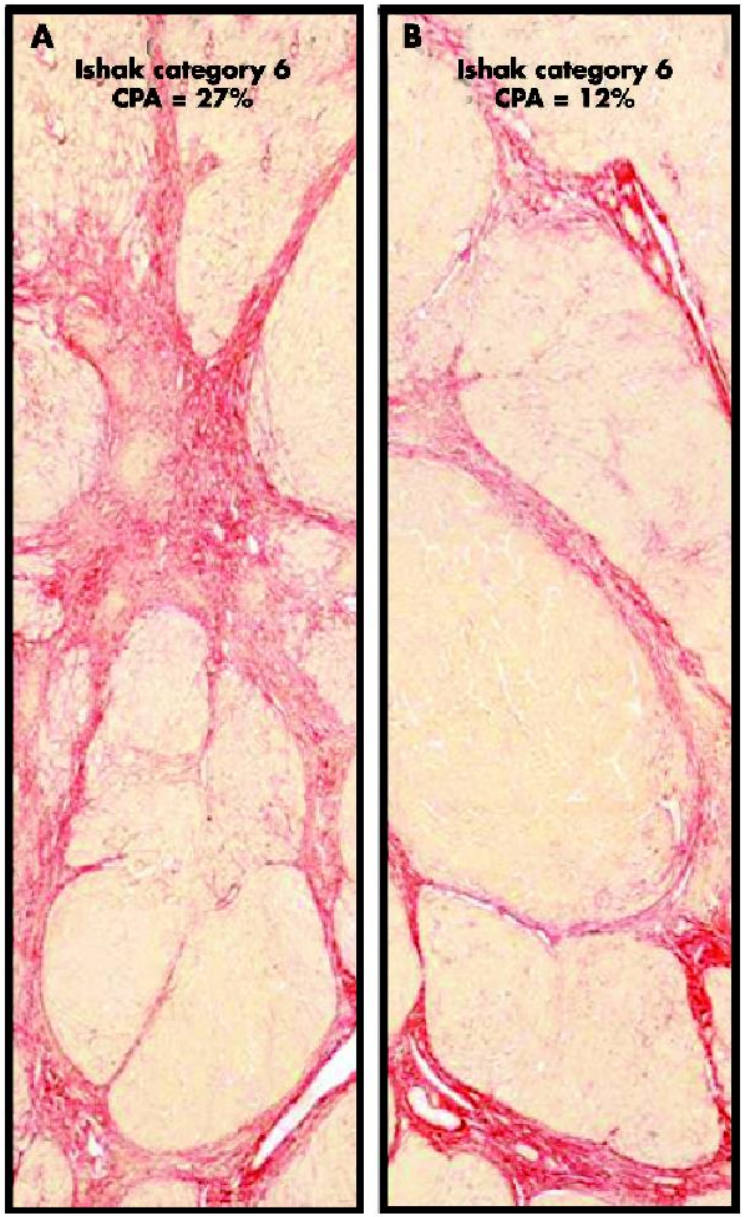
ADVANCED FIBROSIS

Kleiner, NASH CRN, Hepatology 2005

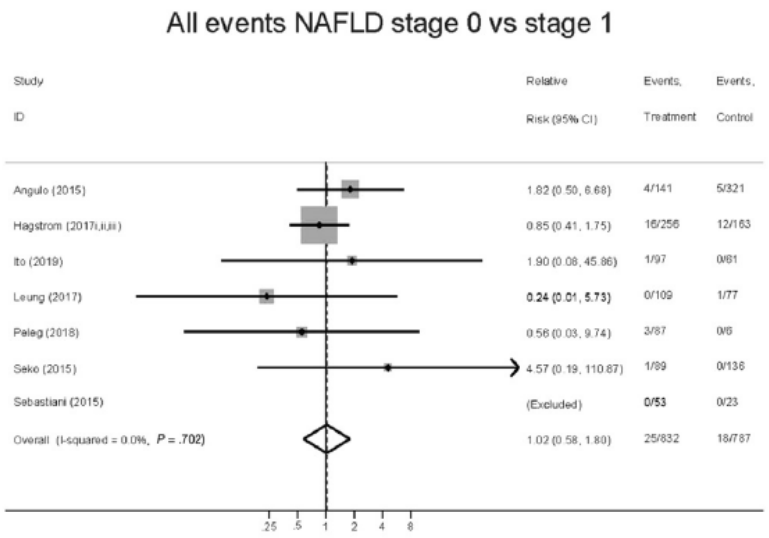
Architectural Changes

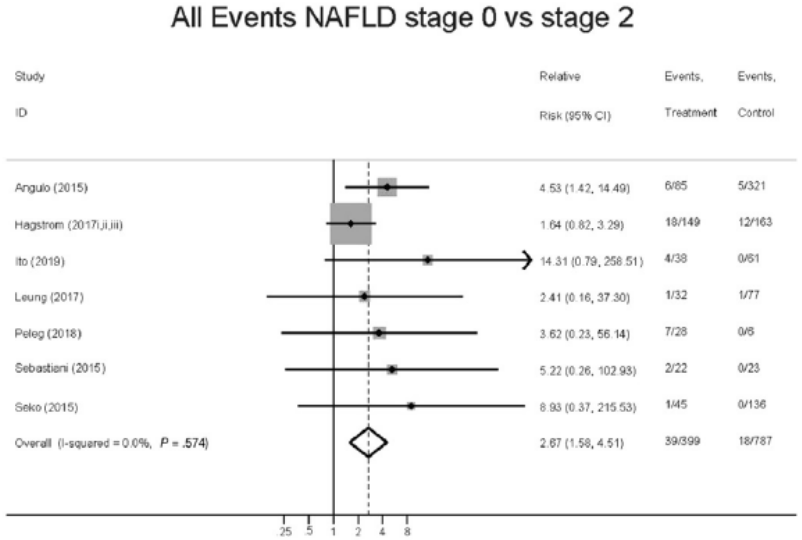


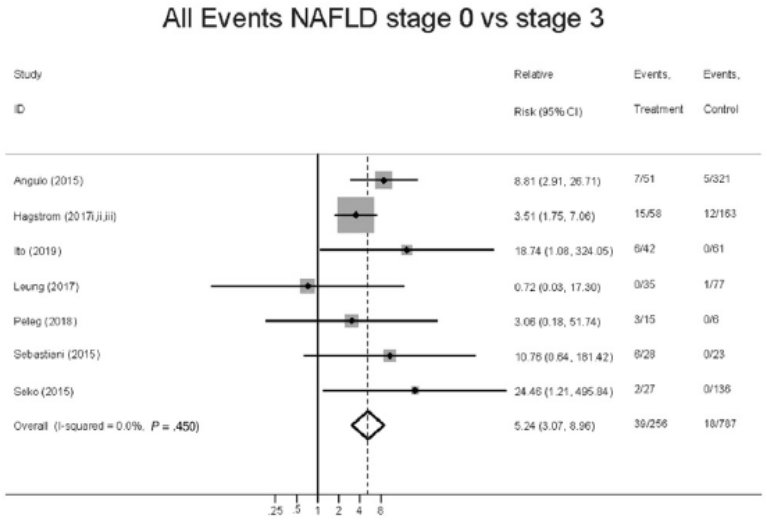
Amount of Fibrosis

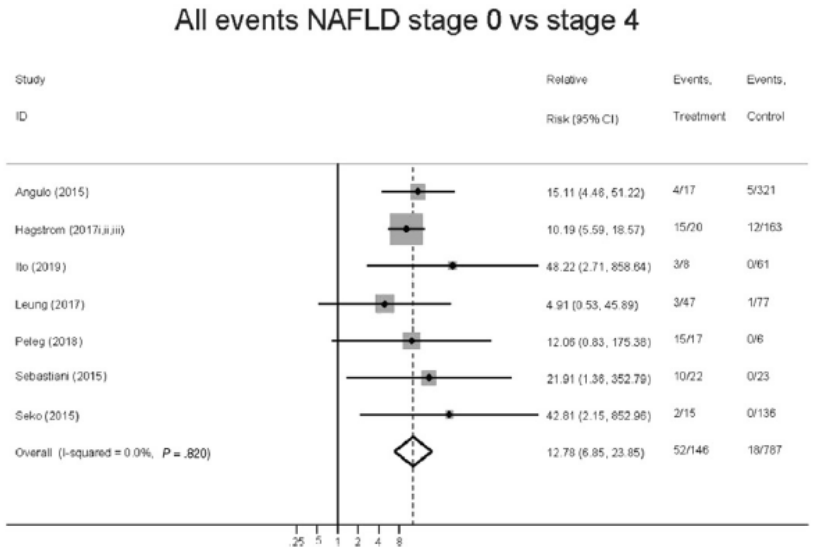


Fibrosis stage and liver-related outcomes





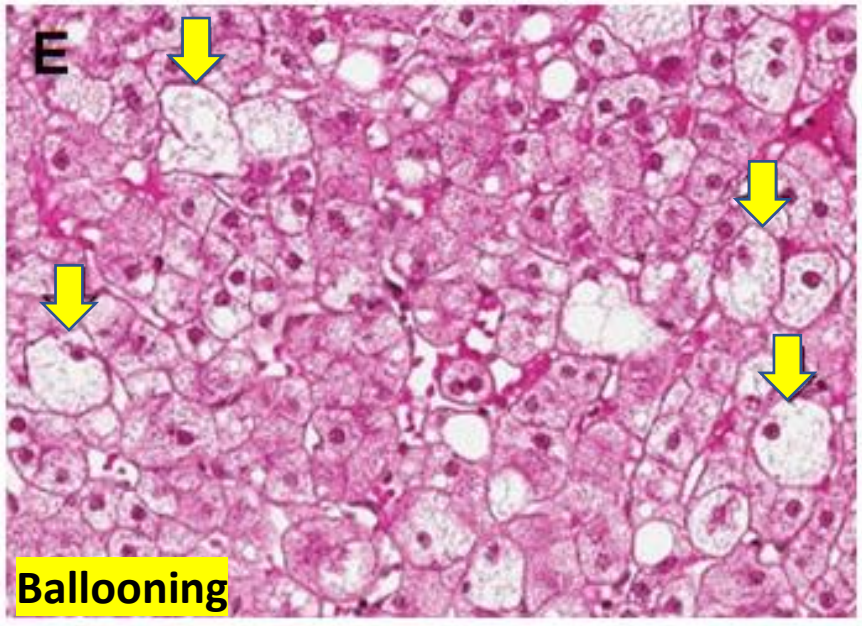


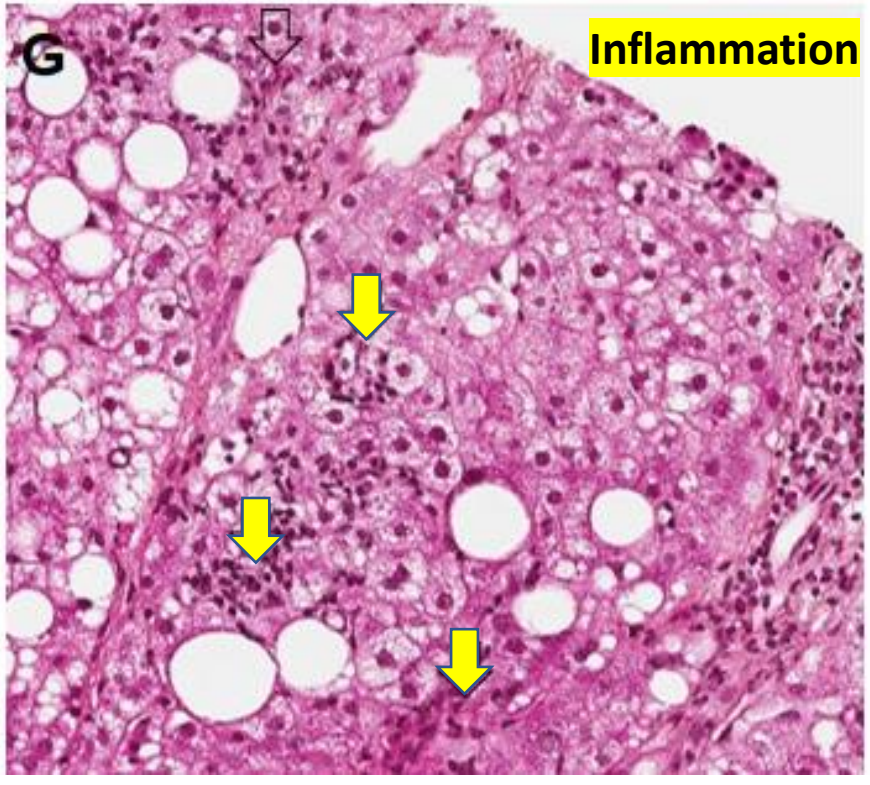


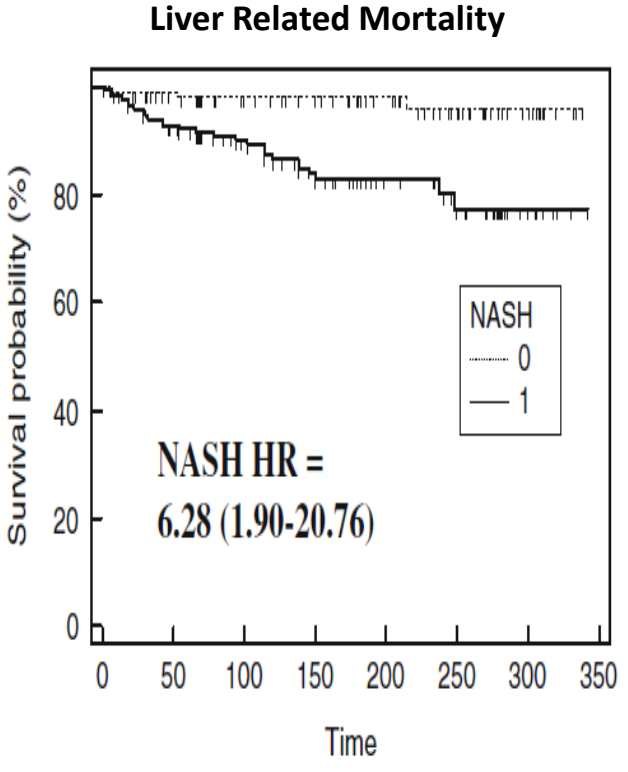
13 studies , 4428 Pts with NAFLD

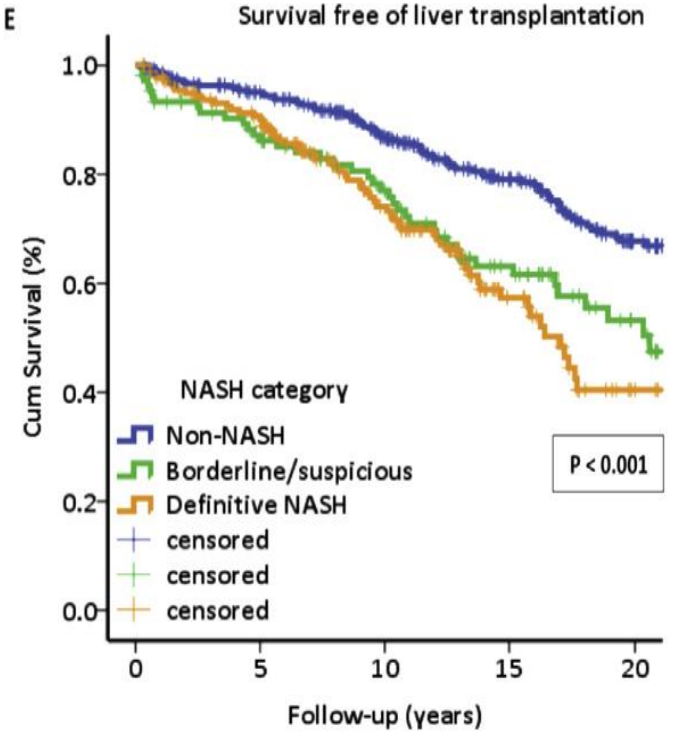
unadjusted RR of liver events by fibrosis stage (vs. stage 0) in all patients with NAFLD

Taylor, Gastroenterology 2020


E
Ballooning


G
Inflammation


Liver Related Mortality
Survival probability (%)
0
20
40
60
80
0
50
100
150
200
250
300
350
Time
NASH
0
1
NASH HR =
6.28 (1.90-20.76)


E
Survival free of liver transplantation
Cum Survival (%)
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
Follow-up (years)
NASH category
Non-NASH
Borderline/suspicious
Definitive NASH
censored
censored
censored
P < 0.001

Journal Pre-proof

Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials

Beth A. Davison, PhD, Stephen A. Harrison, MD, Gad Cotter, MD, Naim Alkhouri, MD, Arun Sanyal, MD, Christopher Edwards, BS, Jerry R. Colca, PhD, Julie Iwashita, Gary G. Koch, PhD, Howard C. Dittrich, MD

Table 1. Inter-reader reliability regarding NASH CRN scores based on 678 Biopsies for 339 patients with NASH

NASH CRN Score	Inter-reader Comparison	% Agreement*	% Agreement Expected by Chance*	Unweighted Kappa (95% CI)*	Weighted Kappa (95% CI)†	Weighted % Agreement Expected by Chance†
Ballooning	Pathologist A v. B	62.83	33.64	0.440 (0.386, 0.494)	0.543 (0.494, 0.592)	57.13
	Pathologist A v. C	64.60	37.28	0.436 (0.382, 0.490)	0.523 (0.474, 0.571)	62.17
	Pathologist B v. C	60.18	35.17	0.386 (0.332, 0.439)	0.486 (0.439, 0.533)	60.48
	Average	62.54	36.03	0.414 (0.374, 0.454)	0.517	---
	Overall‡	45.58	---	---	---	---
Inflammation	Pathologist A v. B	57.96	42.99	0.263 (0.204, 0.321)	0.323 (0.267, 0.378)	78.00
	Pathologist A v. C	65.34	52.00	0.278 (0.209, 0.346)	0.322 (0.257, 0.386)	82.80
	Pathologist B v. C	57.82	42.49	0.267 (0.209, 0.324)	0.338 (0.284, 0.392)	77.55
	Average	60.37	46.19	0.264 (0.220, 0.307)	0.328	---
	Overall‡	42.33	---	---	---	---
Steatosis	Pathologist A v. B	56.34	28.59	0.389 (0.338, 0.439)	0.543 (0.500, 0.587)	66.70
	Pathologist A v. C	67.40	30.15	0.533 (0.484, 0.583)	0.650 (0.609, 0.691)	66.36
	Pathologist B v. C	66.22	30.54	0.514 (0.464, 0.564)	0.635 (0.593, 0.678)	68.25

Journal Pre-proof

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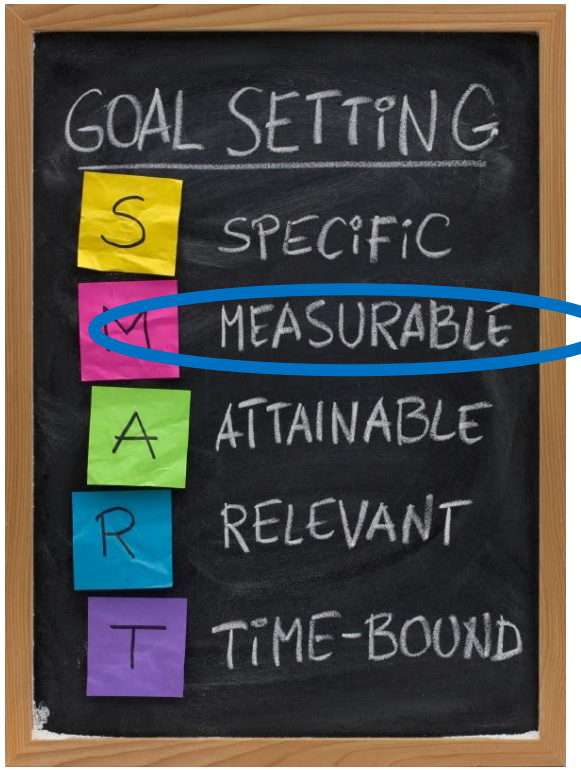
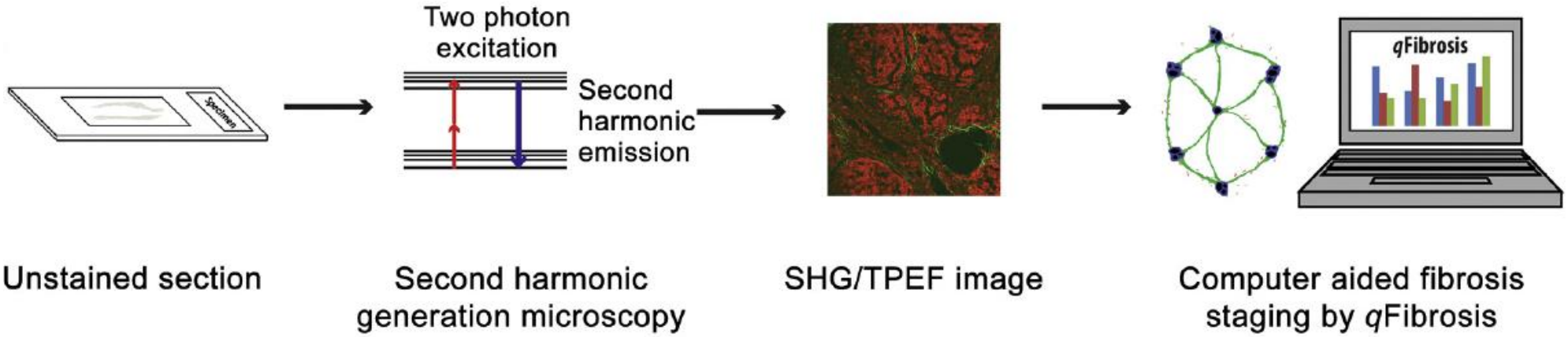
Table 2. Inter-reader reliability regarding endpoints derived from NASH CRN Scores for 339 patients with Paired Biopsies

Endpoint	Inter-reader Comparison	% Agreement*	% Agreement Expected by Chance*	Unweighted Kappa (95% CI)
Hepatic histological improvement in NAS	Original v. H1	71.68	54.62	0.376 (0.276, 0.476)
	Original v. H2	74.04	58.93	0.368 (0.264, 0.472)
	H1 v. H2	74.93	57.36	0.412 (0.310, 0.514)
	Average	73.55	57.17	0.382 (0.308, 0.456)
Resolution of NASH with no worsening of fibrosis	Original v. H1	79.65	60.09	0.490 (0.389, 0.590)
	Original v. H2	81.12	69.45	0.382 (0.268, 0.497)
	H1 v. H2	76.99	65.91	0.325 (0.219, 0.432)
	Average	79.25	65.65	0.396 (0.315, 0.477)
Improvement of fibrosis with no worsening of NASH	Original v. H1	76.11	60.70	0.392 (0.286, 0.497)
	Original v. H2	75.81	65.49	0.299 (0.184, 0.413)
	H1 v. H2	78.76	63.94	0.411 (0.301, 0.521)
	Average	76.89	63.53	0.366 (0.289, 0.444)
Resolution of NASH with at least a 2-point improvement in NAS	Original v. H1	80.53	67.11	0.408 (0.293, 0.523)
	Original v. H2	84.66	75.10	0.384 (0.256, 0.513)
	H1 v. H2	79.35	72.65	0.245 (0.125, 0.365)
	Average	81.51	71.87	0.343 (0.256, 0.430)

* Unevaluable score considered as a response category.

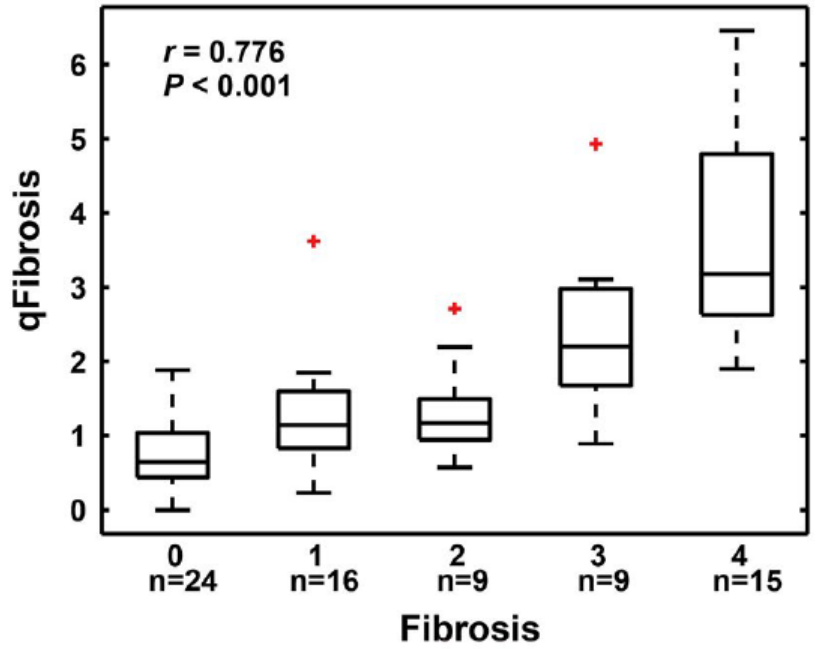


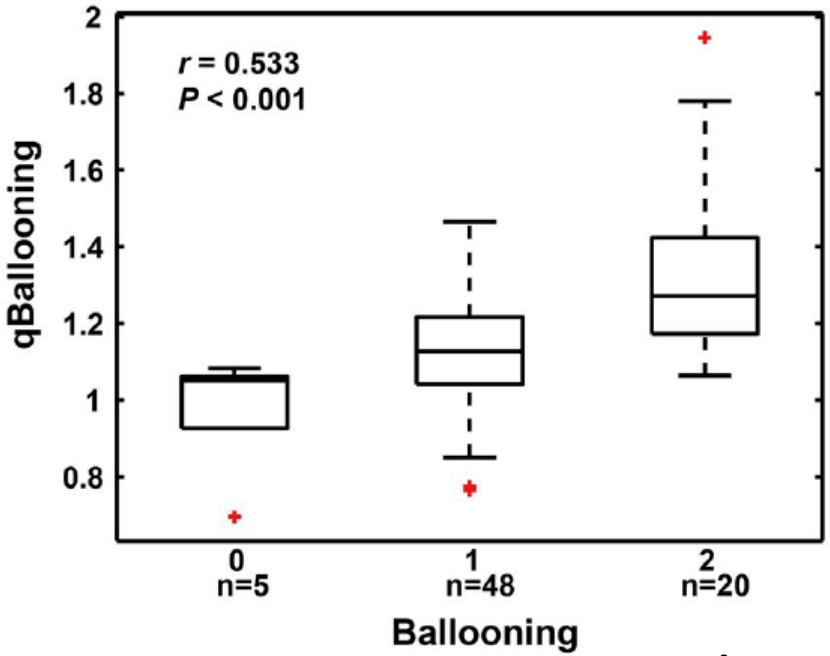
Fully automated fibrosis quantification



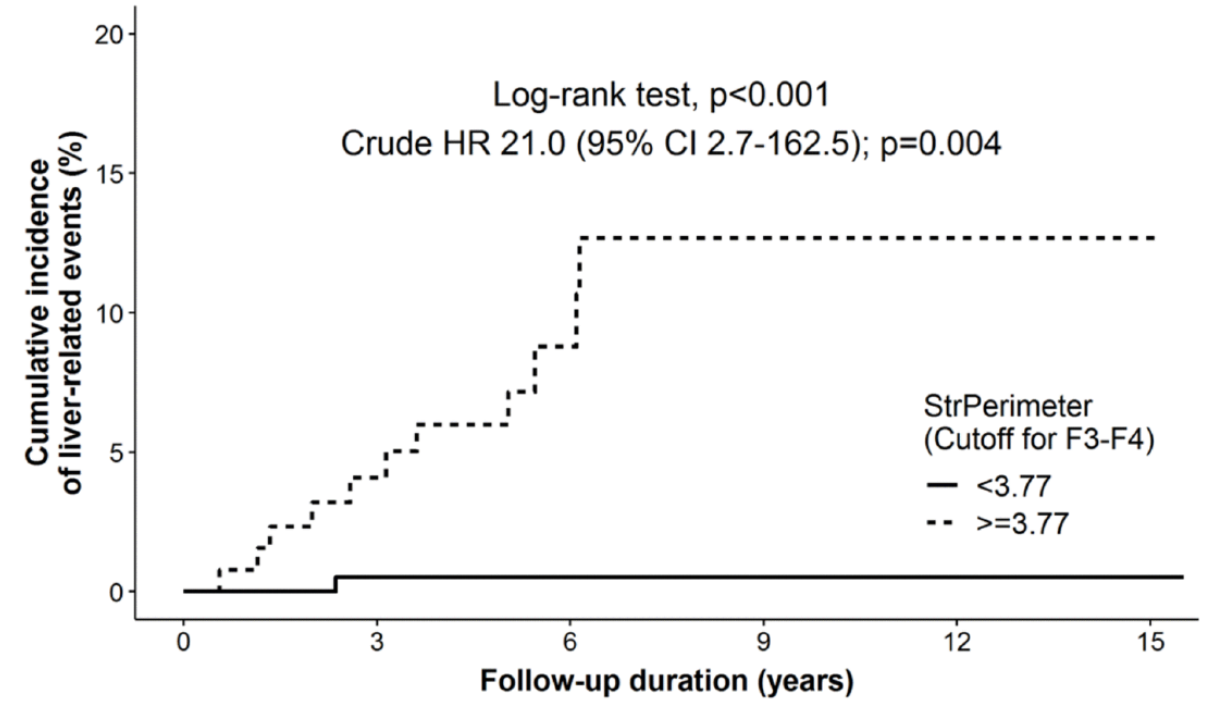
- ***Promise of better discrimination accuracy between early stages of fibrosis***
- ***Promise of less sensitivity to sampling error and to interobserver variability***
- ***Promise of identification of progression /regression at the cirrhotic stage***

Xu, J Hepatol 2014





Liu, Hepatology 2020



Number at risk

<3.77	215	192	109	75	34	6
>=3.77	129	102	50	30	10	2

Wang, Gut, 2020