AASLD The Liver Meeting® Nov. 12-15, 2021
DIGITAL EXPERIENCE

Continuous staging of NASH Patients at low (F1) Fibrosis Severity: Evaluation of the performance of a novel histology-based fibrosis phenotypic composite score and predictive AI tools.

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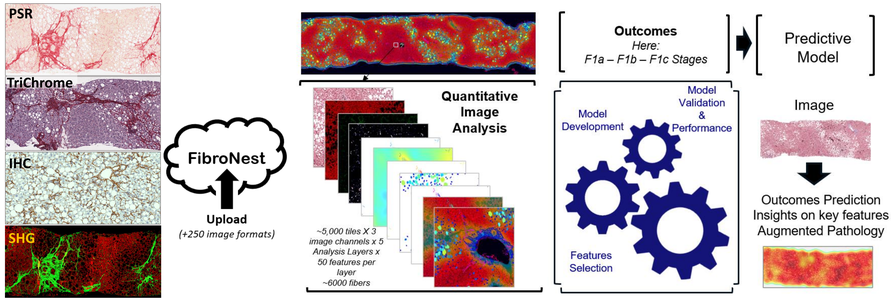
BACKGROUND and AIMS

Fibrosis in the setting of NASH is classified in the NAS scoring system in four stages, with early, stage 1 fibrosis (F1) further categorized by location: F1 (Perisinusoidal or periportal), F1a (Mild, zone 3, perisinusoidal), F1b (Moderate, zone 3, perisinusoidal) and F1c (Portal/periportal). In this study, we present how quantitative Digital Pathology image analysis (FibroNest), and AI-enabled predictive tools (FibroNest-Predict) can be used to generate continuous scores to automate the F1a-b-c classification.

METHOD

TISSUE PREPARATION, INSTRUMENTATION, AND WORKFLOW

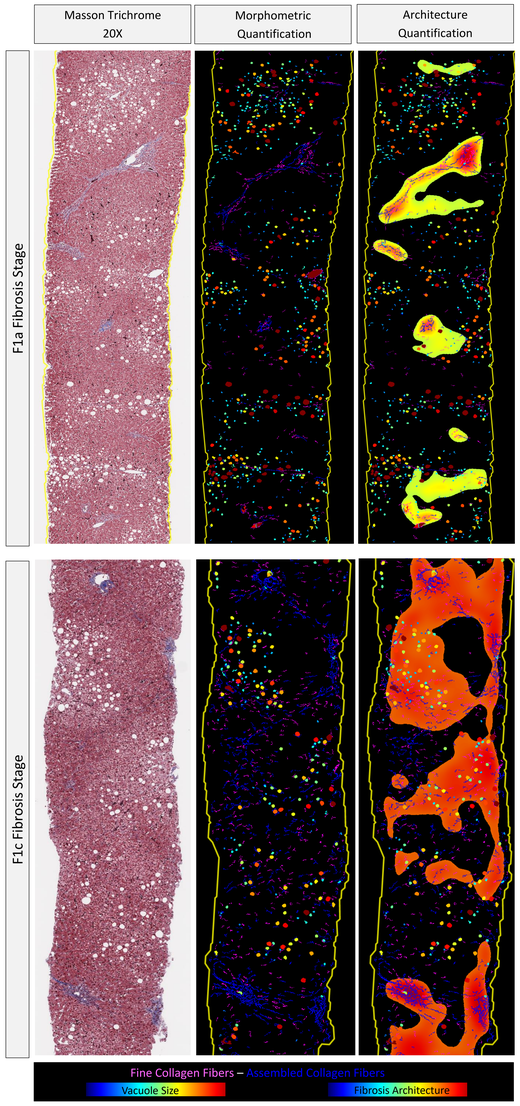


Group	Description	Histological Assessment	Total =17
NASH F1a	Patients with histological diagnosis of NASH and stage 1 fibrosis from the screening biopsies of the LiFT study (NCT04134091)	Histologic assessment and Fibrosis severity stage was assessed by pathologists	N= 10
NASH F1b			N=3
NASH F1c			N=4

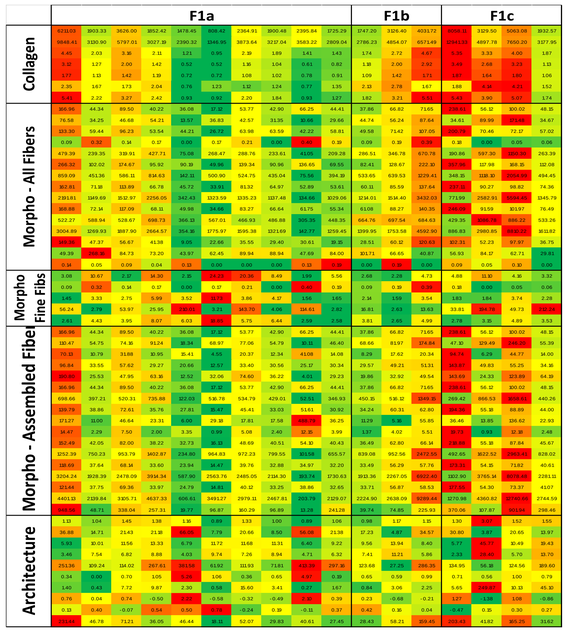
- FFPE sections (~4 microns) of patient liver biopsies were deparaffinized, stained with Masson Trichrome for Collagen and digitized at 20X (0.50 micron/pixel) on a Aperio AT WSI system
- Using Quantitative Image Analysis (FibroNest™) the fibrosis phenotype is described for its collagen content and structure (12 traits), the morphometric traits of the collagen fibers (13 traits), and fibrosis architecture traits (7). In each image, each morphometric and texture trait is represented by a histogram distribution (e.g. Fiber Skeleton Length)
- The histogram for each trait is described by up to seven quantitative fibrosis parameters (qFPs, 315 in total) to account for mean, variance, distortion and progression.
- To detect phenotypic differences between the three F1 sub-groups, principal qFPs are automatically detected if their group mean value difference is statistically (P<0.05, T-Test) greater than 20%.
- Principal qFPS are used individually and collectively to describe the differences in phenotypes between groups. They are combined into a normalized Phenotypic Composite Fibrosis Score (Ph-CFS-F1), a continuous quantifier of the fibrosis phenotype.
- Additionally, local environment and architecture of every fiber ("Fiber Layers"), as well as the whole tissue phenotype is quantified (50x50micron tiles / "Tissue Layers") to generate a dataset of +160k histological quantitative parameters per biopsy. Supervised machine learning (FibroNest-Predict) extracted the histologic quantitative parameters that best predict regions of F1 a-b-c phenotypes in the biopsy and create an enhanced digital image to assist pathologists in their assessment.
- The accuracy of the predictive model is evaluated vs Pathologist assessment.

RESULTS

REPRESENTATIVE IMAGES AND FIBRONEST ANALYSES

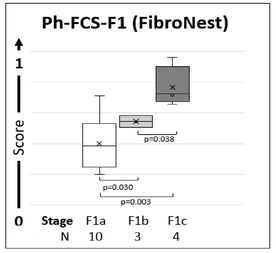


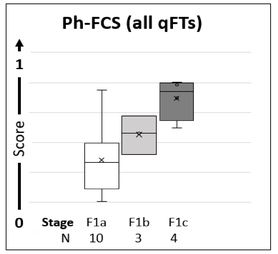
FIBROSIS PHENOTYPIC HEAT MAPS AND COMPOSITE SCORES



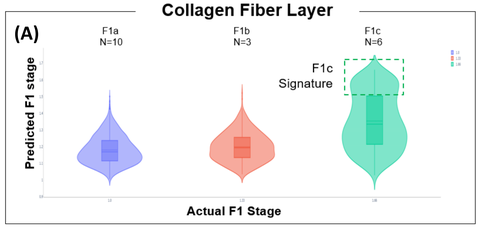
For each patient (column) the Phenotypic maps (above) visualizes the relative severity (green to red) of the quantitative fibrosis traits (qFTs) as quantified from the image, and automatically selected to account for variability between groups. The phenotypic map and enriched images can be used to assist pathologists for staging and reduce their Categorical Staging Incertitude.

The normalized quantitative traits values are combined to generate a phenotypic composite score (below). In order to optimize the specificity of the composite score for F1 Substages (Ph-FCS-F1, left), the qFTs from the "collagen" layer (general descriptors of collagen content and structure) where excluded (Ph-FCS, right for comparison), highlighting the fact that F1 substages are determined by subtle collagen structure and architectural differences.



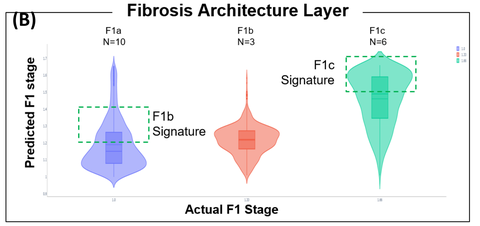


FIBRONEST-PREDICT PERFORMANCE AND OUTCOMES



Label	F1 a	F1 b	F1 c	Accuracy
F1 a	2133	95	100	0.9160
F1 b	497	51	34	0.0880
F1 c	562	17	585	0.50

Two machine learning (ML) models are developed to exploit the quantitative image analysis results related to collagen fibers (A) and fibrosis architecture (B). For each individual collagen fiber, 44 attributes are computed in relation to locality, morphometry, intensity, local texture and neighborhood. Approximately 10,000 adjacent square computational windows of 12 micron are used to compute 22 collagen texture (architecture) parameters in each image. The ML models are developed on 2 representative images from each group (and validated by the Ph-FCS-F1). The accuracy of the models is computed against the whole cohort.



Label	F1 a	F1 b	F1 c	Accuracy
F1 a	1783	246	299	0.7660
F1 b	263	294	25	0.51
F1 c	246	20	898	0.7710

While exploratory by design, the ML Models confirm that the fibrosis architecture phenotypes are the most useful to classify the substages of F1.

Conclusion

At low fibrosis stages, Quantitative Digital Pathology Image analysis and related data analytics methods can be used to generate automatic quantification methods (continuous scores or predictive AI) that can assist pathologists in the accurate classification of F1 substages.

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