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Machine Learning Fibrosis Models Based on Liver Histology Images Accurately Characterize the Heterogeneity of Cirrhosis Due to Nonalcoholic Steatohepatitis

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Introduction

- Nonalcoholic steatohepatitis (NASH) cirrhosis is characterized by heterogeneity in histology, clinical presentation, and prognosis[1]
- In patients with NASH, the presence of cirrhosis is associated with an increased risk of liver-related and all-cause mortality, but identification of those at risk for liver-related clinical events may be challenging[2-4]
- Although machine learning (ML) approaches have been used to evaluate liver histology in NASH,[5,6] the utility of these approaches to characterize fibrosis and risk stratify patients with cirrhosis requires evaluation

Objective

- To evaluate the utility of an ML approach trained on liver histologic images to illustrate the heterogeneity of fibrosis in NASH-related cirrhosis and to risk stratify affected patients

Methods

Study Population

- 674 adults with compensated cirrhosis (F4 according to NASH Clinical Research Network [CRN] classification) due to NASH who were enrolled in the Phase 3 STELLAR-4 trial of selonsertib (NCT01672879)

Liver Histology

- Liver fibrosis at baseline (BL) was staged by a central pathologist (Z.G.) according to NASH CRN and Ishak classifications
- Hepatic collagen content and α-smooth muscle actin (α-SMA) expression were quantified by morphometry

Noninvasive Tests (NITs) of Fibrosis

- Liver stiffness (LS) by transient elastography (TE; FibroScan® [Echosens, Paris, France]), FibroSure® (LabCorp, Burlington, NC)/FibroTest™ (BioPredictive S.A.S, Paris), nonalcoholic fatty liver disease fibrosis score (NFS), and Enhanced Liver Fibrosis Test (ELF™ [Siemens Healthcare GmbH, Erlangen, Germany]) score calculated at BL, with ELF based on serum tissue inhibitor of metalloproteinase-1 (TIMP-1), N-terminal propeptide of type III procollagen (PIII-NP), and hyaluronic acid (HA)

Serum Biochemical Parameters

- Liver biochemistry tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), and Model for End-Stage Liver Disease (MELD)

Liver-Related Clinical Events

- Hepatic decompensation (ascites, hepatic encephalopathy, and variceal hemorrhage), transplantation, MELD ≥15, and death were evaluated by an adjudication committee

Machine Learning Methods

- ML models based on convolutional neural networks with >20 layers and 8 million parameters (PathAI) were trained (n=642) and tested (n=165) on trichrome-stained images from patients screened for STELLAR-4
- ML models were trained to recognize patterns within fibrotic regions associated with each Ishak fibrosis stage using slide-level pathologist assessments of Ishak stage
- The final ML model was deployed on a separate set of trichrome images of BL biopsies from patients randomized in STELLAR-4 (n=674), associating each pixel to an Ishak fibrosis stage; associations were aggregated across the entire image, producing patient-specific scores by averaging the scores across all pixels

Statistical Analyses

- Associations between ML fibrosis scores and other histologic markers and NITs of fibrosis were evaluated using Spearman correlations (ρ)
- Associations between ML fibrosis scores and time to first liver-related clinical event were determined using Cox proportional hazards regression
- Discrimination of the ML fibrosis score for prediction of liver-related clinical events was described using the c-statistic

Results

Baseline Demographics and Clinical Characteristics*

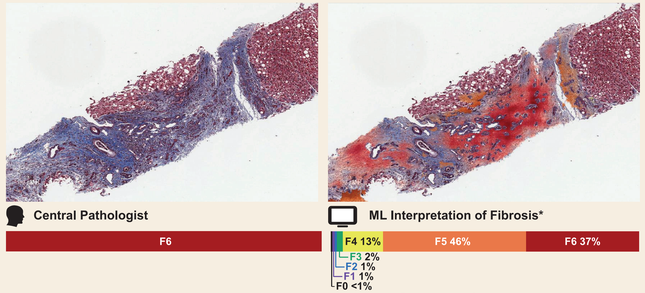
		Total: N=674
Demographics	Age, y	59 (53, 65)
	Female, n (%)	421 (62)
	Diabetes, n (%)	517 (77)
Liver Biochemistry	ALT, U/L	42 (31, 59)
	AST, U/L	44 (33, 61)
	GGT, U/L	83 (50, 139)
	Platelets, x10^3/mL	157 (124, 200)
	Bilirubin, mg/dL	0.6 (0.5, 0.9)
	Albumin, g/dL	4.4 (4.2, 4.6)
	MELD	7 (6, 8)
NITs of Fibrosis and Liver Histology	ELF	10.6 (10.0, 11.3)
	TIMP-1, ng/mL	302.5 (258.9, 368.9)
	PIII-NP, ng/mL	13.1 (9.8, 16.9)
	HA, ng/mL	137.6 (78.7, 239.0)
	FibroSure/FibroTest	0.58 (0.42, 0.74)
	Ishak fibrosis stage 6, n (%)	419 (62)
	Hepatic collagen content, %	10.7 (7.6, 14.7)
	α-SMA expression, %	13.0 (8.6, 19.2)

*Continuous data presented as median (quartile [Q] 1, Q3).

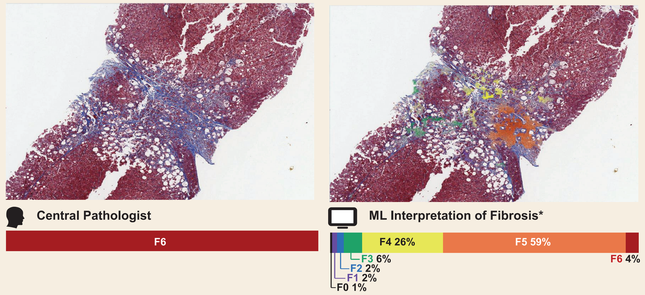
ML Models Quantified Fibrosis and Differentiated Fibrotic Patterns in NASH Cirrhosis

F0 F1 F2 F3 F4 F5 F6

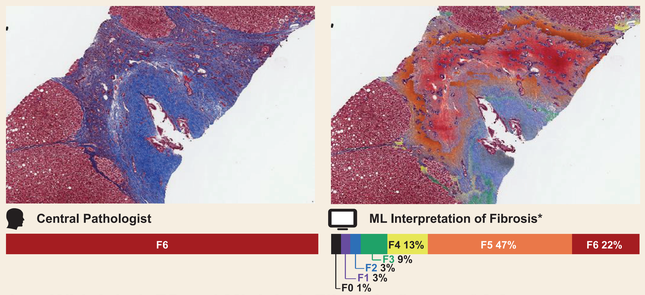
Patient With Ishak F6 and ML Ishak Fibrosis Score of 5.1



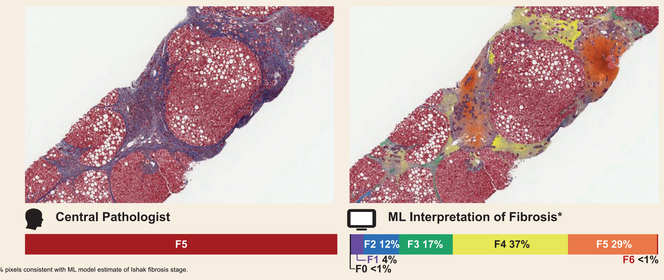
Patient With Ishak F6 and ML Ishak Fibrosis Score of 3.8



Patient With Ishak F6 and ML Ishak Fibrosis Score of 4.5



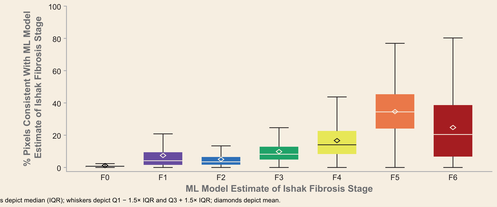
Patient With Ishak F5 and ML Ishak Fibrosis Score of 3.8



*% pixels consistent with ML model estimate of Ishak fibrosis stage.

- Aggregated ML Ishak fibrosis scores were widely distributed: median 4.5 (interquartile range [IQR] 4.0, 4.9)

ML Models Illustrated Heterogeneity of Fibrosis in Patients With Cirrhosis Due to NASH*



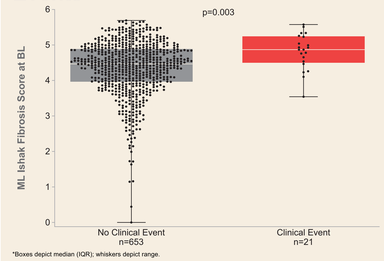
*Outliers not illustrated; boxes depict median (IQR); whiskers depict Q1 − 1.5× IQR and Q3 + 1.5× IQR; diamonds depict mean.

- While medians (IQR) of 20% (7%, 39%) of total pixels were consistent with Ishak F6 and 34% (24%, 45%) with F5 based on the ML models, 14% (8%, 23%), 8% (5%, 13%), 4% (2%, 7%), 4% (2%, 9%), and 0.3% (0.1%, 1.1%) were consistent with F4, F3, F2, F1, and F0, respectively

ML Ishak Fibrosis Score Was Correlated With Histology and NITs of Fibrosis

		Patients, n	Correlation (ρ)	p-Value
Liver Histology	Hepatic collagen content	627	0.36	<0.001
	α-SMA expression	618	0.31	<0.001
NITs	LS by TE	531	0.30	<0.001
	ELF	674	0.27	<0.001
	TIMP-1	674	0.22	<0.001
	PIII-NP	674	0.23	<0.001
	HA	674	0.24	<0.001
	FibroSure/FibroTest	674	0.2	<0.001
	NFS	672	0.27	<0.001
Other Markers	AST	674	0.06	0.11
	Platelets	673	-0.25	<0.001

ML Fibrosis Scores at BL Predicted Time to Liver-Related Clinical Events*



*Boxes depict median (IQR); whiskers depict range.

- During a median follow-up of 13.8 mo, 21 patients (3%) had liver-related clinical events: ascites (n=10), encephalopathy (n=7), portal hypertension-related bleeding (n=2), and qualification for transplantation (n=2)
- Median ML Ishak fibrosis score at BL was significantly higher in patients with vs without events (4.9 vs 4.5; p=0.005)
- ML Ishak fibrosis score was significantly associated with time to first clinical event (hazard ratio 3.2 [95% confidence interval 1.4, 7.1]; p=0.005) and had acceptable discrimination for events (c-statistic 0.67 [95% confidence interval 0.53, 0.80])

Conclusions

- ML models trained on images of trichrome-stained liver biopsy slides illustrated the heterogeneity of fibrosis in patients with cirrhosis due to NASH
- Although ML fibrosis scores demonstrated modest correlations with other histologic and noninvasive markers of fibrosis, they could facilitate risk stratification of patients with cirrhosis
- These data highlight the potential of ML models to characterize fibrosis in patients with cirrhosis beyond conventional histologic staging and to do so in an automated fashion
- The utility of ML learning approaches to monitor changes in fibrosis in patients with cirrhosis due to NASH (eg, due to therapeutic intervention) requires further study

References: 1. Sanyal AJ, et al. Hepatology 2019;Apr 16 [Epub ahead of print]; 2. Angulo P, et al. Gastroenterology 2015;149:389-97; 3. Ekstedt M, et al. Hepatology 2015;61:1547-54; 4. Younossi ZM, et al. Hepatology 2011;53:1874-82; 5. Pokkalla H, et al. AASLD 2019, abstr 0187; 6. Vanderbeck S, et al. Hum Pathol 2015;46:767-75. **Acknowledgments:** We extend our thanks to the patients and their families. This study was funded by Gilead Sciences, Inc.

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