FRI173

Machine Learning Models Accurately Interpret Liver Histology and Are Associated With Disease Progression in Patients With Primary Sclerosing Cholangitis

Nathaniel Travis,[1] Vincent Billaut,[1] Harsha Pokkalla,[1] Kishalve Pethia,[1] Oscar Carrasco-Zevallos,[1] Benjamin Glass,[1] Amaro Taylor-Weiner,[1] Christopher L. Bowlus,[2] Atsushi Tanaka,[3] Douglas Thorburn,[4] Xiaomin Lu,[5] Ryan Huss,[5] Chuhan Chung,[5] G. Mani Subramanian,[5] Robert P. Myers,[5] Andrew J. Muir,[6] Kris V. Kowdley,[7] Zachary Goodman,[8] Aditya Khosla,[1] Andrew Beck,[1] Murray Resnick,[1] Ilan Wapinski,[1] Michael H. Trauner,[9] Cynthia Levy[10]

[1]PathAI, Inc., Boston, Massachusetts, USA; [2]University of California, Davis, USA; [3]Teikyo University School of Medicine, Tokyo, Japan; [4]UCL Institute for Liver & Digestive Health, Royal Free Hospital, London, UK; [5]Gilead Sciences, Inc., Foster City, California; [6]Duke Clinical Research Institute, Durham, North Carolina, USA; [7]Inova Fairfax Hospital, Falls Church, Virginia, USA; [8]Liver Institute Northwest, Seattle, Washington, USA; [9]Medical University of Vienna, Austria; [10]University of Miami, Coral Gables, Florida, USA

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, California, USA 94404
800-445-3235

Introduction

- Primary sclerosing cholangitis (PSC) is a chronic fibrosing cholangiopathy marked by heterogeneous clinical presentation[1,2]
- Fibrosis progression is the primary histologic endpoint in two Phase 3 clinical trials of PSC (ClinicalTrials.gov NCT03872921 and NCT03890120)
- Current histologic staging systems for PSC, including the Nakanuma classification, are predictive of clinical events, but have only fair interobserver agreement and may require specialized staining procedures[3]
- Variability in histologic evaluation in patients with PSC may hinder disease staging and confound clinical trial results

Objectives

- To develop machine learning (ML) models for evaluation of liver histology in PSC
- To determine associations between ML-based histologic parameters and noninvasive markers of fibrosis, cholestasis, and clinical events

Methods

Study Population and Assessments

- Patients with PSC (N=141) from a 96-wk, Phase 2 study of simtuzumab, a monoclonal antibody directed against lysyl oxidase-like-2 (NCT01672853)

CP
- Fibrosis was staged at baseline, and Weeks 48 and 96 by a central pathologist (CP) according to Ishak classification using trichrome (TC)–stained slides

- Other assessments:
  - Liver biochemistry tests (serum alkaline phosphatase [ALP], alanine aminotransferase [ALT], and γ-glutamyltransferase [GGT])
  - Enhanced Liver Fibrosis (ELF™ [Siemens Healthcare GmbH, Erlangen, Germany]) score

ML

Machine Learning Assessment of Histology

- An ML platform (PathAI, Inc., Boston, Massachusetts, USA) based on an annotation-based platform and convolutional neural networks (CNNs; >20 layers and 8 million parameters) developed for nonalcoholic steatohepatitis[4] was used to assess PSC histology
- The annotation-based platform was trained using 44,000 annotations (eg, fibrosis, lobular/portal/interface inflammation, and bile ducts/ductules) from 29 board-certified pathologists on images from 252 hematoxylin and eosin (H&E)–, 254 TC-, and 330 picrosirius red (PSR)–stained slides; the model was trained to recognize and summarize these features at the whole-slide level
- CNNs were deployed on images of TC- and PSR-stained slides using slide-level Ishak stages to recognize patterns associated with each fibrosis stage; these region-based scores were used to generate a slide-level ML Ishak fibrosis score

Statistical Analyses

- Correlations between slide-level score and CP-derived fibrosis stage were evaluated on test images excluded from model training (77 TC and 88 PSR), and associations between ML-derived features with clinical parameters, PSC-related events (eg, decompensation, cholangitis, and transplantation), and progression to cirrhosis at Weeks 48 and/or 96 were determined

Results

Baseline Demographics and Characteristics*

Total Population

			N=141
Demographics	Age, y (range)		45 (18–68)
	Race	European descent	117 (83)
		African-American	19 (14)
		Other	5 (4)
	Women		51 (36)
	BMI, kg/m²		26 (23, 29)
Liver Biochemistry	ALT, U/L		64 (35, 111)
	ALP, U/L		259 (126, 420)
	GGT, U/L		281 (94, 564)
Ishak Fibrosis Stage	F0–2		67 (48)
	F3–4		54 (38)
	F5–6		20 (14)

*Data are median (interquartile range [IQR]) or n (%), unless otherwise specified. BMI, body mass index.

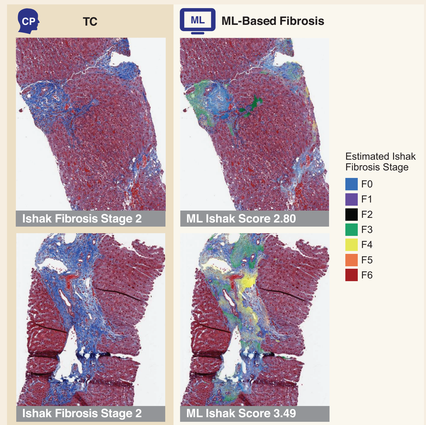
Baseline Demographics and Characteristics*

Training and Validation Sets

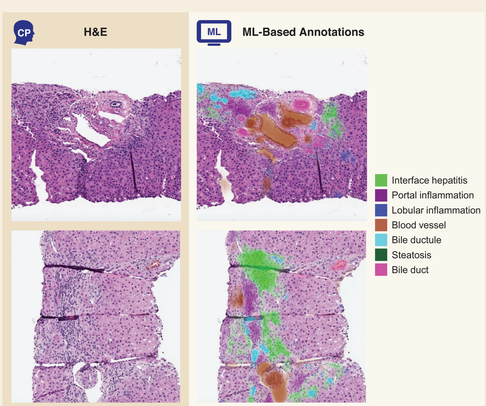
		Training Set n=110	Validation Set n=31	p-Value
Demographics	Age, y	45 (38, 52)	46 (37, 54)	0.77
	Race			
	White	91 (83)	26 (84)	0.67
	African-American	14 (13)	5 (16)	
	Women	39 (36)	12 (39)	0.83
	BMI, kg/m²	26 (23, 29)	26 (25, 30)	0.42
	Inflammatory bowel disease	70 (64)	17 (55)	0.41
	UDCA use	58 (53)	19 (61)	0.42
Liver Biochemistry	ALT, U/L	63 (35, 122)	66 (34, 82)	0.47
	ALP, U/L	266 (125, 455)	250 (126, 367)	0.99
	GGT, U/L	283 (83, 564)	276 (137, 643)	0.72
	ELF	9.5 (8.8, 10.5)	9.5 (8.4, 10.7)	0.68
Ishak Fibrosis Stage	F0–2	49 (45)	18 (58)	0.25
	F3–4	46 (42)	8 (26)	
	F5–6	15 (14)	5 (16)	

*Data are median (IQR) or n (%), unless otherwise specified. UDCA, ursodeoxycholic acid.

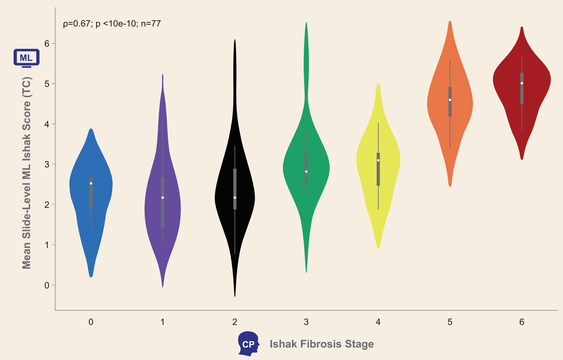
ML-Based Model for PSC-Related Fibrosis



ML-Based Annotation Models for Nonfibrotic Histologic Features in PSC

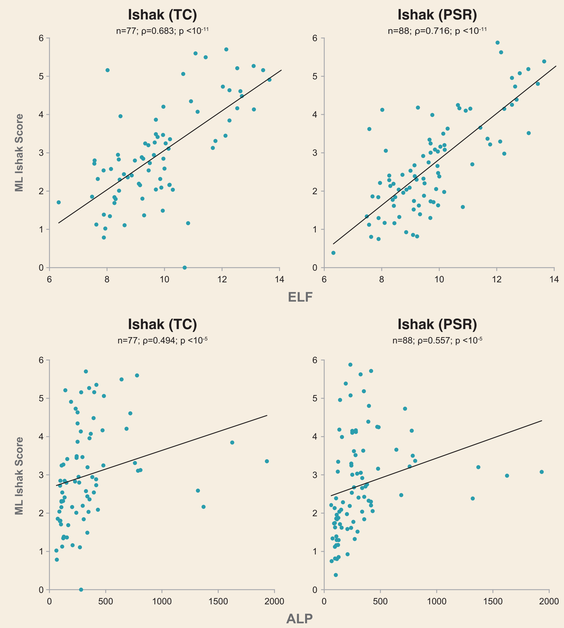


Association Between ML Ishak Score and CP-Based Ishak Fibrosis Stage



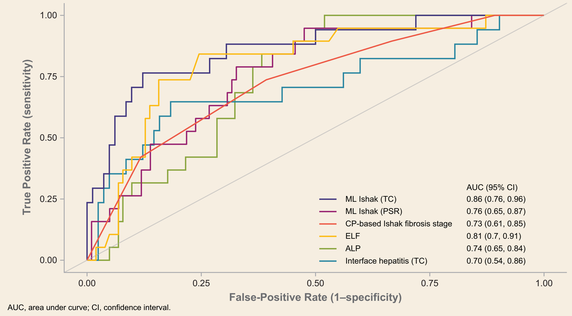
- ML Ishak scores significantly correlated with Ishak stage scored by a CP

Associations Between ML Ishak Score and ELF and Serum ALP



- ML Ishak scores based on both TC- and PSR-stained biopsies were significantly associated with ELF and serum ALP

Discrimination of ML-Based and Other Parameters for Progression to Cirrhosis at Weeks 48/96

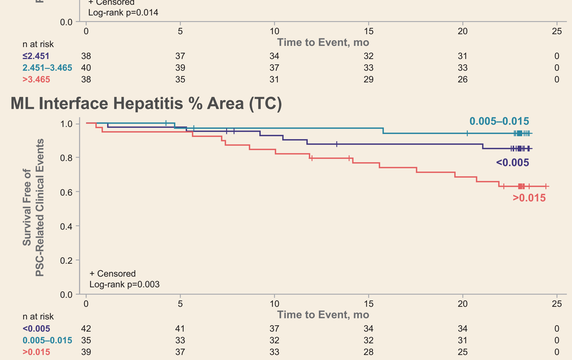


AUC, area under curve; CI, confidence interval.

- 19/121 patients (16%) progressed to cirrhosis
- Baseline ML fibrosis score was predictive of progression to cirrhosis at Weeks 48/96

Associations Between ML-Based Parameters at Baseline and PSC-Related Clinical Events*

ML Ishak Score (TC)



ML Interface Hepatitis % Area (TC)

*Log-rank test assessed clinical events among 3 tertiles of ML fibrosis and 3 tertiles of interface hepatitis score; hazard ratio (HR) from Cox proportional hazard model for PSC-related clinical event-free survival.

- Over a median follow-up of 23 mo (IQR 18.9, 23.1), 21% of patients (29/141) developed a PSC-related event
- Events were associated with higher ML Ishak fibrosis score at baseline (HR per unit: 1.74 [95% CI 1.18, 2.59]) and greater area of interface hepatitis (HR per 1%: 1.39 [95% CI 1.14, 1.70]), both on TC images

Conclusions

- ML models demonstrated high concordance with pathologist assessment of PSC-related fibrosis
- ML-derived measurements of fibrosis and interface hepatitis were associated with risk of PSC-related clinical events
- These data highlight the potential of ML for automated and quantitative assessment of liver histology and risk stratification in PSC

References: **1.** Eaton JE, et al. Gastroenterology 2013;145;3:521-36; **2.** Lazaridis KN, LaRusso NF. N Engl J Med 2016;22;375:1161-70; **3.** DeVries EM, et al. Hepatology 2017;65;3:907-19; **4.** Pokkalla H, et al. AASLD 2019, abstr 187. **Acknowledgments:** We extend our thanks to the patients and their families. This study was funded by Gilead Sciences, Inc.

Presented at The Digital International Liver Congress, 27–29 August 2020