LBP31

Machine Learning Identifies Histologic Features Associated With Regression of Cirrhosis in Treatment for Chronic Hepatitis B

Dinkar Juyal,[1] Chinmay Shukla,[1] Harsha Pokkalla,[1] Amaro Taylor-Weiner,[1] Oscar M. Carrasco-Zevallos,[1] Murray Resnick,[1] Michael Montalto,[1] Andrew Beck,[1] Ilan Wapinski,[1] Patrick Marcellin,[2] John F. Flaherty,[3] Vithika Suri,[3] Anuj Gaggar,[3] G. Mani Subramanian,[3] Ira Jacobson,[4] Edward Gane,[5] Maria Buti[6]

[1]PathAI, Inc., Boston, Massachusetts, USA; [2]Hôpital Beaujon AP-HP, Clichy, France; [3]Gilead Sciences, Inc., Foster City, California, USA; [4]NYU Langone Health, New York, New York, USA; [5]Auckland Clinical Studies, Auckland, New Zealand; [6]Hospital Vall d'Hebron and Centro de Investigación Biomédica en Red en el Área temática de Enfermedades Hepáticas y Digestivas, Barcelona, Spain

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

Introduction

- Hepatitis B virus (HBV) infection is associated with progression to cirrhosis, development of hepatocellular carcinoma, and liver-related mortality[1]
- Although most patients with HBV on suppressive antiviral therapy achieve regression of cirrhosis, a subset do not; histologic features associated with regression of cirrhosis are not well understood[2]
- Image analysis methods have been applied to evaluate liver histology in HBV[3,4]; a machine learning (ML) approach leveraging convolutional neural networks (CNNs) could facilitate characterization of histologic features associated with regression of cirrhosis

Objectives

- To develop ML models for interpreting HBV histology and to evaluate the association of ML-derived scores with regression of cirrhosis

Methods

Study Population

- Liver biopsies were collected from 330 patients enrolled in registrational studies for tenofovir disoproxil fumarate for HBV infection (ClinicalTrials.gov GS-US-174-0102 and GS-US-174-0103)
  - ML models were developed using digital histologic images of hematoxylin and eosin (H&E)– and trichrome-stained slides

Liver Histology[2]

- Histology was assessed by a central pathologist (CP) at baseline (BL), and Years 1 and 5 according to Ishak/Knodell necroinflammatory scoring and Ishak fibrosis staging systems
  - Patients were assessed for regression of cirrhosis, regression of fibrosis, and histologic improvement (≥2-point decrease in Knodell necroinflammatory score and no worsening in fibrosis stage)

ML Assessment of Liver Histology[5,6]

- CNNs with >20 layers and 8 million parameters (PathAI, Inc., Boston, Massachusetts, USA) were developed using H&E and trichrome images (training set: 1090 images from 172 patients), and annotations from 40 board-certified pathologists
- CNNs for H&E images were trained to identify inflamed regions (portal, lobular, and interface inflammation), immune cells (lymphocytes and plasma cells), and features of nonalcoholic fatty liver disease (NAFLD; steatosis and ballooning)
  - Image-level ML scores summarizing histologic features were computed
- CNNs for trichrome images were trained to recognize fibrosis patterns associated with Ishak stage using slide-level pathologist assessments of Ishak stage
  - Image-level ML Ishak scores were derived by computing the weighted average of ML-derived Ishak stages present on the image

Statistical Analyses

- Correlations (Spearman ρ) of ML scores with CP scores were evaluated on test set data from 123 patients (368 H&E and 369 trichrome images across all time points)
- Associations of ML scores with cirrhosis regression were evaluated on test set data from 30 patients with cirrhosis at BL and H&E/trichrome images available for all study time points

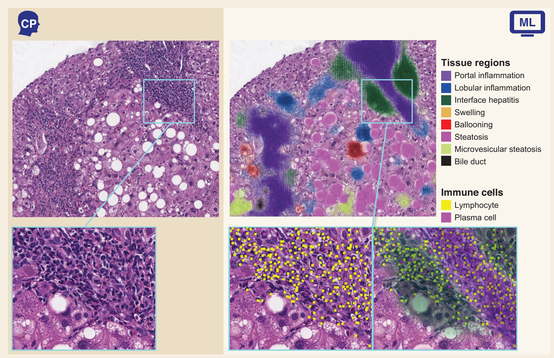
Results

Baseline Demographics

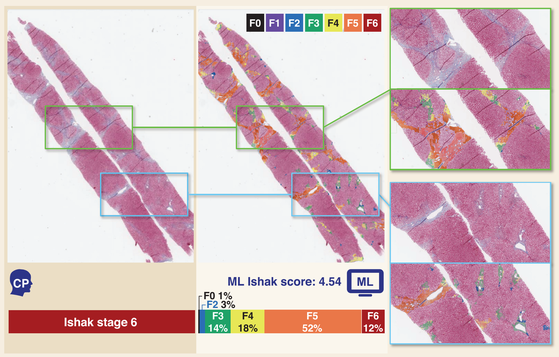
	Total N=123	Patients Without Cirrhosis Regression at Year 5 n=8	Patients With Cirrhosis Regression at Year 5 n=22
Age ≥50 y, n (%)	29 (24)	4 (50)	9 (41)
Men, n (%)	101 (82)	7 (88)	22 (100)
Mean ALT, U/L (SD)	125.46 (89.57)	157.53 (115.34)	101.23 (57.64)
Mean HBV DNA, $\log_{10}$ IU/mL (SD)	6.58 (1.28)	6.01 (1.20)	6.77 (1.19)
HBV genotype, n (%)			
A	28 (23)	3 (38)	8 (36)
B	9 (7)	1 (13)	1 (5)
C	17 (14)	0	4 (18)
D	66 (54)	4 (50)	8 (36)
E	3 (2)	0	1 (5)
HBeAg positive, n (%)	46 (37)	2 (25)	11 (50)
Median Knodell necroinflammatory score (SD)	9 (2.36)	9 (1.41)	9 (1.13)
Cirrhosis, n (%)	30 (25)		
Ishak 5	8 (7)	1 (13)	7 (32)
Ishak 6	22 (18)	7 (88)	15 (68)

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; SD, standard deviation.

ML H&E Model Detected Features of Inflammation and NAFLD



ML Trichrome Model Revealed Distinct Fibrosis Patterns Associated With Ishak Stage



Associations Between ML and Pathologist Scores of Inflammation and Fibrosis

ML Scores	CP Ishak HAI scores	ρ (all p <0.001)
Portal inflammation % area	Portal inflammation	0.64
Lobular inflammation % area	Lobular necrosis	0.60
Interface hepatitis % area	Periportal necrosis	0.71
ML Ishak fibrosis score	Fibrosis stage	0.57

HAI, histology activity index.

- ML-derived scores were significantly correlated with corresponding CP scores on 368 H&E and 369 trichrome images from 123 patients in the test set

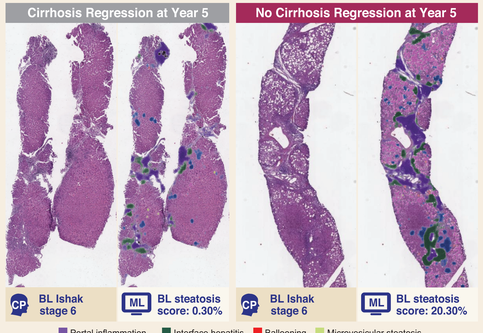
Association of ML Scores With Regression of Cirrhosis*

Median (IQR)	Patients With Cirrhosis Regression at Year 5 n=22	Patients Without Cirrhosis Regression at Year 5 n=8	p-Value
Baseline ML inflammation and NAFLD scores (% area; H&E images)			
Steatosis	0.38 (1.29)	5.52 (11.28)	**0.003**
Changes from BL to Year 5 in ML inflammation and NAFLD scores (% area; H&E images)			
Portal inflammation	-4.24 (3.00)	-2.58 (2.66)	**0.023**
Steatosis	-0.07 (0.55)	-1.51 (4.88)	0.09
Bile duct	-0.08 (0.29)	0.06 (0.24)	0.09
Lymphocyte density	-314.87 (494.48)	-12.69 (366.66)	0.06
Changes from BL to Year 5 in ML fibrosis scores (trichrome images)			
ML Ishak score	-1.46 (1.32)	-0.61 (0.65)	**0.021**
% area of fibrosis	-4.98 (5.32)	-0.74 (5.01)	**0.007**

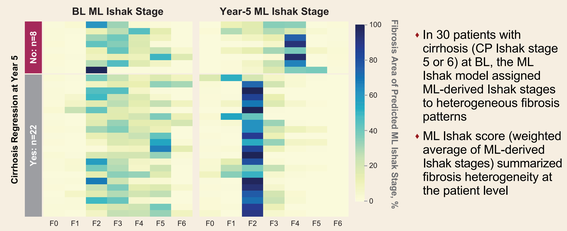
*p <0.10 included in table; *bold*; p <0.05; ML scores with p ≥0.10 were interface hepatitis, lobular inflammation, hepatocellular ballooning, microvesicular steatosis, and plasma cell density. IQR, interquartile range.

- At BL, patients who achieved cirrhosis regression had significantly lower % area of steatosis compared with those without cirrhosis regression at Year 5
- From BL to Year 5, patients who achieved cirrhosis regression had significantly greater reductions in portal inflammation, ML Ishak score, and fibrosis % area

ML Steatosis Score at BL Was Associated With Regression of Cirrhosis at Year 5

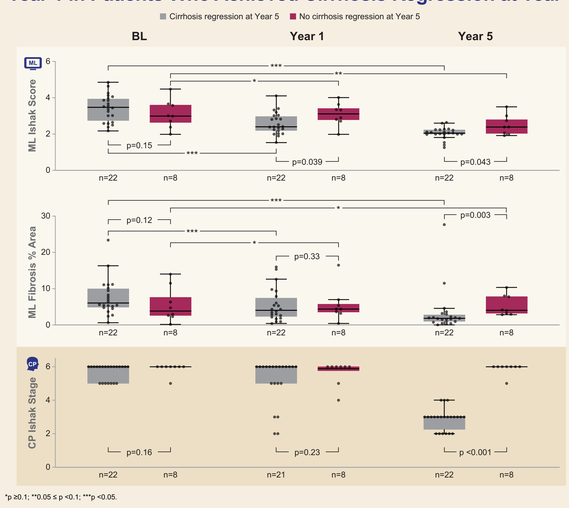


ML Model Quantified Change From BL of Fibrosis Heterogeneity



- In 30 patients with cirrhosis (CP Ishak stage 5 or 6) at BL, the ML Ishak model assigned ML-derived Ishak stages to heterogeneous fibrosis patterns
- ML Ishak score (weighted average of ML-derived Ishak stages) summarized fibrosis heterogeneity at the patient level

ML Ishak Score Revealed Significant Fibrosis Regression at Year 1 in Patients Who Achieved Cirrhosis Regression at Year 5



*p ≥0.1; **0.05 ≤ p <0.1; ***p <0.05.

- At BL, ML Ishak score, ML fibrosis % area, and CP Ishak stage were similar for patients who did and did not achieve cirrhosis regression at Year 5
- At Year 1, patients who achieved cirrhosis regression had significantly lower ML Ishak scores, but similar ML fibrosis % areas and CP Ishak stages compared with those who did not achieve cirrhosis regression
- At Year 5, patients who achieved cirrhosis regression had significantly lower ML Ishak scores and ML fibrosis % areas compared with those who did not achieve cirrhosis regression

Conclusions

- An ML approach quantified histopathologic features from clinical trial biopsies from patients under antiviral treatment
- Greater ML steatosis score at BL was associated with lack of cirrhosis regression at Year 5
- ML Ishak score quantified fibrosis heterogeneity and revealed earlier onset of fibrosis regression compared with manual staging of fibrosis and measures of total collagen deposition (eg, ML fibrosis % area)
- An ML approach for evaluating liver histology in patients with HBV can provide mechanistic insight into both HBV pathogenesis and cirrhosis regression

References: **1.** Mittal S, et al. J Clin Gastroenterol. 2013;47:S2-6; **2.** Marcellin P, et al. Lancet 2013;381:468-75; **3.** Forlano R, et al. Clin Gastroenterol Hepatol 2020 [in press]; **4.** Wang B, et al. Mod Pathol 2018;31:1567-77; **5.** Pokkalla H, et al. AASLD 2019; abstr 0187; **6.** Younossi ZM, et al. AASLD 2019; abstr 1718.

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