1471

A Machine Learning Model Based on Liver Histology Predicts the Hepatic Venous Pressure Gradient in Patients With Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis

Jaime Bosch,[1] Stephen A. Harrison,[2] Manal F. Abdelmalek,[3] Mitchell L. Shiffman,[4] Don C. Rockey,[5] Dinkar Juyal,[6] Zahil Shanis,[6] Harsha Pokkalla,[6] Chinmay Shukla,[6] Oscar M. Carrasco-Zevallos,[6] Murray Resnick,[6] Michael Montalto,[6] Andrew Beck,[6] Ilan Wapinski,[6] Catherine Jia,[7] Chuhan Chung,[7] Robert P. Myers,[7] Zachary Goodman,[8] Nezam Afdhal,[9] Arun J. Sanyal[10]

[1]Inselspital, Bern University, Bern, Switzerland, and University of Barcelona-IDIBAPS, Spain; [2]Pinnacle Clinical Research, San Antonio, TX; [3]Duke Clinical Research Institute, Durham, NC; [4]Bon Secours Liver Institute of Richmond, VA; [5]Medical University of South Carolina, Charleston; [6]PathAI, Inc., Boston, MA; [7]Gilead Sciences, Inc., Foster City, CA; [8]Inova Fairfax Hospital, Falls Church, VA; [9]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston; [10]Virginia Commonwealth University, Richmond

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

Introduction

- The hepatic venous pressure gradient (HVPG) reliably measures portal pressure, including the presence of clinically significant portal hypertension (CSPH; HVPG ≥10 mm Hg)[1]
- CSPH is associated with an increased risk of hepatic decompensation and mortality[2,3]
- Measurement and interpretation of HVPG require expertise, with up to 30% of HVPG readings deemed inaccurate[4]
- We previously utilized a machine learning (ML) research platform (PathAI, Inc., Boston, MA) to quantify fibrosis and other histologic features of nonalcoholic steatohepatitis (NASH), and characterize the heterogeneity of fibrosis in patients with cirrhosis[5-7]

Objectives

- To explore whether HVPG can be estimated using an ML-based algorithm based on liver histology alone
- To determine associations between an ML-based HVPG score and centrally read HVPG measurements
- To assess the performance of an ML HVPG score, hepatic collagen content by morphometry, and the Enhanced Liver Fibrosis test (ELF™; Siemens Healthcare GmbH, Erlangen, Germany) in detecting CSPH and predicting liver-related clinical events in patients with compensated cirrhosis due to NASH

Methods

Study Population

- Adults with compensated cirrhosis (Ishak stages 5–6) due to NASH from a Phase 2b trial of simtuzumab (NCT01672879)[8]
- Simtuzumab was ineffective; thus, treatment groups were combined for this analysis

Standard Histology

- Fibrosis was staged according to Ishak classification by a central pathologist and hepatic collagen content was measured by morphometry on Picrosirius red-stained biopsies
- HVPG was measured according to a standardized protocol, and reviewed centrally at baseline (BL), and Weeks 48 and 96

ML Assessment of Liver Histology (PathAI)

- Images of trichrome-stained biopsies (training set: n=320 slides; n=276 HVPG measurements) were used to develop an "end-to-end" ML model to recognize fibrosis patterns associated with HVPG measurements in 6 clinically relevant bins (0–5, 5.5–9.5, 10–11.5, 12–15.5, 16–19.5, and ≥20 mm Hg)
  - The ML HVPG model assigned each image pixel to an HVPG bin and image-level HVPG scores were computed by averaging pixel-level bins across each image
- For quantification of nonalcoholic fatty liver disease activity score (NAS) and other features, a deep convolutional neural network was trained based on annotations collected from 75 board-certified pathologists on images of hematoxylin and eosin (H&E)–stained slides to produce pixel-level predictions of each feature[5-7]
  - Human identifiable features (HIFs) reflecting proportionate areas of steatosis, and lobular and portal inflammation were included in this study
- The ML models were applied to a test set (n=216 slides; n=181 HVPG measurements) excluded from model training

Statistical Analyses

- Associations between measured (true) HVPG with ML HVPG score and other parameters were evaluated using Spearman correlations (from all study time points) and Mann-Whitney U tests
- Performance of ML HVPG score and other parameters for predicting CSPH was determined using logistic regression models and area under receiver operating characteristic (AUROC) curves
- Associations of ML HVPG score and measured HVPG (at BL and changes over time) with liver-related clinical events (eg, hepatic decompensation, transplantation, qualification for transplantation, and death) were evaluated using log-rank tests and Cox regression models, and discrimination was evaluated using c-statistics

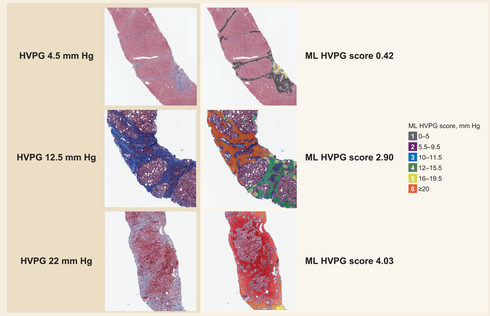
Results

Baseline Demographics and Clinical Data

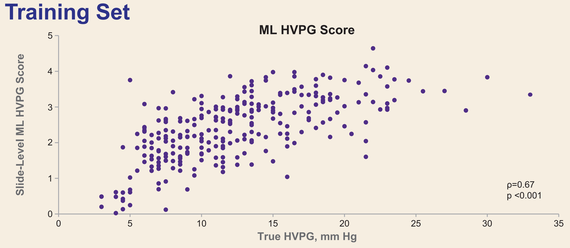
		Training Set n=130; 320 slides	Test Set n=88; 216 slides	p-Value
Demographics and Concomitant Medications	Age, y	56 (50, 60)	58 (53, 62)	0.11
	White	121 (93)	83/88 (94)	0.79
	Hispanic	21 (16)	14/88 (16)	1.00
	Women	76 (58)	60/88 (68)	0.16
	BMI, kg/m²	33.11 (29.91, 38.63)	35.02 (30.11, 39.17)	0.54
	β-blocker therapy	20 (15)	13 (15)	1.00
Liver Biochemistry	ALT, U/L	36 (27, 50)	35 (24, 47)	0.42
	Albumin, g/dL	3.9 (3.7, 4.2)	3.7 (3.5, 4.1)	0.018
	Total bilirubin, mg/dL	0.7 (0.4, 1.1)	0.6 (0.5, 1.0)	0.54
	Platelets, x10³/µL	138 (97, 191)	151 (96, 192)	0.49
	ELF™	10.82 (9.91, 11.48)	10.65 (9.92, 11.52)	0.86
	MELD	7 (6, 8)	7 (6, 8)	0.08
Ishak Fibrosis Stage and HVPG	F5	37/128 (29)	23/87 (26)	0.39
	F6	77/128 (60)	57/87 (66)	
	Hepatic collagen content, %	11.15 (7.80, 17.40)	14.25 (7.80, 20.10)	0.10
	HVPG, mm Hg	12.0 (8.5, 16.0)	12.0 (8.5, 16.0)	0.99
	CSPH (HVPG ≥10 mm Hg)	72 (67)	48 (69)	1.00

Data are median (interquartile range [IQR]) or n (%). ALT, alanine aminotransferase; BMI, body mass index; MELD, Model for End-Stage Liver Disease score.

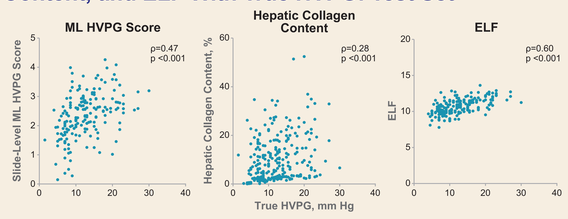
ML-Based Models for Annotating HVPG on Trichrome Slides



Correlation Between ML HVPG Score and True HVPG: Training Set

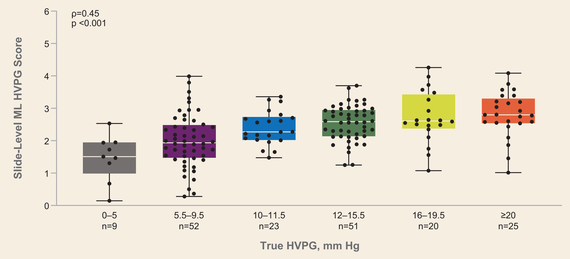


Correlations of ML HVPG Score, Hepatic Collagen Content, and ELF With True HVPG: Test Set

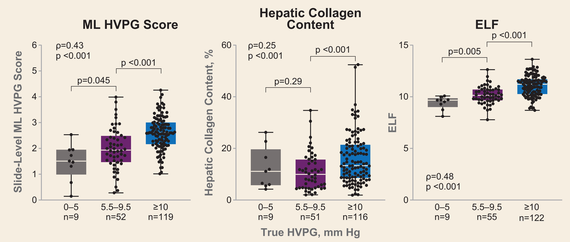


- ML HVPG score and ELF were more strongly correlated with true HVPG than hepatic collagen content by morphometry

Association Between ML HVPG Score and True HVPG: Test Set



Associations of ML HVPG Score, Hepatic Collagen Content, and ELF With True HVPG: Test Set



- ML HVPG score and ELF had higher correlations with true HVPG than hepatic collagen content by morphometry

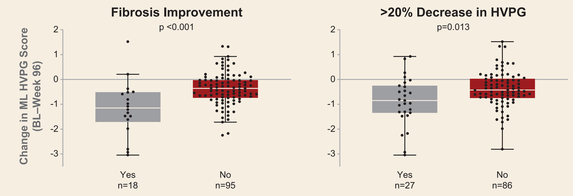
Discrimination of ML HVPG and Other Parameters for CSPH

	Training Set		Test Set			
Predictors*	No. of Images	AUROC	No. of Images	AUROC	PPV	NPV
ML HVPG	**231**	**0.838**	**161**	**0.757**	**0.782**	**0.667**
ELF	231	0.855	161	0.787	0.789	0.596
Hepatic collagen content	231	0.639	161	0.673	0.717	0.652
ML HVPG + H&E HIFs	231	0.849	161	0.797	0.835	0.692
ML HVPG + H&E HIFs + ELF	**231**	**0.902**	**161**	**0.844**	**0.866**	**0.603**

*HIFs based on ML models on H&E-stained slides (portal and lobular inflammation, and steatosis). Positive predictive value (PPV) and negative predictive value (NPV) determined at 0.5 cutoff according to logistic regression models including each marker. Cutoffs for ELF and hepatic collagen content were ±10.17 and ±5.21%, respectively.

- ML HVPG score had good discrimination for CSPH (AUROC 0.757 in test set)
  - Performance was not affected by β-blocker therapy (AUROC in patients on vs not on β-blockers at BL: 0.656 vs 0.775; p=0.55)
- Detection of CSPH with ML HVPG was improved by the addition of ELF and other ML-based histologic features (AUROC 0.844 in test set)

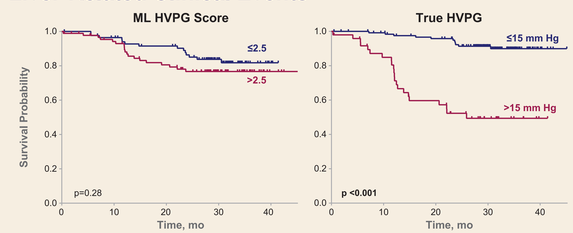
Associations Between Changes in ML HVPG Score and Improvements in Fibrosis and HVPG Between BL and Week 96*



*Analyses include training and test sets.

- ML HVPG score improved with fibrosis regression and >20% decrease in HVPG between BL and Week 96
- Although changes in ML HVPG score and true HVPG between BL and Week 96 were correlated (ρ=0.24; p=0.012), changes in true HVPG were not associated with fibrosis improvement (median [IQR] change with vs without improvement: 0.5 [-2.5, 2.0] vs 0 [-2.0, 2.0] mm Hg; p=0.93)

Association of ML HVPG Score and True HVPG With Liver-Related Clinical Events*



	Hazard Ratio (95% CI)	p-Value
ML HVPG score (BL), per unit	1.349 (0.836, 2.178)	0.22
Change from BL, per 1-unit increase	2.129 (1.264, 3.585)	0.005
True HVPG (BL), per mm Hg	1.181 (1.107, 1.261)	<0.001
Change from BL, per 1-mm Hg increase	1.133 (1.052, 1.219)	<0.001

Hazard Ratio (95% CI)

*Cutoffs for ML HVPG score and true HVPG based on maximal sum of sensitivity and specificity for discrimination of clinical events; analyses include training and test sets; models for change from BL adjusted for BL value. CI, confidence interval.

- During a median follow-up of 31.0 mo (IQR 27.9, 35.0), 33/176 patients (19%) in the training and test sets had liver-related clinical events
- Discrimination for events was greater for true HVPG than ML HVPG score at BL (c-statistics 0.705 vs 0.558; p=0.036)
- At BL, true HVPG, but not ML HVPG score, was significantly associated with clinical events, whereas increases from BL in both parameters were associated with increased risk of events

Conclusions

- ML models based on liver biopsy alone demonstrated good concordance with actual HVPG measurements and were superior to hepatic collagen content by morphometry for the detection of CSPH
- ML HVPG score combined with ELF and other ML-based histologic features had excellent discrimination for CSPH
- ML HVPG score improved in patients with fibrosis regression and reductions in HVPG
- ML HVPG score at BL was inferior to conventional HVPG measurement for prediction of liver-related clinical events, but changes in both parameters were prognostic
- These data highlight the potential of the ML HVPG score to identify CSPH in NASH patients with cirrhosis based on liver biopsy alone, but suggest that other factors that influence portal hypertension (eg, vascular features) should be evaluated using this approach, particularly for risk stratification

References: **1.** Bosch J, et al. J Hepatol 2015;62:S121-30; **2.** Feu F, et al. Lancet 1995;346:1056-9; **3.** Silva-Junior G, et al. Hepatology 2015;62:1584-92; **4.** Groszmann RJ, et al. Hepatology 2004;39:280-3; **5.** Pokkalla H, et al. AASLD 2019, abstr 187; **6.** Pokkalla H, et al. EASL 2020, abstr FRI1003; **7.** Younossi ZM, et al. AASLD 2019, abstr 1718; **8.** Harrison SA, et al. Gastroenterology 2018;155:1140-53.

Acknowledgments: We extend our thanks to the patients, their families, and participating investigators. This study was funded by Gilead Sciences, Inc.

Disclosures: **J. Bosch** and **N. Afdhal:** nothing to disclose; **S.A. Harrison:** Gilead, Akero, Altimmune, Arrowhead, Camfile, Cirius, CiVi, CymaBay, Echosens, Enyo, Foresite, Fortress, Galectin, Genfit, Hepion, HighTide, HistoIndex, Intercept, Kowa, Liminal, Madrigal, Medpace, Metacrine, NGM, NorthSea, Novartis, Novo Nordisk, Poxel, Ridgeline, Sagimet, Terns, Viking; **M.F. Abdelmalek:** AbbVie, Alexion, AstraZeneca, BMS, Celgene, Clinical Care Options, Durect, Fishawack, Galmed, Genfit, Hanmi, Intercept, Inventiva, Madrigal, MedScape, NGM, Novartis, Novo Nordisk, Poxel, Progenity, Promethera, TaiwanJ, TARGET-NASH, Terra Ferma, Viking; **M.L. Shiffman:** Gilead, AbbVie, Aurora, Celgene, Conatus, CymaBay, Daiichi Sankyo, Eisai, Enanata, Exalenz, Genfit, HepQuant, Intercept, Madrigal, Mallinckrodt, NGM, Shionogi, Viking; **D.C. Rockey:** Salix; **D. Juyal, Z. Shanis, H. Pokkalla, C. Shukla, O.M. Carrasco-Zevallos, M. Resnick, M. Montalto, A. Beck,** and **I. Wapinski:** PathAI; **C. Jia, C. Chung,** and **R.P. Myers:** Gilead; **Z. Goodman:** Gilead, AbbVie, Affimmune, Allergan, Alexion, Ardelyx, Chemomab, Conatus, Exalenz, Galectin, Exalenz; **A.J. Sanyal:** Gilead, Akarna, Bird Rock, Boehringer Ingelheim, Conatus, Cumberland, Durect, Echosens, Elsevier, Enyo, Exalenz, Fractyl, Galectin, Genfit, Hemoshear, Immuron, Indalo, Intercept, Lilly, Mallinckrodt, MSD, Nimbus, Nitto Denko, Novartis, Novo Nordisk, Pfizer, Salix, Sequana, Terns, Teva, Tiziana, UpToDate.

Presented at AASLD: The Liver Meeting® Digital Experience, November 13–16, 2020