Combining PAGE-B Score With FibroTest Improves Hepatocellular Carcinoma Risk Stratification in Patients Treated With Tenofovir-Based Treatment

Milan J Sonneveld[1], Grace Lai-Hung Wong[2], Wai-Kay Seto[3], Kosh Agarwal[4], Jinlin Hou[5], Ming-Lung Yu[6,7], Hiroshi Yatsuhashi[8], Frida Abramov[9], Hongyuan Wang[9], Leland J Yee[9], Maria Buti[10,11], Young-Suk Lim[12], Harry LA Janssen[1,13]

[1]Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, the Netherlands; [2]Medical Data Analytics Centre, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong; [3]Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Pok Fu Lam, Hong Kong; [4]Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, UK; [5]Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China; [6]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [7]College of Medicine and Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University, Kaohsiung, Taiwan; [8]Clinical Research Center, National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan; [9]Gilead Sciences, Inc., Foster City, CA, USA; [10]Liver Unit, Hospital Universitario Vall d'Hebron, Barcelona, Spain; [11]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD) del Instituto Carlos III, Madrid, Spain; [12]Asan Medical Centre, University of Ulsan College of Medicine, Seoul, South Korea; [13]Toronto Centre for Liver Disease, Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada

Copies of this poster obtained through QR (Quick Response) and/or text key codes are for personal use only and may not be reproduced without written permission of the authors.

Conclusions

- Both PAGE-B (platelet, age, gender, hepatitis B) score and FibroTest stratified long-term hepatocellular carcinoma (HCC) risk in patients with chronic hepatitis B (CHB) receiving tenofovir-based therapy, with very low HCC incidence observed in the lowest-risk groups
- FibroTest values ≤0.48 identified a large subset of patients at low risk of HCC and provided complementary risk stratification to PAGE-B
- Combining PAGE-B and FibroTest increased the proportion of patients classified as low risk from 39% (PAGE-B alone) to 72% (combined strategy) while maintaining a high negative predictive value for HCC
- These findings support the feasibility of refined HCC risk stratification among people with CHB who have achieved virologic suppression

Plain Language Summary

- Chronic hepatitis B is a serious global health issue that led to approximately 1.1 million deaths in 2024, with most of these deaths associated with complications including liver cancer
- The PAGE-B score is a common tool to predict the risk of developing liver cancer, but it classifies only a small portion of patients with chronic hepatitis B as having a low risk
- This analysis looked at patients enrolled in 2 long-running trials of tenofovir-based treatment and whether FibroTest, a noninvasive method for determining the severity of liver damage, can be combined with PAGE-B scores to optimize prediction of liver cancer risk
- The results suggest that this combined strategy could better identify patients who are at low risk of developing liver cancer compared with PAGE-B alone

References: **1.** World Health Organization. Hepatitis B. 2026. Accessed July 10, 2026. https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-b. **2.** European Association for the Study of the Liver. *J Hepatol.* 2025;83(2):502-83. **3.** Ghany MG, et al. *Hepatology.* 2026;83(4):974-97. **4.** Sarin SK, et al. *Hepatol Int.* 2016;10(1):1-98. **5.** Huang Z-H, et al. *BMC Cancer.* 2022;22(1):287. **6.** Papatheodoridis GV, et al. *J Hepatol.* 2015;62(4):956-67. **7.** Yip TC-F, et al. *J Hepatol.* 2020;72(5):847-54. **8.** Papatheodoridis G, et al. *J Hepatol.* 2016;64(4):800-6. **9.** Buti M, et al. *Lancet Gastroenterol Hepatol.* 2016;1(3):196-206. **10.** Agarwal K, et al. *J Hepatol.* 2018;68(4):672-81. **11.** Hou J, et al. *J Clin Transl Hepatol.* 2021;9(3):324-34. **12.** Chan HL, et al. *Lancet Gastroenterol Hepatol.* 2016;1(3):185-95. **13.** Poynard T, et al. *J Hepatol.* 2014;61(5):994-1003.

Acknowledgments: This study was sponsored by Gilead Sciences, Inc. Medical writing and editorial support were provided by Stephanie Biedka, PhD, of Red Nucleus, and funded by Gilead Sciences, Inc.

Disclosures: Conflict of interest disclosures may be viewed using the QR code at the top right.

Correspondence: Frida Abramov; frida.abramov@gilead.com

Introduction

- Chronic hepatitis B (CHB) is a major global health problem; in 2024, approximately 240 million individuals worldwide were living with CHB, and an estimated 1.1 million deaths were attributed to CHB, most of which were associated with complications including hepatocellular carcinoma (HCC)[1]
- Nucleos(t)ide analogues (NAs), such as tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF), are recommended as first-line antiviral treatments for CHB[2-4]
- NA therapy reduces, but does not eliminate, the risk of HCC in patients with CHB[5,6]
- The PAGE-B (platelet, age, gender, hepatitis B) score is widely used to stratify HCC risk, but it identifies only a limited proportion of patients at low risk of developing HCC during long-term NA therapy[7,8]
- Fibrosis is an important determinant of HCC risk, and incorporation of fibrosis assessment (eg, FibroTest) may improve risk stratification beyond PAGE-B alone

Objective

- To evaluate the utility of FibroTest and PAGE-B for refining HCC risk stratification in patients with CHB receiving long-term tenofovir-based therapy

Methods

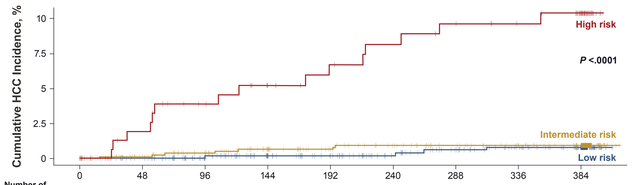
- Patients in this pooled analysis were enrolled in two Phase 3 trials (global and China cohorts) with similar designs
  - Study 108: hepatitis B e antigen (HBeAg)-negative patients (NCT01940341 and NCT02836236)[9-11]
  - Study 110: HBeAg-positive patients (NCT01940471 and NCT02836249)[10-12]
- Patients were randomized 2:1 to the following treatment groups:
  - TAF 25 mg once daily (QD) for up to 144 weeks (3 years) followed by open-label (OL) TAF
  - TDF 300 mg QD for up to 144 weeks (3 years) followed by OL TAF
- All patients then received OL TAF 25 mg QD through up to 384 weeks (8 years)
- The presence of HCC was assessed by local standards of care; beginning at week 96, hepatic ultrasonography was introduced via a protocol amendment to be performed every 6 months to enrich HCC surveillance
- HCC risk was evaluated using the validated PAGE-B prediction model. PAGE-B scores were calculated at baseline for all patients with available data
  - Patients were assigned to low-risk (≤9 points), intermediate-risk (10–17 points), and high-risk (≥18 points) groups based on previously reported cutoffs[8]
- Fibrosis status at baseline was assessed by FibroTest (BioPredictive, Paris, France)
  - Patients were classified as having no to mild fibrosis (≤0.48), moderate to severe fibrosis (0.49–0.74), or cirrhosis (≥0.75) based on previously reported cutoffs[13]
- A combined risk stratification approach was evaluated, defining low risk as a PAGE-B score ≤9 and/or FibroTest value ≤0.48. All remaining patients were classified as having high risk
- The Kaplan-Meier method was used to estimate cumulative HCC incidence at year 8

Results

Baseline Demographics and Characteristics and 8-Year Cumulative HCC Incidence by Baseline PAGE-B Category

	Low Risk (PAGE-B ≤9) n = 642	Intermediate Risk (PAGE-B 10–17) n = 830	High Risk (PAGE-B ≥18) n = 159	Overall[a] N = 1631
Age, y, median (range)	33 (18–69)	42 (18–73)	55 (40–80)	39 (18–80)
Sex, male, n (%)	257 (40)	646 (78)	159 (100)	1062 (65)
Race, Asian, n (%)	520 (81)	704 (85)	129 (81)	1353 (83)
HBeAg positive, n (%)	466 (73)	504 (61)	68 (43)	1038 (64)
HBV DNA, $\log_{10}$ IU/mL, median (Q1, Q3)	7.7 (5.9, 8.4)	7.0 (5.5, 8.1)	6.7 (5.4, 7.8)	7.3 (5.6, 8.2)
ALT, U/L, median (Q1, Q3)	80 (51, 127)	82 (56, 137)	85 (62, 118)	82 (54, 132)
FibroTest value, median (Q1, Q3)	0.21 (0.13, 0.34)	0.40 (0.24, 0.58)	0.68 (0.51, 0.81)	0.33 (0.19, 0.54)
PAGE-B score, median (Q1, Q3)	6 (4, 8)	14 (12, 14)	18 (18, 20)	12 (6, 14)
Cirrhosis,[b] n (%)	9 (1)	83 (10)	63 (40)	155 (10)
DB phase treatment arm, n (%)				
TAF 25 mg	429 (67)	568 (68)	95 (60)	1092 (67)
TDF 300 mg	213 (33)	262 (32)	64 (40)	539 (33)

[a]Overall, 1631 patients had baseline PAGE-B scores. [b]Cirrhosis was defined as a FibroTest value ≥0.75.



Number of patients at risk									
Low risk	642	622	589	550	508	482	465	447	346
Intermediate risk	830	801	777	749	702	688	674	663	544
High risk	159	151	143	137	129	125	122	118	101

	Low Risk (PAGE-B ≤9) n = 642	Intermediate Risk (PAGE-B 10–17) n = 830	High Risk (PAGE-B ≥18) n = 159
HCC cases at year 8, n (%)	4 (0.6)	7 (0.8)	15 (9.4)
Incidence rate, events/1000 PY (95% CI)	0.95 (0.26–2.44)	1.21 (0.48–2.48)	14.07 (7.88–23.21)
Cumulative incidence at year 8, % (95% CI)	0.8 (0.0–1.6)	0.9 (0.2–1.6)	10.4 (5.4–15.4)

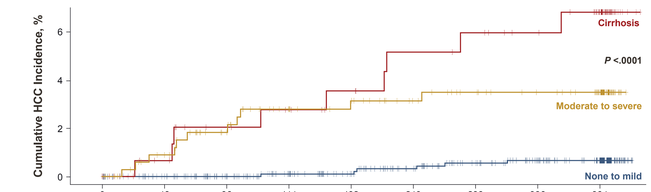
Risk categories were defined as follows: low risk, PAGE-B score ≤9; intermediate risk, PAGE-B score 10–17; high risk, PAGE-B score ≥18.
ALT, alanine aminotransferase; DB, double-blind; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PAGE-B, platelet, age, gender, hepatitis B; PY, person-years; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- HCC cases were enriched among patients with baseline characteristics associated with higher HCC risk, including older age, more advanced fibrosis/cirrhosis by FibroTest, and higher baseline risk categorization by PAGE-B score
- Baseline PAGE-B score effectively stratified HCC risk, with progressively higher cumulative HCC incidence observed across low-risk, intermediate-risk, and high-risk categories over 8 years
  - Overall, 642/1631 (39%) patients were in the low-risk category, and only 4 (0.6%) developed HCC through year 8 (negative predictive value [NPV] for HCC at year 8 = 99.4%)

Baseline Demographics and Characteristics and 8-Year Cumulative HCC Incidence by Baseline FibroTest Category

	None to Mild (FibroTest ≤0.48) n = 1103	Moderate to Severe (FibroTest 0.49–0.74) n = 336	Cirrhosis (FibroTest ≥0.75) n = 155	Overall[a] N = 1594
Age, y, median (range)	36 (18–69)	45 (18–73)	52 (25–80)	39 (18–80)
Sex, male, n (%)	663 (60)	248 (74)	131 (85)	1042 (65)
Race, Asian, n (%)	902 (82)	287 (85)	136 (88)	1325 (83)
HBeAg positive, n (%)	759 (69)	172 (51)	80 (52)	1011 (63)
HBV DNA, $\log_{10}$ IU/mL, median (Q1, Q3)	7.6 (5.7, 8.4)	6.6 (5.2, 7.8)	6.8 (5.6, 7.9)	7.3 (5.6, 8.2)
ALT, U/L, median (Q1, Q3)	75 (52, 116)	88 (57, 165)	101 (72, 213)	81 (54, 126)
FibroTest value, median (Q1, Q3)	0.24 (0.15, 0.34)	0.60 (0.54, 0.66)	0.83 (0.79, 0.88)	0.33 (0.19, 0.54)
PAGE-B score, median (Q1, Q3)	8 (6, 12)	14 (10, 16)	16 (12, 18)	12 (6, 14)
DB phase treatment arm, n (%)				
TAF 25 mg	747 (68)	223 (66)	100 (65)	1070 (67)
TDF 300 mg	356 (32)	113 (34)	55 (35)	524 (33)

[a]Overall, 1594 patients had baseline FibroTest values.



Number of patients at risk									
None to mild	1103	1071	1033	985	907	880	855	832	660
Moderate to severe	336	324	308	290	280	268	261	255	217
Cirrhosis	155	145	137	131	122	118	116	112	90

	None to Mild (FibroTest ≤0.48) n = 1103	Moderate to Severe (FibroTest 0.49–0.74) n = 336	Cirrhosis (FibroTest ≥0.75) n = 155
HCC cases at year 8, n (%)	6 (0.5)	11 (3.3)	9 (5.8)
Incidence rate, events/1000 PY (95% CI)	0.80 (0.29–1.73)	4.81 (2.40–8.61)	8.88 (4.06–16.86)
Cumulative incidence at year 8, % (95% CI)	0.7 (0.1–1.2)	3.5 (1.5–5.5)	6.8 (2.5–11.2)

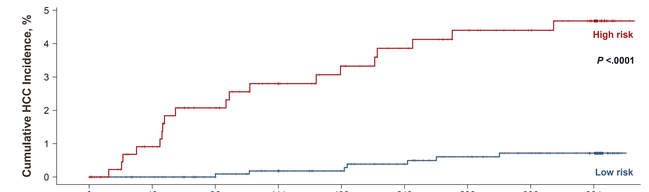
Fibrosis severity was classified as follows: none to mild, Metavir F0–F1, FibroTest value ≤0.48; moderate to severe, Metavir F2–F3, FibroTest value 0.49–0.74; cirrhosis, Metavir F4, FibroTest value ≥0.75.
ALT, alanine aminotransferase; DB, double-blind; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PAGE-B, platelet, age, gender, hepatitis B; PY, person-years; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- Baseline FibroTest category was associated with long-term HCC risk, with progressively higher cumulative HCC incidence observed with increasing fibrosis severity
- Patients with FibroTest values ≤0.48 had a very low risk of HCC through year 8; only 6 (0.5%) patients developed HCC (NPV for HCC at year 8 = 99.5%)

Baseline Demographics and Characteristics and 8-Year Cumulative HCC Incidence by Combined PAGE-B and FibroTest Risk Group

	Low Risk (PAGE-B ≤9 and/or FibroTest ≤0.48) n = 1179	High Risk (PAGE-B >9 and FibroTest >0.48) n = 453	Overall[a] N = 1632
Age, y, median (range)	36 (18–69)	48 (19–80)	39 (18–80)
Sex, male, n (%)	698 (59)	365 (81)	1063 (65)
Race, Asian, n (%)	968 (82)	386 (85)	1354 (83)
HBeAg positive, n (%)	807 (68)	232 (51)	1039 (64)
HBV DNA, $\log_{10}$ IU/mL, median (Q1, Q3)	7.6 (5.7, 8.3)	6.6 (5.3, 7.8)	7.3 (5.6, 8.2)
ALT, U/L, median (Q1, Q3)	77 (53, 120)	92 (61, 174)	82 (55, 131)
FibroTest value, median (Q1, Q3)	0.25 (0.16, 0.36)	0.67 (0.57, 0.79)	0.33 (0.19, 0.54)
PAGE-B score, median (Q1, Q3)	8 (6, 12)	14 (12, 18)	12 (6, 14)
Cirrhosis,[b] n (%)	9 (1)	146 (34)	155 (10)
DB phase treatment arm, n (%)			
TAF 25 mg	796 (68)	297 (66)	1093 (67)
TDF 300 mg	383 (32)	156 (34)	539 (33)

[a]Overall, 1632 patients had baseline PAGE-B scores and/or FibroTest values. [b]Cirrhosis was defined as a FibroTest value ≥0.75.



Number of patients at risk									
Low risk	1179	1145	1101	1049	970	938	912	887	707
High risk	453	430	409	388	370	358	350	342	284

	Low Risk (PAGE-B ≤9 and/or FibroTest ≤0.48) n = 1179	High Risk (PAGE-B >9 and FibroTest >0.48) n = 453
HCC cases at year 8, n (%)	7 (0.6)	19 (4.2)
Incidence rate, events/1000 PY (95% CI)	0.87 (0.35–1.80)	6.23 (3.75–9.74)
Cumulative incidence at year 8, % (95% CI)	0.7 (0.2–1.2)	4.7 (2.6–6.7)

Risk categories were defined as follows: low risk, PAGE-B score ≤9 and/or FibroTest value ≤0.48; high risk, PAGE-B score >9 and FibroTest value >0.48.
ALT, alanine aminotransferase; DB, double-blind; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PAGE-B, platelet, age, gender, hepatitis B; PY, person-years; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- A combined strategy defining low risk as either a PAGE-B score ≤9 and/or a FibroTest value ≤0.48 expanded the low-risk population to 1179/1632 (72%) patients while maintaining a very high NPV for HCC at year 8 (NPV = 99.4%)
- The cumulative incidence of HCC development differed between low-risk and high-risk groups for the combined strategy (0.7% vs 4.7% at year 8; 0.87 vs 6.23 events per 1000 person-years; *P* <.0001)