HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2023 April 01.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2022 April ; 20(4): 953–955.e2. doi:10.1016/j.cgh.2021.04.018.

Doylestown Plus and GALAD Demonstrate High Sensitivity for HCC Detection in Patients with Cirrhosis

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INTRODUCTION

Hepatocellular carcinoma (HCC) surveillance is associated with early tumor detection and improved survival in patients with cirrhosis.[1] Surveillance is performed using semi-annual abdominal ultrasound with or without alpha fetoprotein (AFP); however, this strategy misses over one-third of HCC at an early stage.[2] These data highlight a need for novel surveillance strategies with higher accuracy for early HCC detection. GALAD and Doylestown Plus are novel biomarker panels that combine multiple biomarkers with patient demographic and clinical characteristics; both demonstrated promising accuracy in phase II case-control studies;[3,4] however, case-control studies can overestimate biomarker performance, highlighting a need for phase III cohort and nested case-control studies.[5] Our study aimed to compare multiple biomarkers – including AFP, GALAD, and Doylestown Plus – in a nested case-control study of patients with cirrhosis.

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Author Contributions Dr. Singal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design (Singal); Acquisition, analysis and interpretation of the data (all authors); Drafting of the manuscript (Singal); Critical revision of the manuscript for intellectual content (all authors); Obtained funding (Singal); Administrative, technical, and material support (Singal, Parikh, Marrero); Study supervision (Singal). All authors approve final version of the manuscript.

Conflicts of Interest: Amit Singal has served as a consultant or on advisory boards for Genentech, Bayer, Eisai, Bristol Myers Squibb, Exelixis, AstraZeneca, FujiFilm Wako Diagnostics, Exact Sciences, Roche, Glycotest, GRAIL, and TARGET RWE. Neehar Parikh has served as a consultant or on advisory boards for Genentech, Bayer, Bristol Myers Squibb, Fujifilm Wako Diagnostics, Exact Sciences, and Eli Lilly. Jorge Marrero has served as a consultant for Glycotest. Anand Mehta has served as a consultant for Glycotest. None of the other authors have relevant conflicts to disclose.

METHODS

Study Population

We leveraged a previously described prospective cohort of patients with Child Pugh A or B cirrhosis who were enrolled into an HCC surveillance program between January 2004 and September 2006 and followed for a median of 2.0 years (Supplemental Methods).[6] Serum and plasma were collected at each visit and stored at −80C, without interval thawing. Patients were followed with semi-annual surveillance until incident HCC, liver transplantation, death, or study termination. HCC was defined using AASLD criteria, and early-stage HCC was defined as BCLC stage 0 or A.

Statistical Analysis

Biomarker evaluation was performed using a prospective-specimen-collection, retrospective-blinded-evaluation (PRoBE) design.[5] We performed a nested case-control study, with cases defined as patients with HCC and controls as those without incident HCC. Controls were required to have a lack of suspicious hepatic lesions for >1 year to minimize misclassification bias. All assays were performed blinded to HCC vs. non-HCC status, with biomarkers described in Supplemental Methods. GALAD combines gender, age, AFP, AFP-L3, and DCP; while, Doylestown Plus algorithm is comprised of age, logAFP, PEG-precipitated IgG, and fucosylated kininogen.[3,4] Biomarker performance was evaluated using 1) area under the receiver operating characteristic curve (AUROC) and 2) patient-level sensitivity with screening-level specificity fixed at 90% - an acceptable level to minimize screening-related harms.[7] Our primary outcome was any-stage HCC detection and secondary outcome was early-stage HCC detection. To calculate 95% confidence intervals for biomarker performance, we used a bootstrap procedure among 2000 datasets, constructed by random sampling with replacement. All analyses were conducted using R v4.0.3.

RESULTS

Patient Characteristics

Among 408 patients with cirrhosis, we conducted a nested case-control study with 29 HCC cases and 58 cirrhosis controls. Patient characteristics are detailed in Supplemental Table 1. Median age of patients was 52.0 years, and 60.9% were male. Median Child Pugh score was 7, and the most common cirrhosis etiologies were hepatitis C, alcohol-related liver disease and cryptogenic/NAFLD. Of HCC cases, 58.6% had BCLC 0/A HCC. Among HCC cases, four patients had biomarker assessment at HCC diagnosis, 10 within six months prior to diagnosis, and 13 patients at 6–12 months prior to diagnosis.

Biomarker Performance

Doylestown Plus had the highest accuracy for any-stage HCC detection, with an AUROC of 0.92 and sensitivity of 65.5% (47.6% – 92.6%) with specificity fixed at 90% (Supplemental Figure 1A). If restricted to samples within six months of HCC diagnosis, the highest sensitivity was observed with Doylestown Plus (78.6%, 95%CI 50.0% – 100%) and GALAD (71.4%, 95%CI 28.6% – 92.3%) – both exceeding sensitivity of AFP (57.1%,

95%CI 33.3 – 90.0) (Table 1). Results were consistent when restricting analyses to early-stage HCC (Supplemental Figure 1B), with the highest sensitivity observed for Doylestown Plus (63.2%, 95%CI 37.5% – 93.8%) and GALAD (57.9%, 95%CI 29.4% – 80.0%) with 90% specificity (Table 1).

DISCUSSION

Our study results highlight the potential for novel biomarker panels including Doylestown Plus and GALAD to improve early HCC detection, with sensitivity >70% for any-stage HCC and >55% for early-stage HCC. The high accuracy of these biomarker panels likely relates to inclusion of multiple biomarkers – reflecting intra-tumoral heterogeneity – as well as demographics (age and gender) that are associated with higher HCC risk. Performance of these biomarker panels compares favorably to ultrasound alone, which had a sensitivity below 50% in a recent systematic review.[2] Blood-based biomarkers also have high patient acceptance and are easy to implement in clinical practice so would likely also address surveillance underuse and thereby further increase surveillance effectiveness.[8] While our study provides important nested case-control data derived from a prospective cohort, our results are limited by small samples sizes and wide confidence intervals. Phase III studies including Hepatocellular Carcinoma Early Detection Strategy (HEDS) and the Texas HCC Consortium studies are maturing and should provide further data for these novel biomarkers in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial Source:

This study was conducted with support from NIH U01 CA230694 and R01 222900. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funding agencies had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation of the manuscript.

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Table 1:

Comparison of the patient-level true positive rate at the 10% screening-level false positive rate in the overall cohort

	Any-stage HCC		Early-stage HCC	
	Any time prior to diagnosis	**0–6 months prior to diagnosis**	**Any time prior to diagnosis**	**0–6 months prior to diagnosis**
GALAD	51.7 (95%CI: 29.–68.8)	71.4 (95% CI: 28.6–92.3)	57.9 (95% CI: 29.4–80.0)	70.0 (95%CI: 18.2–100.0)
Doylestown Plus	65.5 (95%CI: 47.6–92.6)	78.6 (95%CI: 50.0–100.0)	63.2 (95%CI: 37.5–93.8)	80.0 (95%CI: 42.9–100.0)
AFP	37.9 (95%CI: 23.3–68.2)	57.1 (95%CI: 33.3–90.0)	47.4 (95%CI: 25.0–75.0)	70.0 (95%CI: 37.5–100.0)
AFP-L3%	55.2 (95%CI: 28.1–73.1)	61.5 (95%CI: 26.7–84.6)	52.6 (95%CI: 17.6–75.0)	55.6 (95%CI: 11.7–83.3)
DCP	20.7 (95%CI: 0.0–41.4)	7.1 (95%CI: 0.0–26.7)	26.3 (95%CI: 0.0–52.6)	10.0 (95%CI: 0.0–33.3)