GAAD and GALAD algorithmic scores demonstrate equivalent clinical performance for hepatocellular carcinoma (HCC) surveillance in prospective, multicenter, case-control studies

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P2089

Introduction

- Early detection of HCC is essential to improve patient outcomes, and so current guidelines recommend surveillance programs, including ultrasound scans every six months with or without alpha-fetoprotein (AFP) testing, to screen at-risk patients. However, these programs do not identify early-stage HCC effectively.[1–5]

- Serum biomarkers, such as AFP, protein induced by vitamin K absence-II (PIVKA-II) and *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3), have been proposed to improve the detection of HCC, but taken individually they show inadequate sensitivity and accuracy, thus, their inclusion in guidelines has been inconsistent.[1–6]

- Both the GALAD (combining gender [sex] and age plus a three-serum biomarker panel [AFP-L3, AFP and PIVKA-II]) and the novel GAAD (gender [sex] and age plus two biomarkers [AFP and PIVKA-II]), algorithms have demonstrated good clinical performance for the detection of early-stage HCC.[7, 8]

Aim

- To compare the clinical performance of the GALAD and GAAD algorithms for differentiating between early-stage HCC and benign chronic liver disease (CLD).

Methods

- Two independent prospective studies (STOP-HCC-MCE and STOP-HCC-Panel B) were conducted with recruiting participants in an international, multicenter, case-control design.

    - **STOP-HCC-MCE**: Patients aged ≥18 years were enrolled at 10 clinics in China (including the Hong Kong Special Administrative Region), Germany, Thailand, and Japan and included in clinical performance analysis or specificity panel (**Figure 1A**).
        - Results from the specificity panel will be included in a subsequent publication.

    - **STOP-HCC-Panel B**: Patients (≥18 years) were enrolled at 7 clinics across Germany, Spain, Thailand and Hong Kong (**Figure 1B**).

- In both studies, eligible HCC cases had first-time HCC diagnosis confirmed by ultrasound or pathology. Eligible CLD controls had imaging-confirmed absence of HCC (within 12 months), and presence of cirrhosis or non-cirrhotic liver disease (viral [hepatitis B or hepatitis C virus] or non-viral [non-alcoholic steatohepatitis, alcohol-related liver disease or other]).

- Serum levels of PIVKA-II, AFP and AFP-L3 were measured using Elecsys® assays on the cobas® e 601 analyzer, or µTASWAKO™ assays on the Fujifilm Micro Total Analysis System Wako analyzer.

- The established cut-offs for HCC detection were 2.47 for GALAD (cobas) and 2.57 for GAAD (cobas) (range 0–10 for both algorithms using Elecsys assays), and -0.63 for the Fujifilm GALAD algorithm (using µTASWAKO assays).
    - An additional cut-off of -1.89 for the Fujifilm GALAD algorithm (using µTASWAKO assays) was also assessed which corresponds to matching GAAD (cobas) specificity of 90%.

- The clinical performance of the GAAD algorithm was compared with that of the GALAD algorithm. Performance was assessed using receiver operating characteristic (ROC) analysis and area under the curve (AUC) values were calculated.

Results

STOP-HCC-MCE

Participants

- A total of 1142 patients (366 with HCC with 48% early stage; 303 CLD controls; and 468 specificity panel) were included in the STOP-HCC-MCE study (**Table 1**).
    - One CLD control had incomplete AFP-L3 biomarker data and was excluded from the analysis.

Table 1: Participant demographics and clinical characteristics in STOP-HCC-MCE (clinical performance panel).

	HCC cases (n=366)	CLD controls (n=303)
Age, years		
Mean (SD)	59.8 (11.4)	49.5 (12.5)
Sex, n (%)		
Male	308 (84.2%)	192 (63.4%)
Female	58 (15.8%)	111 (36.6%)
Race, n (%)		
Asian	226 (61.7%)	181 (59.7%)
White	138 (37.7%)	113 (37.3%)
Black or African American	1 (0.3%)	3 (1%)
Other	0 (0%)	1 (0.3%)
Missing	1 (0.3%)	5 (1.7%)
Etiology, n (%)		
Cirrhosis	287 (71.9%)	112 (28.1%)
Cirrhotic viral	222 (74.5%)	76 (25.5%)
Cirrhotic non-viral	126 (69.6%)	55 (30.4%)
Non-cirrhotic	79 (29.3%)	191 (70.7%)
Non-cirrhotic viral	60 (27.3%)	160 (72.7%)
Non-cirrhotic non-viral	21 (16.5%)	106 (83.5%)
HCC stage		
Early (BCLC 0, A)	174 (47.5)	–
Late (BCLC B, C, D)	192 (52.5)	–

BCLC, Barcelona Clinic Liver Cancer; CLD, chronic liver disease; HCC, hepatocellular carcinoma; SD, standard deviation.

Clinical performance
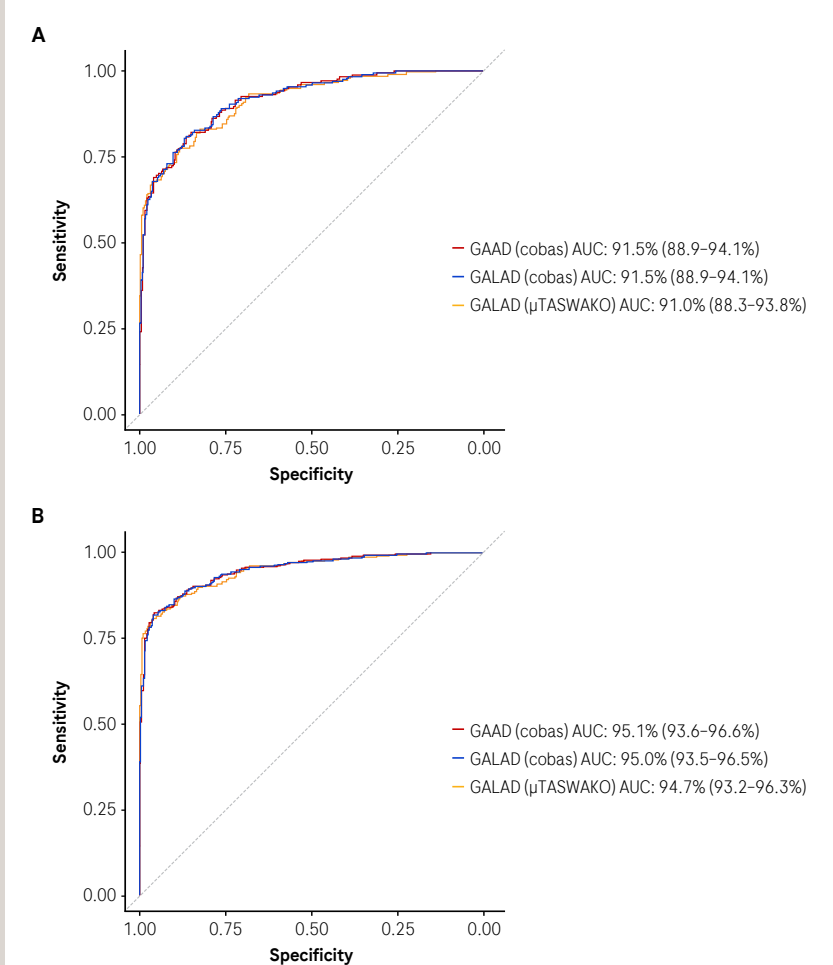
- The GAAD and GALAD (cobas) algorithms, and the GALAD (µTASWAKO) algorithm showed similar performance (AUC) for discriminating between HCC and CLD for both early- and all-stage HCC (**Figure 2**).

- However, sensitivity was higher with the GAAD and GALAD (cobas) algorithms compared with GALAD (µTASWAKO) for both early and all-stage HCC (**Table 2**). Specificity for CLD controls was above 90% with all three algorithms
    - Using a comparable cut-off for GALAD (µTASWAKO), clinical performance was comparable to GAAD and GALAD (cobas) (**Table 2**).

- The AUCs of GAAD and GALAD (cobas) algorithms were similar across cirrhotic and non-cirrhotic etiologies (**Figure 3**).

Table 2: Clinical performance of GAAD and GALAD algorithms for the detection of early-stage and all-stage HCC in STOP-HCC-MCE (clinical performance panel) [all results shown as % (95% CI)].

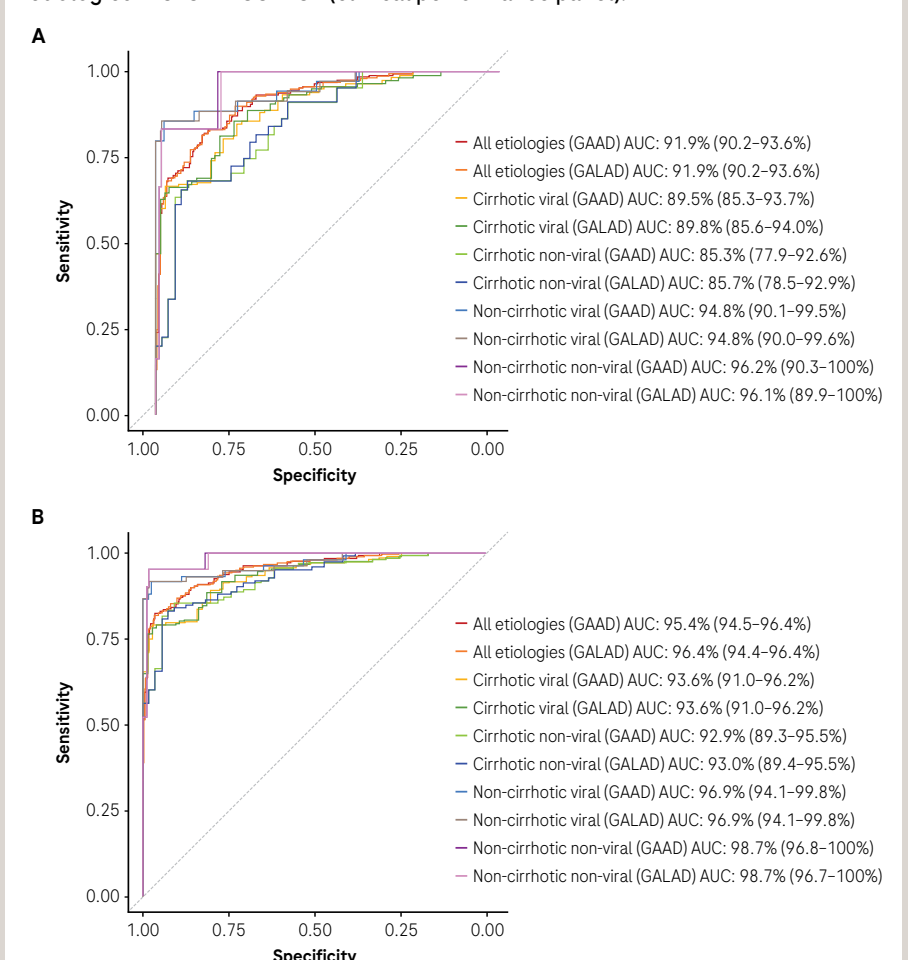| Algorithm (cut-off score)	Early-stage HCC (N=174) Sensitivity	HCC cases (N=366) Sensitivity	CLD controls (N=302) Specificity
GAAD (cobas, 2.57)	70.1 (62.7–76.8)	83.1 (78.8–86.8)	94.0 (90.7–96.4)
GALAD (cobas, 2.47)	70.1 (62.7–76.8)	83.3 (79.1–87.0)	93.0 (89.5–95.6)
GALAD (µTASWAKO, -0.63)	56.7 (44.0–68.8)	68.3 (59.2–76.5)	100 (95.7–100)
GALAD (µTASWAKO, -1.89)	72.4 (65.1–78.8)	82.8 (78.5–86.5)	89.1 (85.0–92.4)

CI, confidence interval; CLD, chronic liver disease; HCC, hepatocellular carcinoma.

Figure 2: ROC plot of the GAAD and GALAD (cobas) algorithms and GALAD (µTASWAKO) algorithm for discriminating between CLD controls and early-stage (A) or all-stage (B) HCC patients in STOP-HCC-MCE (clinical performance panel).

A
- GAAD (cobas) AUC: 91.5% (88.9–94.1%)
- GALAD (cobas) AUC: 91.5% (88.9–94.1%)
- GALAD (µTASWAKO) AUC: 91.0% (88.3–93.8%)

B
- GAAD (cobas) AUC: 95.1% (93.6–96.6%)
- GALAD (cobas) AUC: 95.0% (93.5–96.5%)
- GALAD (µTASWAKO) AUC: 94.7% (93.2–96.3%)

AUC, area under the curve; CLD, chronic liver disease; HCC, hepatocellular carcinoma; ROC, receiver operating characteristic.

Figure 3: ROC plot of GAAD and GALAD (cobas) algorithms for discriminating between CLD controls and early-stage (A) or all-stage (B) HCC patients across etiologies in STOP-HCC-MCE (clinical performance panel).

A
- All etiologies (GAAD) AUC: 91.9% (90.2–93.6%)
- All etiologies (GALAD) AUC: 91.9% (90.2–93.6%)
- Cirrhotic viral (GAAD) AUC: 89.5% (85.3–93.7%)
- Cirrhotic viral (GALAD) AUC: 89.8% (85.6–94.0%)
- Cirrhotic non-viral (GAAD) AUC: 85.3% (77.9–92.6%)
- Cirrhotic non-viral (GALAD) AUC: 85.7% (78.5–92.9%)
- Non-cirrhotic viral (GAAD) AUC: 94.8% (90.1–99.5%)
- Non-cirrhotic viral (GALAD) AUC: 94.8% (90.0–99.6%)
- Non-cirrhotic non-viral (GAAD) AUC: 96.2% (90.3–100%)
- Non-cirrhotic non-viral (GALAD) AUC: 96.1% (89.9–100%)

B
- All etiologies (GAAD) AUC: 95.4% (94.5–96.4%)
- All etiologies (GALAD) AUC: 96.4% (94.4–96.4%)
- Cirrhotic viral (GAAD) AUC: 93.6% (91.0–96.2%)
- Cirrhotic viral (GALAD) AUC: 93.6% (91.0–96.2%)
- Cirrhotic non-viral (GAAD) AUC: 92.9% (89.3–95.5%)
- Cirrhotic non-viral (GALAD) AUC: 93.0% (89.4–95.5%)
- Non-cirrhotic viral (GAAD) AUC: 96.9% (94.1–99.8%)
- Non-cirrhotic viral (GALAD) AUC: 96.9% (94.1–99.8%)
- Non-cirrhotic non-viral (GAAD) AUC: 98.7% (96.8–100%)
- Non-cirrhotic non-viral (GALAD) AUC: 98.7% (96.7–100%)

The ROC curves and AUC values might slightly differ from the overall analysis, as patients are counted several times, when having several etiologies. AUC, area under the curve; CLD, chronic liver disease; HCC, hepatocellular carcinoma; ROC, receiver operating characteristic.

STOP-HCC-Panel B

Participants

- A total of 1,050 patients were enrolled in this study; of these, 290 had HCC and 727 were CLD controls.
    - 33 patients had a CCC, mixed HCC/CCC, or variable HCC diagnosis and were excluded from the analysis.

Clinical validation

- The AUCs of GAAD and GALAD (cobas) algorithms demonstrated similar performance for discriminating between HCC and CLD:
    - Early-stage HCC: 90.7% vs 90.5%;
    - All-stage HCC: 94.9% vs 95.2%.

Figure 1: Study Designs of STOP-HCC-MCE (A) and STOP-HCC-PanelB (B).
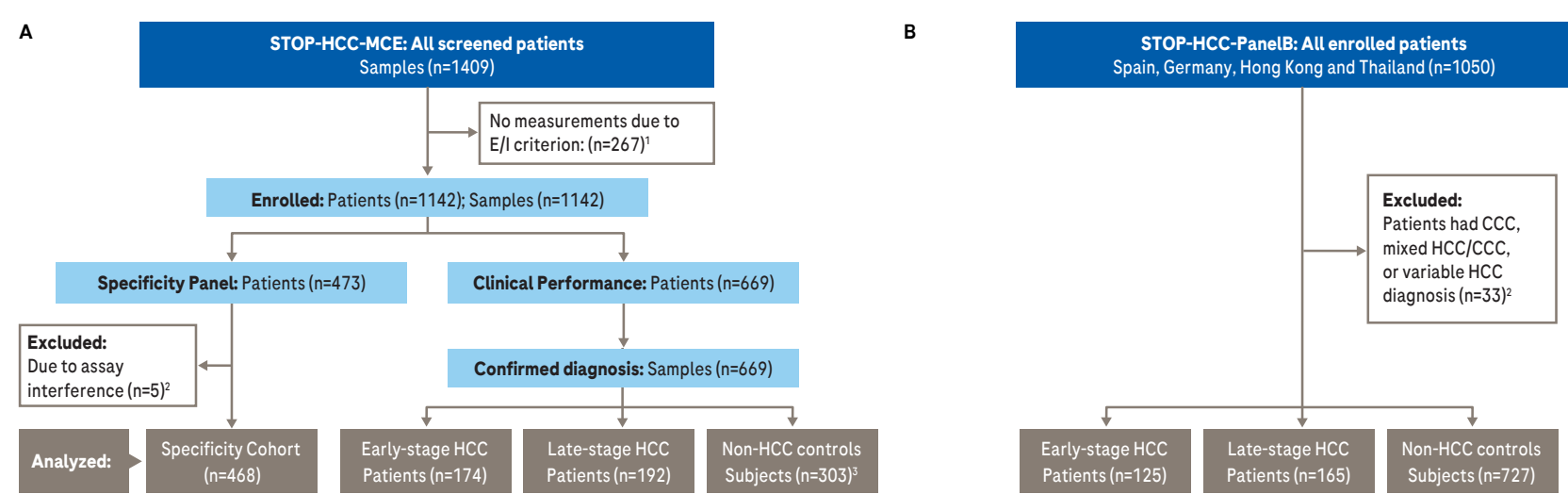
[1] Excluded because of exclusion criteria e.g. renal failure, informed consent, etc.; [2] Excluded because of interferences with assays; [3] One Non-HCC control subject was excluded for GALAD (cobas) analysis due to interference with AFP-L3 assay. Results from the specificity panel in STOP-HCC-MCE will be presented in a subsequent publication. HCC, hepatocellular carcinoma.

Conclusions

- The GAAD and GALAD (cobas) algorithms, and the GALAD (µTASWAKO) algorithm demonstrated similar performance in differentiating HCC and CLD controls.

- The GAAD and GALAD (cobas) algorithms both demonstrated good clinical performance in differentiating HCC and CLD controls.
    - Performance of GAAD and GALAD (cobas) algorithms was similar across all disease stages and etiologies.

- This suggests that the Elecsys AFP-L3 assay had a negligible impact as part of the GALAD (cobas) algorithm in this cohort.

- The GAAD (cobas) algorithm may represent a useful and time-efficient tool for early HCC detection in HCC surveillance, with the potential to increase curative treatment opportunities and reduce mortality.

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