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A comparative analysis of Elecsys GALAD and Elecsys GAAD score to detect early-stage hepatocellular carcinoma in an international cohort

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Introduction

- Hepatocellular carcinoma (HCC), which develops mainly in patients with hepatitis B virus (HBV) infection or excessive alcohol intake, is a major cause of cancer-related mortality (>830,000 deaths/year).[1,2]
- The early detection of HCC is essential to allow prompt treatment and increase survival. Current guidelines therefore recommend the routine surveillance of patients at risk with ultrasonography. However, this technique does not identify early-stage HCC effectively.[3,4]
- Various serum biomarkers associated with HCC, such as alpha-fetoprotein (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 detection. However, the use of these biomarkers alone do not provide adequate specificity or sensitivity and their inclusion in guidelines has been inconsistent.[3-6]
- Both the Roche Elecsys® GALAD, combining gender (sex) and age with a three-serum biomarker panel (AFP-L3, AFP and PIVKA-II), and Elecsys GAAD, combining gender (sex) and age with two biomarkers (AFP and PIVKA-II), algorithms have demonstrated good clinical performance for the detection of early-stage HCC.[4,7-10]

Aim

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

Methods

- Patients aged ≥18 years were prospectively enrolled at 9 clinics in Germany, Thailand, Hong Kong, and Japan.
- Eligible HCC cases had first-time HCC diagnosis confirmed by ultrasound according to national guidelines or by liver biopsy. Eligible CLD controls had absence of HCC confirmed by imaging in the past 12 months, and presence of cirrhosis, non-cirrhotic chronic HBV or hepatitis C virus (HCV) infection, non-cirrhotic alcoholic liver disease or non-cirrhotic non-alcoholic steatohepatitis (NASH).
- Serum levels of PIVKA-II, AFP and AFP-L3 were measured using the respective Elecsys assays on the cobas e 601 analyzer.
- The predefined established cut-offs for benign liver controls (CLD) vs HCC detection were:
  - 20 ng/mL for AFP
  - 2.3 ng/mL for AFP-L3
  - 28.4 ng/mL for PIVKA-II
  - 2.47 for Elecsys GALAD (range 0–10)
  - 2.57 for Elecsys GAAD (range 0–10)
- The clinical performance of the GALAD algorithm was compared with that of the GAAD algorithm and individual biomarkers alone. Performance was assessed using receiver operating characteristic (ROC) analysis and area under the curve (AUC) values were calculated.

Results

Participants

- A total of 465 patients were enrolled in the study; of these, 246 had HCC and 219 were CLD controls (**Table 1**).
- Among the HCC cohort, mean age was 63.5 years, 201 (81.7%) were male, 199 (71.1%) had cirrhosis, and 107 (43.5%) had early-stage HCC (Barcelona Clinic Liver Cancer [BCLC] 0 and A) (**Table 1**).
- In the CLD cohort, mean age was 52.5 years, 131 (59.8%) were male, and 81 (28.9%) had cirrhosis (**Table 1**).
- One CLD control had incomplete biomarker data and was excluded from the analysis.

Table 1: Participant demographics and clinical characteristics.

	HCC cases (n=246)	CLD controls (n=219)	Total (n=465)
Mean age, years			
Mean	63.5	52.5	58.4
SD	10	12.3	12.4
Gender, n (%)			
Male	201 (81.7%)	131 (59.8%)	332 (71.4%)
Female	45 (18.3%)	88 (40.2%)	133 (28.6%)
Missing	0 (0%)	0 (0%)	0 (0%)
Race, n (%)			
Asian	106 (43.1%)	99 (45.2%)	205 (44.1%)
White	138 (56.1%)	112 (51.1%)	250 (53.8%)
Black or African American	1 (0.4%)	3 (1.4%)	4 (0.9%)
Other	0 (0%)	0 (0%)	0 (0%)
Missing	1 (0.4%)	5 (2.3%)	6 (1.3%)
Disease etiology, n (%)			
Cirrhosis	199 (71.1%)	81 (28.9%)	280 (60.2%)
Cirrhotic HBV	94 (74.6%)	32 (25.4%)	126 (27.1%)
Cirrhotic HCV	41 (71.9%)	16 (28.1%)	57 (12.3%)
Cirrhotic NASH	18 (75%)	6 (25%)	24 (5.2%)
Cirrhotic ALD	54 (74%)	19 (26%)	73 (15.7%)
Cirrhotic other	51 (63.8%)	29 (36.3%)	80 (17.2%)
Non-cirrhosis	47 (25.4%)	138 (74.6%)	185 (39.8%)
Non-cirrhosis HBV	22 (22.2%)	77 (77.8%)	99 (21.3%)
Non-cirrhosis HCV	5 (12.8%)	34 (87.2%)	39 (8.4%)
Non-cirrhosis NASH	7 (15.6%)	38 (84.4%)	45 (9.7%)
Non-cirrhosis ALD	2 (33.3%)	4 (66.7%)	6 (1.3%)
Non-cirrhosis other	10 (17.5%)	47 (82.5%)	57 (12.3%)
HCC stage, n (%)			
Early (BCLC 0, A)	107 (43.5)	–	–
Late (BCLC B, C, D)	139 (56.5)	–	–

ALD, alcoholic liver disease; CLD, chronic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; SD, standard deviation.

Clinical Performance

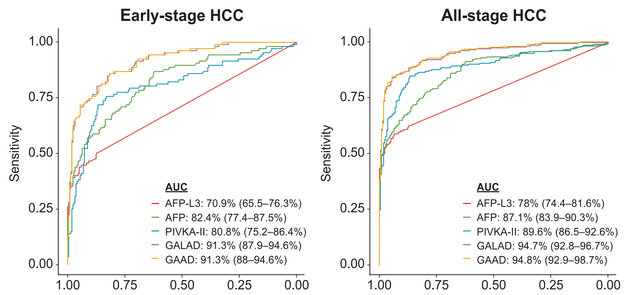
- Elecsys GAAD and GALAD algorithms showed a similar performance for discriminating between HCC and CLD (**Figure 1 and Table 2**):
  - Sensitivity: 72.9% vs 73.8% for early stage, 85% vs 85.8% for all-stage HCC
  - Specificity: 92.2% vs 90.8% for CLD controls.
- The performance of the Elecsys GAAD and GALAD algorithms was superior to individual biomarkers (AFP, AFP-L3 and PIVKA-II) alone (**Figure 1 and Table 2**).

Table 2: Clinical performance of Elecsys GAAD and GALAD algorithms and individual biomarkers for the detection of early-stage and all-stage HCC [all results shown as % (95% CI)].

	Early-stage HCC	All-stage HCC	CLD controls
Elecsys assay/algorithm (cut-off)	**Sensitivity**	**Sensitivity**	**Specificity**
AFP-L3 (2.3 ng/ml)	39.3 (30.0–49.2)	52.8 (46.4–59.2)	97.7 (94.7–99.3)
PIVKA-II (28.4 ng/ml)	69.2 (59.5–77.7)	83.7 (78.5–88.1)	87.2 (82.1–91.3)
AFP (20 ng/ml)	36.4 (27.4-46.3)	50.4 (44-56.8)	98.2 (95.4-99.5)
GAAD (2.57)	72.9 (63.4-81.0)	85.0 (79.9-89.2)	92.2 (87.9-95.4)
GALAD (2.47)	73.8 (64.4-81.9)	85.8 (80.8-89.9)	90.8 (86.2-94.3)

AFP, alpha-fetoprotein; AFP-L3, Lens culinaris agglutinin-reactive fraction of AFP; CLD, chronic liver disease; HCC, hepatocellular carcinoma.

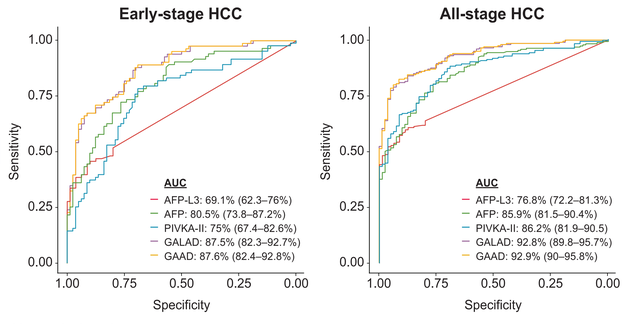
Figure 1. ROC plot of the Elecsys GAAD and GALAD algorithms and Elecsys AFP-L3, PIVKA-II and AFP assays for discriminating between disease controls and early-stage (left) or all-stage (right) HCC patients



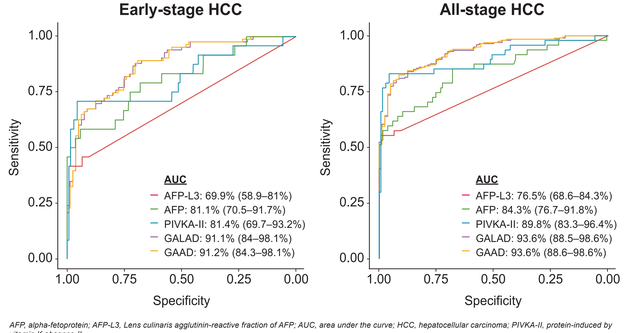
AFP, alpha-fetoprotein; AFP-L3, Lens culinaris agglutinin-reactive fraction of AFP; AUC, area under the curve; HCC, hepatocellular carcinoma; PIVKA-II, protein-induced by vitamin K absence-II.

Figure 2: ROC plot of Elecsys GAAD and GALAD algorithms for discriminating between disease control and early-stage (left) or all-stage (right) HCC patients with cirrhotic (top) and non-cirrhosis (bottom) etiologies.

Cirrhosis



Non-cirrhosis



AFP, alpha-fetoprotein; AFP-L3, Lens culinaris agglutinin-reactive fraction of AFP; AUC, area under the curve; HCC, hepatocellular carcinoma; PIVKA-II, protein-induced by vitamin K absence-II.

- The AUCs of Elecsys GAAD and GALAD algorithms were similar across cirrhotic and non-cirrhosis etiologies (**Figure 2**):
  - Cirrhotic: 87.6% vs 87.5% for early-stage, 92.9% vs 92.8% for all-stage HCC;
  - Non-cirrhosis: 91.2% vs 91.1% for early-stage; 93.6% both for all-stage HCC.

Conclusions

- The Elecsys GALAD and Elecsys GAAD algorithms showed good performance in differentiating HCC and CLD controls, and were similar irrespective of etiology and disease stages.
- For the detection of both early- and all-stage HCC, the Elecsys GAAD and GALAD scores performed better than Elecsys AFP, AFP-L3 and PIVKA-II assays alone.
- These findings suggest that the Elecsys AFP-L3 assay had a negligible impact as part of the Elecsys GALAD algorithm in the tested cohort.

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- ELECSYS and COBAS are trademarks of Roche.
- The Elecsys GAAD assay is approved for clinical use in the CE-marked countries. The Elecsys GALAD assay is used for research purposes only and not approved for clinical use.

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