

The clinical utility of Elecsys GAAD score in the diagnosis of hepatocellular carcinoma

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Background

Regional guidelines have suggested sonography with or without adding serum tumor markers as the standard of hepatocellular carcinoma (HCC) surveillance. The performance of Elecsys® GAAD score, which includes the parameters of gender, age, alpha-fetoprotein (AFP) and protein induced by Vitamin K absence or antagonists-II (PIVKA-II) in the diagnosis of HCC is elusive.

Aims

The current study aims to address the diagnostic accuracy of HCC using Elecsys GAAD algorithmic score as compared to AFP and PIVKA-II with or without the complementation of sonography.

Methods

A total of 430 subjects including 200 healthy controls, 117 non-cirrhotic patients with chronic liver disease (chronic hepatitis B [CHB, n=67] and chronic hepatitis C [CHC, n=50]), 60 cirrhotic patients ([CHB, n=11] and [CHC, n=49]) and 53 HCC ([CHB, n=33], [CHC, n=19] and [non CHB/CHC, n=1]) were enrolled. Sonography was performed every 6 months in patients with liver disease. Blood sampling was collected within 3 months before HCC diagnosis in the 53 HCC patients.

Results

Of the 53 HCC patients, the distribution of Barcelona Clinic Liver Cancer (BCLC) classification was BCLC 0 (n=7, 13.2%), BCLC A (n=19, 35.8%), BCLC B (n=12, 22.6%) and BCLC C (n=15, 28.3%), respectively. By adopting the clinically validated Elecsys GAAD cut-off value of 2.57, the sensitivity of AFP, PIVKA-II and GAAD in the diagnosis of HCC was 43.4%, 69.8% and 77.4%, respectively, whereas the area under ROC (AUROC) was 0.79, 0.92 and 0.92, respectively. Notably, GAAD has a substantially better sensitivity than PIVKA-II in HCC patients with very early stage (BCLC 0, 57.1% vs. 26.6%). While comparing the different performances between PIVKA-II and GAAD among the 26 patients with early HCC (BCLC 0-A), there was only one patient who had elevated PIVKA-II but with a normal GAAD score. By contrast, 4 early HCC patients had normal PIVKA-II but presented with abnormal GAAD scores. By the complementation of sonography, the sensitivity of GAAD was 92.5%, and reached up to 100% in the subgroups of BCLC C, non-cirrhotic as well as CHC patients.

Conclusions

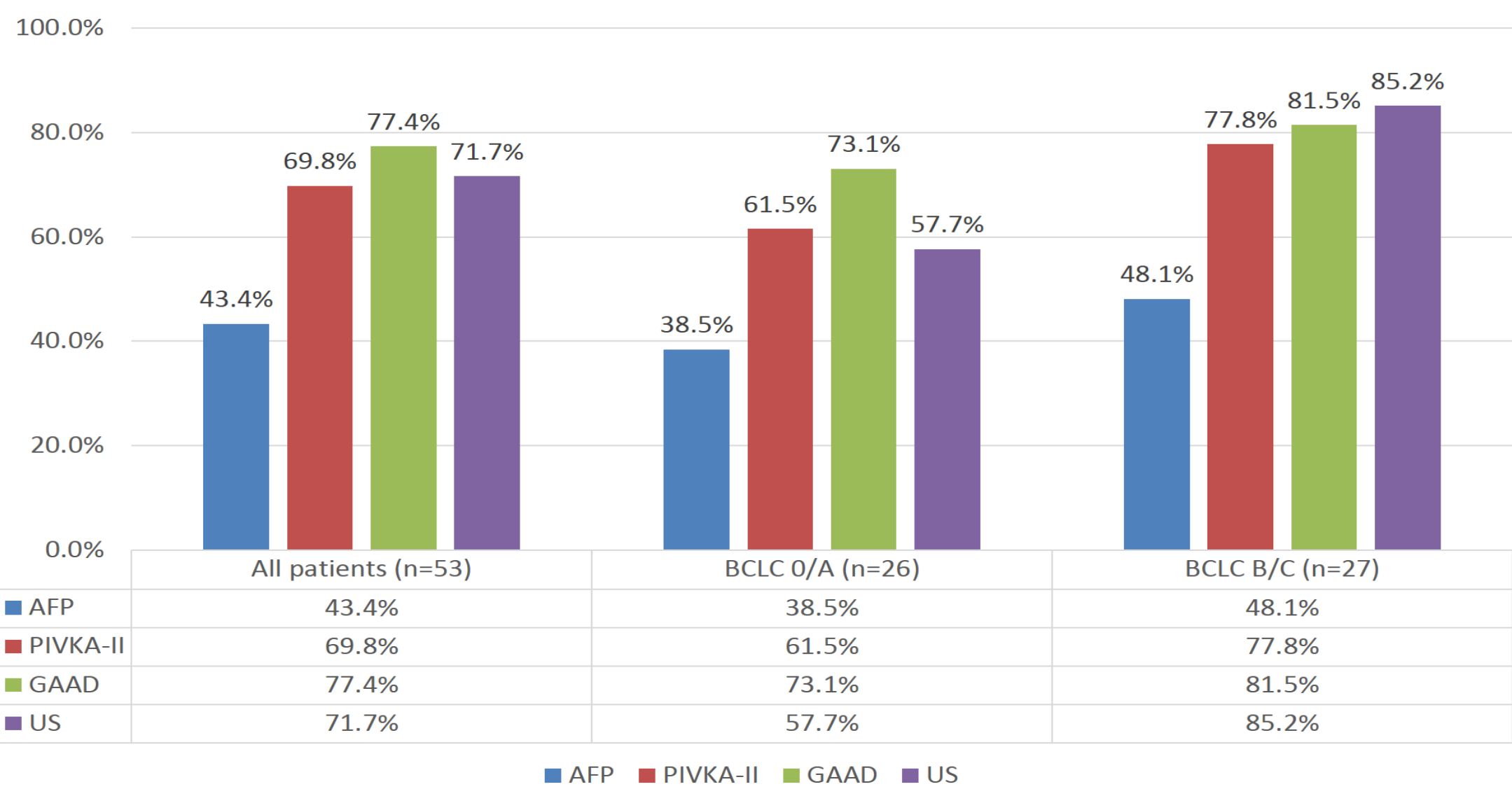
PIVKA-II and GAAD are more sensitive than AFP in HCC diagnosis. Elecsys GAAD score is highly accurate in the diagnosis of HCC, which may outperform PIVKA-II in particular in patients with early HCC. The complementation with sonography further added value for HCC diagnosis.

	Healthy control (n=200)	CHC/non-LC (n=50)	CHB/non-LC (n=67)	CHC/LC (n=49)	CHB/LC (n=11)	HCC* (n=53)
Male gender, n (%)	53 (26.5)	25 (50.0)	45 (67.2)	23 (46.9)	7 (63.6)	40 (75.5)
Age, yrs (mean±SD)	54.4±15.9	58.4±13.1	56.0±13.0	66.4±11.2	58.7±9.0	64.1±9.9
Platelet count, x1000 /mm ³ (mean±SD)	263±64	198±59	207±90	144±66	115±49	192±94
AST, IU/L (mean±SD)	20±5	51±32	255±527	54±35	1007±926	66.8±77.2
ALT, IU/L (mean±SD)	18±7	70±51	372±965	55±46	1201±992	48.7±62.1
AFP, ng/ ml, (mean±SD)	2.8±1.7	4.3±3.8	6.3±10.0	5.1±5.5	15.6±23.0	2808±10788
AFP, ng/ ml, (median, range)	2.4 (0.6-13.8)	3.1 (0.6-19.0)	3.0 (0.8-56.1)	3.4 (0.6-25.5)	7.5 (1.3-79.4)	10.2 (1.5-60138)
PIVKA-II, ng/mL, (mean±SD)	16.6±2.8	16.9±4.7	21.8±38.8	31.9±50.2	34.1±70.1	898±2077
PIVKA-II, ng/mL (median, range)	16.5 (10.3-33.2)	15.9 (11.5-41.4)	15.6 (3.8-316.9)	16.9 (10-319.6)	14.3 (7.4-245.4)	108.4 (13.2-10108)
GAAD score (mean±SD)	0.45±0.59	0.79±0.72	0.97±1.30	1.50±1.74	1.78±1.83	6.06±3.71
GAAD score (median, range)	0.23 (0.01-3.41)	0.59 (0.03-3.3)	0.47 (0.05-6.33)	0.97 (0.11-8.34)	0.90 (0.11-4.79)	6.6 (0.14-10.0)

Note: CHC: chronic hepatitis C. CHB: chronic hepatitis B. LC: liver cirrhosis. HCC*: henatocellular carcinoma. AFP: aloha fetoprotein. PIVKA-II: Protein induced by Vitamin K absence or antagonists-II. SD: standard deviation. *blood testing within 6 months before HCC occurrence

Sensitivity of the biomarkers and US

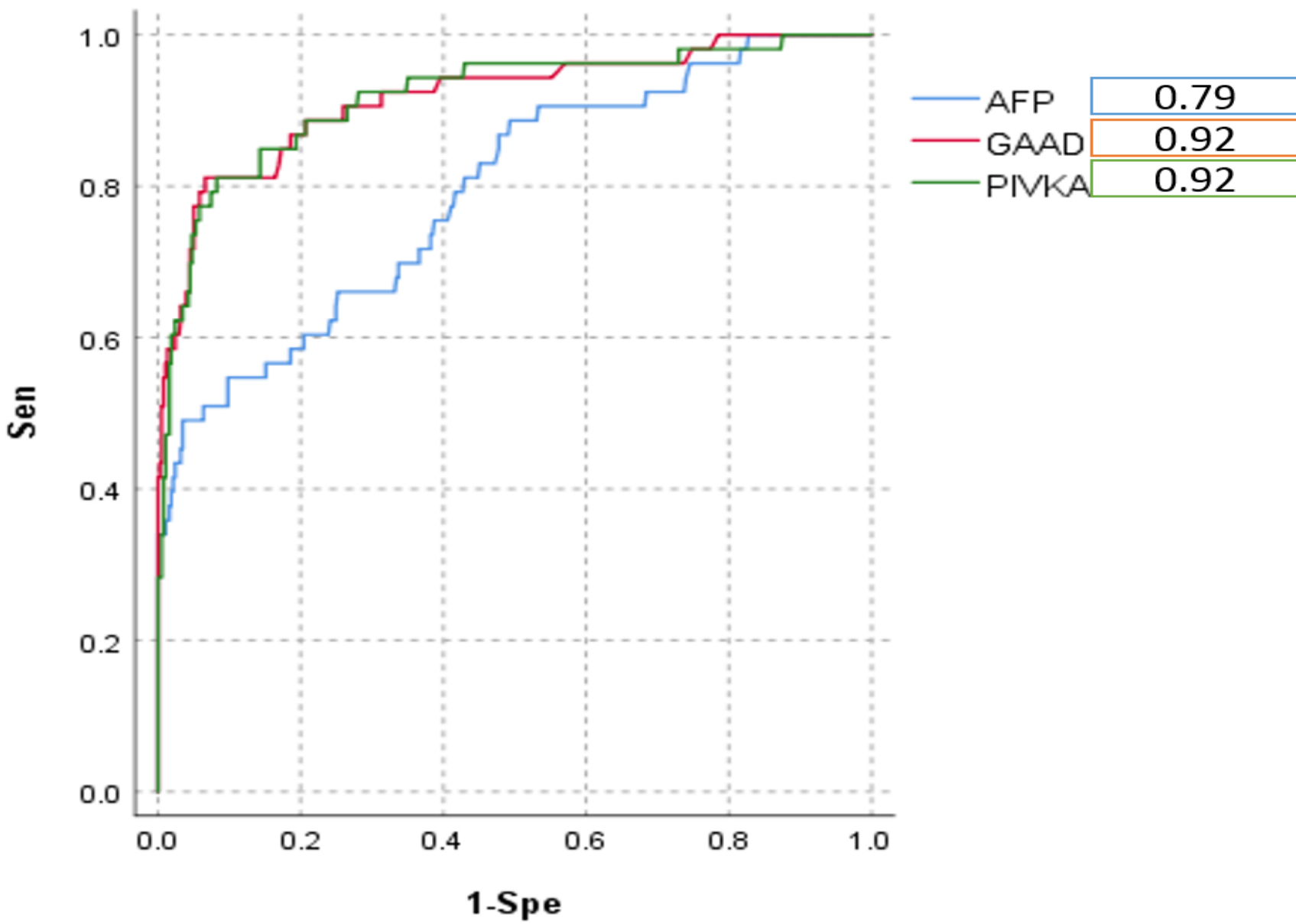
Cutoff value: AFP-20 ng/mL, PIVKA-II 28.4 ng/mL, GAAD 2.57



Characteristics of the 53 HCC patients

Male gender, n (%)	40 (75.5)
Age, yrs (mean±SD)	64.1±9.9
Body mass index, kg/m ² (mean±SD)	25.2±3.5
Platelet count, x1000 /mm ³ (mean±SD)	192±94
AST, IU/L (mean±SD)	66.8±77.2
ALT, IU/L (mean±SD)	48.7±62.1
Total bilirubin, mg/dL (mean±SD)	1.10±0.70
Liver cirrhosis, n (%)	32 (60.4)
Child-Pugh A, n (%)	25 (47.2)
Child-Pugh B, n (%)	7 (13.2)
Etiology	
HBV, n (%)	33 (62.3)
HCV, n (%)	19 (35.8)
NBNC, n (%)	1 (1.9)
BCLC stage	
BCBC 0, n (%)	7 (13.2)
BCLC A, n (%)	19 (35.8)
BCLC B, n (%)	12 (22.6)
BCLC C, n (%)	15 (28.3)
Largest tumor size, cm (mean±SD)	5.0±3.6
AFP, ng/ ml, (mean±SD)	2808±10788
AFP> 20 ng/mL, n (%)	23 (43.4)
PIVKA-II, ng/mL, (mean±SD)	898±2077
PIVKA> 28.4 ng/mL, n (%)	37 (69.8)
GAAD score, (mean±SD)	6.06±3.71
GAAD score >2.57, n (%)	41 (77.4)

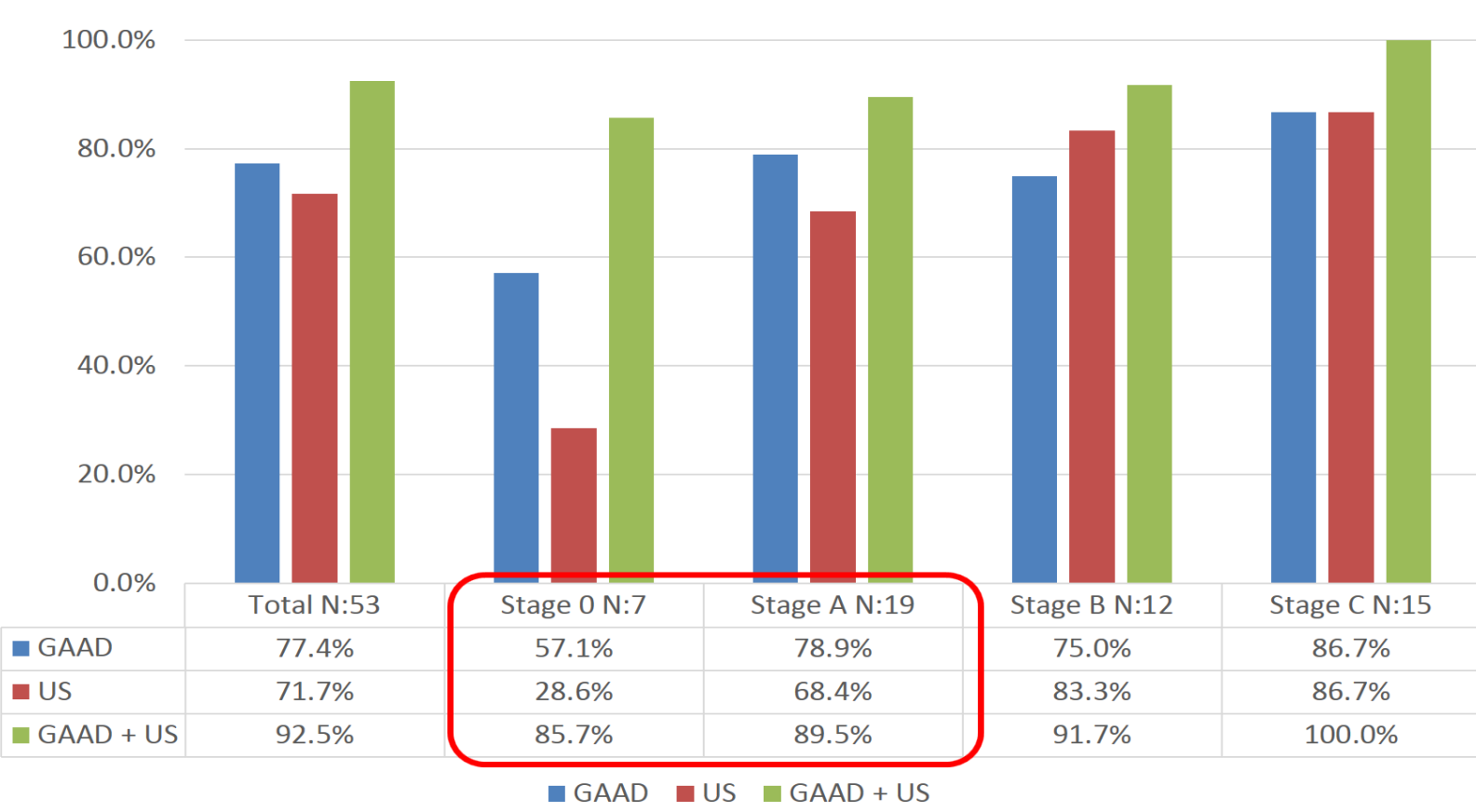
AUROC



Cutoff value: AFP-20 ng/mL, PIVKA-II 28.4 ng/mL, GAAD 2.57

GAAD adds SEN to US in detecting early HCC

BCLC 0	US +	US -
GAAD >	0	4
GAAD ≤	2	1
BCLC A	US +	US -
GAAD >	11	4
GAAD ≤	2	2
BCLC B	US +	US -
GAAD >	8	1
GAAD ≤	2	1
BCLC C	US +	US -
GAAD >	11	2
GAAD ≤	2	0



Comparison of GAAD and other markers and US in HCC patients

GAAD score serves a complementary tool with sonography in the diagnosis of HCC

US+GAAD sensitivity = 92.5%												
All stage N=53	US +		US -		AFP >		AFP ≤		PIVKA-II >		PIVKA-II ≤	
	GAAD >		30		11		GAAD >		22		19	
	GAAD >		34		7		GAAD >		3		9	
	GAAD ≤		8		4		GAAD ≤		1		11	
US+GAAD sensitivity = 88.5%												
Early stage N=26	US +		US -		AFP >		AFP ≤		PIVKA-II >		PIVKA-II ≤	
	GAAD >		11		8		GAAD >		9		10	
	GAAD >		15		4		GAAD >		1		6	
	GAAD ≤		4		3		GAAD ≤		1		6	
US+GAAD sensitivity = 96.3%												
Late stage N=27	US +		US -		AFP >		AFP ≤		PIVKA-II >		PIVKA-II ≤	
	GAAD >		19		3		GAAD >		13		9	
	GAAD >		19		3		GAAD >		2		3	
	GAAD ≤		4		1		GAAD ≤		0		5	

Sensitivity/Specificity stratified by cirrhotic status

	Non-HCC, n (%)	HCC, n (%)	AUROC	P value	SEN (%)	SPE (%)	PPV (%)	NPV (%)	ACC (%)
Non-LC									
AFP> 20 ng/ml	5 (1.6)	6 (28.6)	0.78	<0.001	28.6	98.4	54.5	95.4	94.1
PIVKA-II> 28.4 ng/mL	6 (1.9)	14 (66.7)	0.94	<0.001	66.7	98.1	70.0	97.8	96.1
GAAD score >2.57	10 (3.2)	15 (71.4)	0.87	<0.001	71.4	96.8	60.0	98.1	95.2
GAAD score >2.57 plus sonography	10 (3.2)	21 (100)		<0.001	100	96.8	67.7	100	97.0
LC									
AFP> 20 ng/ml	5 (8.3)	17 (53.1)	0.76	<0.001	53.1	91.7	77.3	78.6	78.3
PIVKA-II> 28.4 ng/mL	12 (20.0)	23 (71.9)	0.87	<0.001	71.9	80.0	65.7	84.2	77.2
GAAD score >2.57	10 (16.7)	26 (81.3)	0.90	<0.001	81.3	83.3	72.2	89.3	82.6
GAAD score >2.57 plus sonography	10 (16.7)	28 (87.5)		<0.001	87.5	83.3	73.7	92.6	84.7

Note: HCC: hepatocellular carcinoma. AUROC: Area Under the Receiver Operating Characteristic curve. SEN: sensitivity. SPE, specificity. PPV: positive predictive value. NPV: neg predictive value. ACC: accuracy.
*Patient distribution in terms of BCLC stages (BCLC 0-A vs. BCLC B-C) was similar between cirrhosis and non-cirrhosis.

Sensitivity/Specificity stratified by etiology

	Non-HCC, n (%)	HCC, n (%)	AUROC	P value	SEN (%)	SPE (%)	PPV (%)	NPV (%)	ACC (%)
HBV									
AFP> 20 ng/ml	7 (9.0)	16 (48.5)	0.75	<0.001	48.5	91.0	69.6	80.7	78.4
PIVKA-II> 28.4 ng/mL	5 (6.4)	21 (63.6)	0.92	<0.001	63.6	93.6	80.8	85.9	84.7
GAAD score >2.57	9 (11.5)	24 (72.7)	0.88	<0.001	72.7	88.5	72.7	88.5	83.8
GAAD score >2.57 plus sonography	9 (11.5)	29 (87.9)		<0.001	87.9	88.5	76.3	94.5	88.3
HCV									
AFP> 20 ng/ml	3 (3.0)	7 (36.8)	0.75	<0.001	36.8	97.0	70.0	88.9	87.3
PIVKA-II> 28.4 ng/mL	12 (12.1)	15 (78.9)	0.89	<0.001	78.9	87.9	55.6	95.6	86.4
GAAD score >2.57	8 (8.1)	16 (84.2)	0.90	<0.001	84.2	91.9	66.7	96.8	90.7
GAAD score >2.57 plus sonography	8 (8.1)	19 (100)		<0.001	100	91.9	70.4	100	93.2

Note: HCC: hepatocellular carcinoma. AUROC: Area Under the Receiver Operating Characteristic curve. SEN: sensitivity. SPE, specificity. PPV: positive predictive value. NPV: negative predictive value. ACC: accuracy.
*Patient distribution in terms of BCLC stages (BCLC 0-A vs. BCLC B-C) was similar between viral etiology.