Biomarkers of oncogenesis, adipose tissue dysfunction and systemic inflammation for the detection of hepatocellular carcinoma in patients with non-alcoholic fatty liver disease

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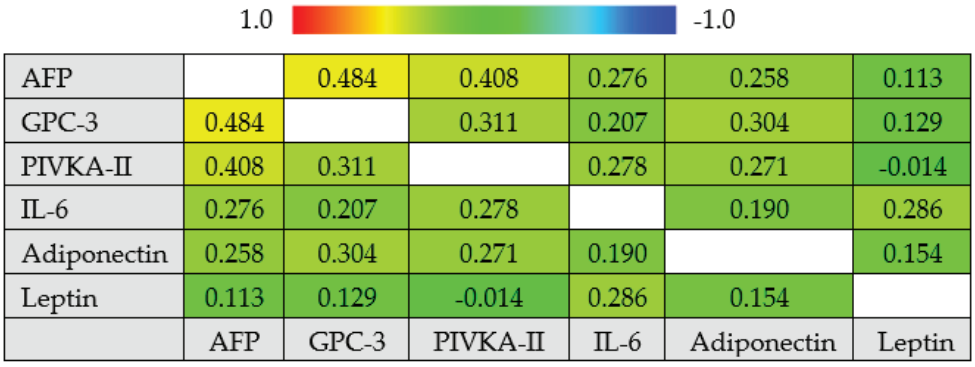
Summary: This study aimed to investigate the diagnostic accuracy of alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist-II (PIVKA-II), Glypican-3, adiponectin, leptin and interleukin-6 (IL-6), alone or in combination, for differentiating patients with non-alcoholic fatty liver disease (NAFLD) with or without hepatocellular carcinoma (HCC). For this study, a total of 191 NAFLD patients (121 males and 70 females) with advanced fibrosis/cirrhosis were enrolled, 72 (38%) of which were also diagnosed with HCC.

Results: Median serum levels of AFP, PIVKA-II, Glypican-3, adiponectin and IL-6 were significantly higher in HCC patients compared to controls (all $p < 0.001$). Only plasma leptin values were not significantly different between the two groups of patients ($p = 0.649$).

Biomarkers	Controls	HCC	P Value
AFP (ng/mL), median IQR	3.8 (2.7–5.1)	6.0 (4.5–13.5)	<0.001
PIVKA-II (mAU/mL), median IQR	33 (27–45)	121 (54–1135)	<0.001
Glypican-3 (pg/mL), median IQR	35 (20–56)	75 (40–104)	<0.001
Adiponectin (µg/mL), median IQR	2.17 (1.35–3.30)	4.95 (2.87–7.03)	<0.001
Leptin (ng/mL), median IQR	20.6 (9.8–33.4)	20.3 (13.2–34.9)	0.649
IL-6 (pg/mL), median IQR	3.1 (1.9–5.8)	6.0 (4.1–12.5)	<0.001

Furthermore, correlation analysis showed moderate correlation between serum Glypican-3 and serum AFP ($r_s = 0.484$, 95% CI 0.368–0.586, $p < 0.001$), serum PIVKA-II ($r_s = 0.311$, 95% CI 0.177–0.434, $p < 0.001$) and serum adiponectin ($r_s = 0.304$, 95% CI 0.169–0.428, $p < 0.001$).



Correlogram of the biomarkers' concentrations. Cells are colored according to the magnitude of the correlations, raging from dark red for positive correlations to dark blue for negative correlations. Correlation coefficients (rs) has been calculated by Spearman test. Abbreviations: alpha-fetoprotein (AFP), Glypican-3 (GPC-3) hepatocellular carcinoma (HCC), interleukin-6 (IL-6).

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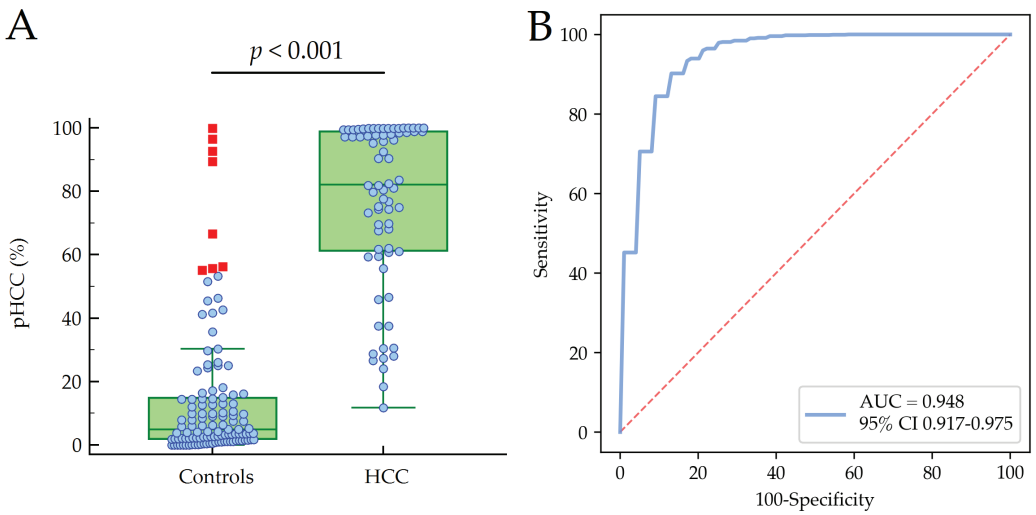
As for diagnostic accuracy for HCC detection, PIVKA-II showed the best performance with an area under the curve (AUC) of 0.853, followed by adiponectin (AUC = 0.770), AFP (AUC = 0.763), Glypican-3 (AUC = 0.759) and IL-6 (AUC = 0.731).

Biomarker	AUC, 95% CI	Cut-off*	Se	Sp	+LR	-LR
AFP (ng/mL)	0.763, 0.696-0.821	>4.4	76.4	68.9	2.46	0.34
PIVKA-II (mAU/mL)	0.853, 0.794-0.900	>56	75.0	85.7	5.25	0.29
Glypican-3 (gp/mL)	0.759, 0.691-0.817	>64	62.5	82.4	3.54	0.46
Adiponectin (µg/mL)	0.770, 0.704-0.828	>3.68	62.5	81.5	3.38	0.46
IL-6 (pg/mL)	0.731, 0.662-0.792	>3.6	79.2	62.2	2.09	0.34

*Identified by Youden J statistic. AUC values were calculated by receiver operating characteristic curve analysis. Abbreviations: alpha-feto-protein (AFP), area under the curve (AUC), confidence interval (CI), hepatocellular carcinoma (HCC), interleukin-6 (IL-6), protein induced by vitamin K absence or antagonist II (PIVKA-II), sensitivity (Se), specificity (Sp), positive likelihood ratio (+LR), negative likelihood ratio (-LR).

Lastly, the accuracy of biomarker combinations was assessed using a stratified cross-validation approach. The combination of age, gender, PIVKA-II, Glypican-3, and adiponectin further improved the diagnostic accuracy (AUC = 0.948), allowing this model to correctly identify 87% of HCC patients, with a sensitivity of 86.9% and a specificity of 88.1% (at a cut-off pHCC = 50%).



Median values of pHCC in patients with and without HCC (A) and diagnostic accuracy of the model (B). Red squares indicate values that are larger than the upper quartile plus 3 times the interquartile range. p value was calculated by Mann-Whitney U test. Abbreviations: area under the curve (AUC), confidence interval (CI), hepatocellular carcinoma (HCC), probability of hepatocellular carcinoma (pHCC).

Conclusions: The development of prediction models including age, gender, PIVKA-II, Glypican-3, and adiponectin, further improved the diagnostic accuracy for HCC detection.