

Supplementary Materials

Table S1. Median biomarkers values according to the different stages of liver disease.

Biomarkers	Controls		HCC		p-Value
	Advanced Fibrosis	Cirrhosis	Early (BCLC = 0/A)	Advanced (BCLC = B/C/D)	
AFP (ng/mL), median IQR	3.0 (2.0–3.8)	4.2 (3.5–5.4)	5.0 (3.7–8.6)	7.8 (5.7–36.7)	<0.001
PIVKA-II (mAU/mL), median IQR	33 (27–47)	33 (28–44)	74 (45–204)	658 (145–2144)	<0.001
GPC-3 (pg/mL), median IQR	27 (17–40)	43 (20–71)	73 (39–101)	80 (40–108)	<0.001
Adiponectin (µg/mL), median IQR	1.79 (1.21–3.01)	2.42 (1.47–3.54)	4.64 (2.64–6.62)	5.54 (3.03–10.11)	<0.001
Leptin (ng/mL), median IQR	15.5 (5.9–28.3)	26.3 (15.4–37.7)	19.5 (13.5–31.2)	20.4 (9.4–56.6)	0.020
IL-6 (pg/mL), median IQR	2.9 (1.8–4.6)	3.3 (2.5–7.0)	5.8 (3.8–11.3)	9.5 (4.6–18.5)	<0.001

p values were calculated by Kruskal-Wallis test. Abbreviations—alpha-fetoprotein (AFP), Barcelona Clinic Liver Cancer (BCLC), glypican 3 (GPC3), hepatocellular carcinoma (HCC), interquartile range (IQR), interleukin-6 (IL-6).

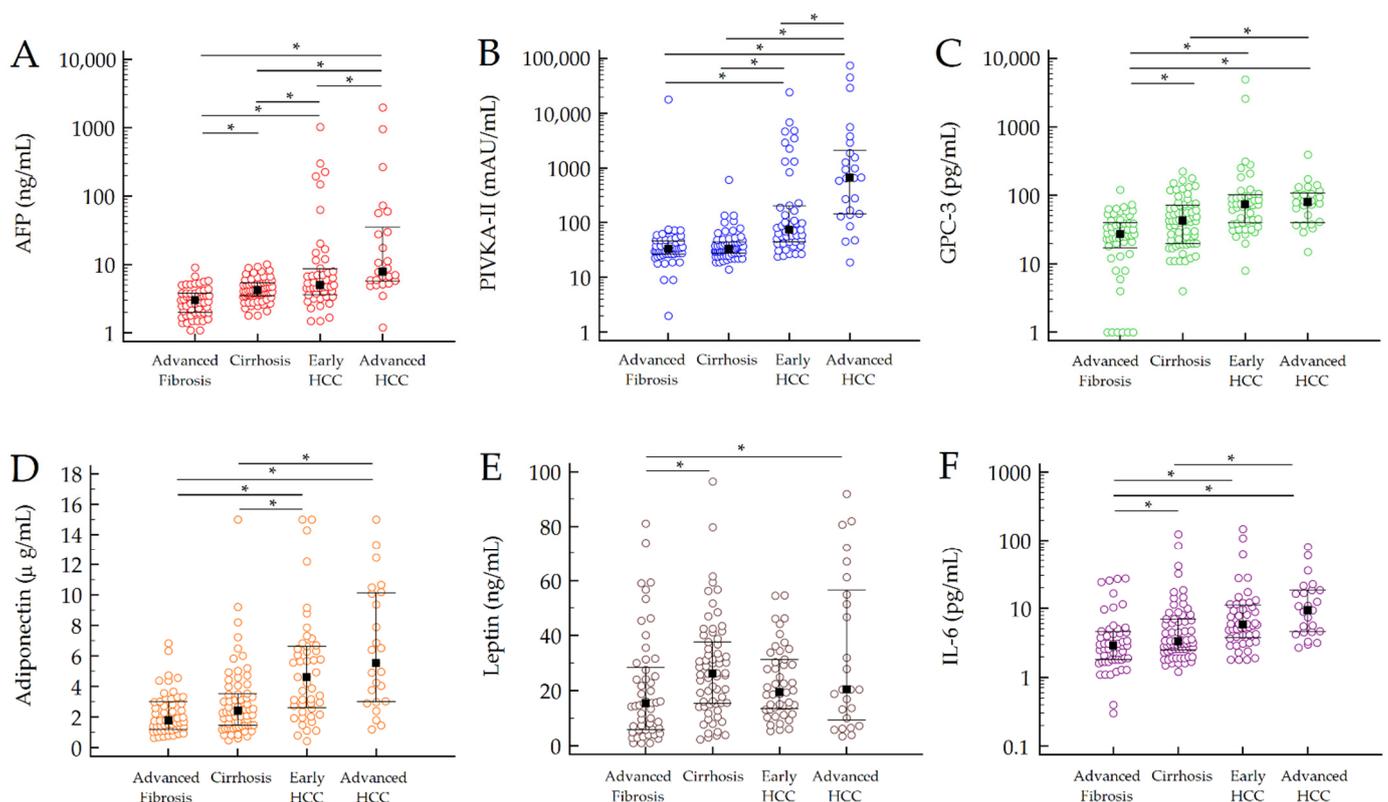


Figure S1. Median values of AFP (A), PIVKA-II (B), GPC-3 (C), adiponectin (D), leptin (E) and IL-6 (F) according to the different stages of liver disease. **p* < 0.05; *p* values have been calculated by Mann-Whitney test. Black squares and error bars represent respectively the median value and the IQR in each group of patients. The values of AFP, PIVKA-II, GPC-3 and IL-6 have been depicted in Log scale due to data skewness. Abbreviations—alpha-fetoprotein (AFP), Barcelona Clinic Liver Cancer (BCLC), glypican 3 (GPC3), hepatocellular carcinoma (HCC), interquartile range (IQR), interleukin-6 (IL-6), protein induced by vitamin K absence or antagonist II (PIVKA-II).

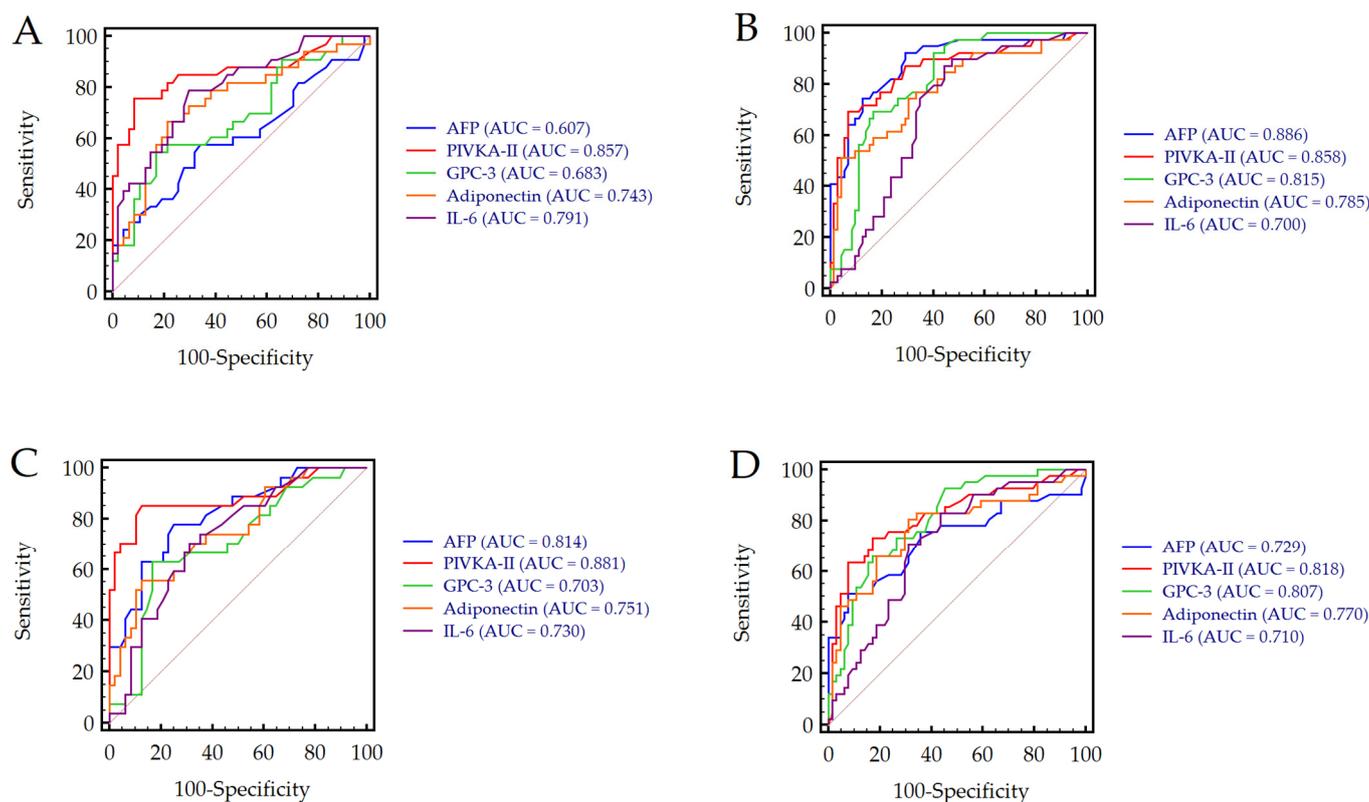


Figure S2. Diagnostic accuracy of AFP, PIVKA-II, GPC-3, adiponectin and IL-6 for the detection of HCC in lean (A) and obese patients (B), and in normal-glucose tolerant (C) and diabetic patients (D). Abbreviations—alpha-fetoprotein (AFP), glypican 3 (GPC3), hepatocellular carcinoma (HCC), interleukin-6 (IL-6), protein induced by vitamin K absence or antagonist-II (PIVKA-II).

Table S2. Comparison of the diagnostic accuracy of AFP, PIVKA-II, GPC-3, adiponectin and IL-6 for the detection of HCC.

Biomarkers	AFP	PIVKA-II	GPC-3	Adiponectin	IL-6
AFP		Δ AUC = 0.090 $p = 0.044$	Δ AUC = 0.004 $p = 0.918$	Δ AUC = 0.007 $p = 0.888$	Δ AUC = 0.032 $p = 0.513$
PIVKA-II	Δ AUC = 0.090 $p = 0.044$		Δ AUC = 0.094 $p = 0.035$	Δ AUC = 0.083 $p = 0.075$	Δ AUC = 0.122 $p = 0.009$
GPC-3	Δ AUC = 0.004 $p = 0.918$	Δ AUC = 0.094 $p = 0.035$		Δ AUC = 0.011 $p = 0.818$	Δ AUC = 0.028 $p = 0.575$
Adiponectin	Δ AUC = 0.007 $p = 0.888$	Δ AUC = 0.083 $p = 0.075$	Δ AUC = 0.011 $p = 0.818$		Δ AUC = 0.039 $p = 0.423$
IL-6	Δ AUC = 0.032 $p = 0.513$	Δ AUC = 0.122 $p = 0.009$	Δ AUC = 0.028 $p = 0.575$	Δ AUC = 0.039 $p = 0.423$	

Abbreviations—alpha-fetoprotein (AFP), glypican 3 (GPC3), interleukin-6 (IL-6).

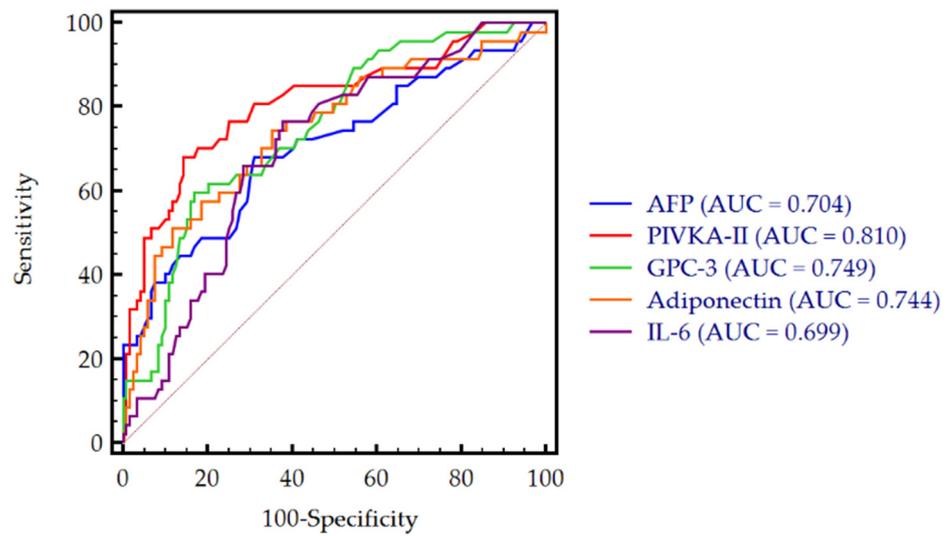


Figure S3. Diagnostic accuracy of AFP, PIVKA-II, GPC-3, adiponectin and IL-6 for the detection of early HCC. Abbreviations—alpha-fetoprotein (AFP), glypican 3 (GPC3), hepatocellular carcinoma (HCC), interleukin-6 (IL-6), protein induced by vitamin K absence or antagonist-II (PIVKA-II).

25

26

27

28

29

30