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ORIGINAL ARTICLE

Assessment of Serum Fibroblast Growth factor 19 and Des-gamma Carboxy Prothrombin for Early Diagnosis of Hepatocellular Carcinoma.

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is one of the most common primary malignancies worldwide where abnormal production of des-γ-carboxyl prothrombin (DCP) and fibroblast growth factor 19 (FGF19) has been seen. **Aim:** Evaluation of the usefulness of DCP and serum fibroblast growth factor 19 for hepatocellular cancer early detection. **Methods:** A case control study which was conducted on 105 subjects at Zagazig University Hospitals. Subjects enrolled in the study were divides into 3 groups: group 1: (35) Cases of HCC patients, recently diagnosed by laboratory, ultrasound and triphasic CT, haven't received any treatment, group 2: (35) Cases of chronic liver disease patients, diagnosed by laboratory and ultrasound and group 3: (35) healthy controls. Fibroblast Growth factor 19 and Des-gamma Carboxy Prothrombin were measured in all cases. **Results:** Regarding serum FGF-19, DCP, and alfa feto protein, there is a statistically significant difference between the groups under investigation.For HCC detection, ROC analysis showed the best cut off value for FGF-19 was >238.2 pg/ml with area under the curve (AUC) 0.857, sensitivity 82.9%, specificity 80%, positive predictive value (PPV) 67.4%, negative predictive value (NPV) 90.3%, and total accuracy 81%. However, DCP at a cut-off point >31.5 ng/ml had an AUC 0.902, sensitivity 85.7%, specificity 88.6%, PPV 78.9%, NPV 92.5%, and total accuracy 87.6%. **Conclusion**: FGF-19, when used in conjunction with traditional markers like AFP and DCP, may enhance the detection of HCC, especially at an early stage, and may have potential clinical utility in HCC diagnosis and monitoring.

Keywords: Fibroblast Growth factor 19, Des-gamma Carboxy Prothrombin, Hepatocellular Carcinoma.

INTRODUCTION

Hepatocellular carcinoma (HCC) is regarded as the second most prevalent cause of mortality globally and the fifth most common malignant tumor. HCC represents 75~85% of primary liver cancers. Despite the advanced imaging modalities and the recent treatment guidelines, the 5th year survival rate is less than 20% **[1].**

Most HCC cases arise on top of cirrhosis. Metabolic causes (e.g., diabetes, obesity) and non-alcoholic fatty liver (NAFLD) are very common risk factors of cirrhosis, whereas HCV and HBV associated cirrhosis prevalence has decreased **[2].**

For early cancer detection we need simple, quick, and inexpensive economic methods. Thus, tumour markers have a vital role for this purpose for their easy detection, being non-invasive, and inexpensive. Histopathology and imaging modalities such as triphasic MRI and Ultrasound are also useful in detection of hepatocellular carcinoma but they are expensive **[3].**

Fibroblast growth factors (FGFs) are important regulators of various physiological and

pathological functions through the regulation of cell differentiation, proliferation, migration, and survival. FGF-19, in instance, is mostly produced in the ileum and is essentially nonexistent in the normal human liver. It has recently been proposed that hepatocytes may manufacture FGF-19 in cases of cholestasis, cirrhosis, and HCC. It plays a part in the onset and development of HCC and is released as protective negative feedback to shield hepatocytes from the cytotoxicity of bile acids **[4].**

On the other hand, a high level of FGF-19 in patients with HCC is associated with a poor prognosis and may stimulate tumor development by the application of an antiapoptotic impact through the fibroblast growth factor receptor 4 (FGFR4) **[5].**

Additionally, the liver produces prothrombin, a clotting agent, in an aberrant form known as des-gamma-carboxy prothrombin (DCP). Tumor cells manufacture it abnormally because of the prothrombin precursor's post-translational carboxylation, which eliminates its activity. In the event of a vitamin K deficiency, DCP is comparable to the prothrombin deficit. As DCP could be overexpressed in liver cancer, it could be used as a serum biomarker in HCC **[6].**

SUBJECTS AND METHODS

This was a case control study which was conducted on 105 subjects at Zagazig University Hospitals during the period of January 2023 to August 2023 and the samples were analyzed at Zagazig University Hospital Laboratories.

Subjects enrolled in the study were divides into 3 groups: group 1: (35) Cases of HCC patients, recently diagnosed by laboratory, ultrasound and triphasic CT, haven't received any treatment, and admitted to Tropical medicine department, Faculty of medicine Zagazig University Hospitals, group 2: (35) Cases of chronic liver disease patients, diagnosed by laboratory and ultrasound, admitted to Tropical medicine department, Faculty of medicine Zagazig University Hospitals and group 3: (35) age and gender matched, apparently healthy volunteer controls.

Inclusion criteria included adult patients recently diagnosed with HCC laboratory and radiologically admitted to Zagazig University Hospitals with age above 18 years and chronic liver disease patients admitted to Zagazig University Hospitals.

Exclusion criteria included patients underwent tumor resection or ablation and patients with other malignancies.

A complete history, clinical examination, routine laboratory investigations, including a complete blood picture, liver function tests (AST, ALT, total bilirubin, albumin), kidney function tests (creatinine, urea), coagulation profile (prothrombin time, INR, partial thromboblastin time), AFP, and serum levels of FGF19 and DCP by ELISA for patients and control groups were performed on all study participants.

Ethics approval

Approval was obtained from Zagazig University Institutional Review Board (IRB# 9997). Consent from all patients on participating in the study. The Declaration of Helsinki, the international Medical Association's guideline of ethics for studies involving humans, was followed in the conduct of this study.

Specimen collection and storage

For serum needed for liver, kidney functions and AFP, three milliliters of venous blood were drawn from everyone via vein puncture while maintaining strict aseptic conditions. The blood was then placed in a sterile, clean separator gel tube and allowed to coagulate. After 20 minutes of centrifugation in 2000–3000 r.p.m., the supernatant was extracted and refrigerated at -4 C until analysis. The material is centrifuged once more if precipitation shows up. For the CBC test, two milliliters of venous blood from everyone were drawn via vein puncture while everything was done aseptically. The blood was then placed in a sterile EDTA vacutainer. Everyone had two milliliters of venous blood drawn via vein puncture while everything was kept aseptic, and the blood was then placed in a sterile citrate vacutainer to measure the coagulation profile.

Serum level of FGF19 measurement

ELISA was used to assess FGF19 in serum samples. The kit, Catalogue No. 201-12-2199, was supplied by SunRed Biotechnology Company (China).

Test principle: We performed the assay according to manufacture recommendation.

Serum level of DCP measurement

ELISA was used to measure DCP in serum samples. The kit was sent by SunRed Biotechnology Company (China), reference number 201-12-5324 in their catalog.

Test principle: We performed the assay according to manufacture recommendation.

STATISTICAL ANALYSIS

Microsoft Office Excel 2010 and the Statistical Package for Social Sciences, version 26, were used to tabulate and statistically analyze the data (SPSS: An IBM Company). Chi-squared test ($\chi 2$), Mann Whitney test, Independent "t" test, single test "t" test, Kruskal Wallis Test, ROC curves, Kplain Meier curve and log rank test were one-way analysis of variance (ANOVA), used to compare the mean of one group with the mean of another using Fisher's Least Significant Difference (LSD) test.

RESULTS

Regarding age and gender, there is a statistically non-significant difference between the groups under study (Table 1).

Regarding albumin and total bilirubin, there is a statistically significant difference between the groups under investigation. When comparing LSD, there is a considerable difference between each of the two groups. Between the groups under study, there is a statistically significant difference in hemoglobin, AST, platelet count, INR, WBCs, and serum urea. When comparing the LSD groups, there is a substantial difference between the control group and the other groups. Regarding ALT, there is a statistically significant difference between the groups under investigation. A pairwise analysis reveals a substantial difference between the groups with cirrhosis and HCC. Regarding serum creatinine, there is a statistically significant difference between the groups under investigation. Pairwise analysis reveals a substantial difference between the HCC group and all other groups. (Table 2).

Serum FGF-19, DCP, and alfa feto protein levels in the investigated groups differ statistically significantly. When two groups are compared pairwise, there is a significant difference between them (Table 3).

A cutoff value of ≥48ng/ml is the most effective for predicting HCC, with an area under curve of 0.793, sensitivity of 71.4%, specificity of 74.3%, positive predictive value of 58.1%, negative predictive value of 83.9%, and overall accuracy of 73.3% observed. ≥238.2 pg/ml is the optimal cutoff value for FGF-19 in the prediction of HCC, with an area under the curve of 0.857, sensitivity of 82.9%, specificity of 80%, positive predictive value of 67.4%, negative predictive value of 90.3%, and overall accuracy of 81%. The optimal DCP cutoff value for predicting HCC is less than 31.5 ng/ml, with an area under the curve of 0.902, sensitivity of 85.7%, specificity of 88.6%, positive predictive value of 78.9%, negative predictive value of 92.5%, and overall accuracy of 87.6%. Considering presence of FGF≥238.2 pg/ml, AFP≥48 pg/ml and DCP≥31.4 ng/ml, sensitivity is to 97.1% and specificity became 67.1%, PPV 59.6%, NPV 97.9% and overall accuracy 76.2%. Considering presence of AFP≥48 pg/ml and DCP≥31.4 ng/ml, sensitivity is to 97.1% and specificity became 80%, PPV 70.8%, NPV 98.2% and overall accuracy 85.7%. Considering presence of FGF≥238.2 pg/ml and/or AFP≥48 pg/ml, sensitivity is 94.3% and specificity became 72.9%, PPV 63.5%, NPV 96.2% and overall accuracy 80% (Table 4).

For the purpose of predicting small HCC nodules, the optimal cutoff value for AFP is ≥31.4 ng/ml, with an area under curve of 0.82, sensitivity of 82.2%, specificity of 70%, positive predictive value of 52.3%, negative predictive value of 92.5%, and overall accuracy of 75.3%. The DCP cutoff value that yields the best results for small HCC nodule prediction is ≥27.3 pg/ml. Its area under the curve is 0.854, and its sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy are 82.2%, 71.4%, and 53.5%, respectively. In terms of predicting small Hcc, 230.539 pg/ml is the optimal cutoff value for FGF-19, with an area under the curve of 0.899, sensitivity of 82.5%, specificity of 80%, positive predictive value of 62.2%, negative predictive value of 93.3%, and overall accuracy of 81.4%.. Considering presence of AFP≥31.4 ng/ml, and DCP≥27.3 g/ml, sensitivity is to 96.3% and specificity became 72.9%, PPV 57.8%, NPV 98.1% and overall accuracy 79.4%. Considering presence of FGF≥230.539 pg/ml, and AFP≥31.4 ng/ml, sensitivity is to 96.3% and specificity became 64.3%, PPV 51%, NPV 97.8% and overall accuracy 75.3% (Table 5).

The relationships between FGF-19 and DCP, alfa fetoprotein, and age are all statistically significantly favorable. A statistically insignificant association has been observed between FGF-19 and other indices. (Table 6).

A statistically significant positive association has been observed between DCP and FGF-19, alfa fetoprotein, and age. The relationship between DCP and other factors is statistically not significant. (Table 7).

Table (1): Comparison between the studied groups regarding demographic data:

	HCC group	Cirrhosis group	Control group	χ^2	p
	N=35(%)	N=35(%)	N=35(%)		
Gender: **Female** **Male**	 17 (48.5%) 18 (51.4%)	 15 (42.9%) 20 (57.1%)	 19 (54.3%) 16 (45.7%)	MC	0.734
	Mean±SD	Mean ± SD	Mean ± SD	F	p
Age (year)	64.0 ± 6.39	52.14 ± 8.57	59.06 ± 8.9	0.780	0.463

χ^2Chi square test F One way ANOVA test **p >0.05 is statistically non-significant. There is statistically non-significant difference between the three groups regarding age and sex.

Table (2): Comparison between the studied groups regarding laboratory data:

	HCC group	Cirrhosis group	Control group	χ^2	p
	Mean ± SD	Mean ± SD	Mean ± SD		
Albumin (g/dl)	2.28 ± 0.43	2.66 ± 0.78	3.8 ± 0.16	80.559	<0.001**
LSD	P_1 0.001*	P_2 <0.001**	P_3 <0.001**		
Hemoglobin (g/dl)	9.8 ± 1.87	9.26 ± 1.82	14.03 ± 1.36	123.319	<0.001**
LSD	P_1 0.186	P_2 <0.001**	P_3 <0.001**		
	Median (IQR)	Median (IQR)	Median (IQR)	KW	p
Total bilirubin (mg/dl)	9(2 – 15)	1.8(1.02 – 2.4)	1(1 – 1.2)	53.607	<0.001**
Pairwise	P_1 <0.001**	P_2 <0.001**	P_3 <0.001**		
AST (U/L)	168(99 – 236)	79(65 – 111)	33(32 – 34)	58.322	<0.001**
Pairwise	P_1 0.001	P_2 <0.001**	P_3 <0.001**		
ALT (U/L)	39(30 – 44)	28(22 – 43)	32(32 – 34)	7.679	0.022*
Pairwise	P_1 0.006*	P_2 0.239	P_3 0.113		
Urea (mg/dl)	97(96 – 98)	44(27 – 68)	33(22 – 55)	55.649	<0.001**
Pairwise	P_1 0.01**	P_2 <0.001**	P_3 <0.001**		
Creatinine (mg/dl)	1(0.9 – 1)	0.96(0.79 – 1)	0.9(0.8 – 0.9)	12.53	0.002*
Pairwise	P_1 0.012*	P_2 0.372	P_3 <0.001**		
WBC (10^3/mm^3)	9(7 – 14)	8.5(7 – 12)	5(5 – 6)	45.766	<0.0^
Pairwise	P_1 0.879	P_2 <0.001**	P_3 <0.001**		
Platelet(10^3/mm^3)	130(88 – 220)	133(110 – 165)	380(360 – 400)	65.691	<0.001**
Pairwise	P_1 0.639	P_2 <0.001**	P_3 <0.001**		
INR	2.5(2.4 – 2.8)	1.5(1.1 – 1.8)	1 (0.9 – 1.2)	41.667	<0.001**
Pairwise	P_1 0.001**	P_2 <0.001**	P_3 <0.001**		

χ^2Chi square test F One way ANOVA test **p0.001 is statistically highly significant LSD Fisher least significant difference p1 difference between HCC group and cirrhosis group p2 difference between cirrhosis and control groups p3 difference between HCC and control groups IQR interquartile range KW Kruskal Wallis test *p<0.05 is statistically significant

Table (3): Comparison between the studied groups regarding Serum Fibroblast Grow2th factor 19 and Des-gamma Carboxy Prothrombin and AFP:

	HCC group	Cirrhosis group	Control group	KW	p
	Median (IQR)	Median (IQR)	Median (IQR)		
FGF-19(pg/ml)	288.88 (236.08–399.63)	230 (193 – 287)	201 (172 – 217)	32.989	<0.001**
Pairwise	P_1 0.007*	P_2 0.002*	P_3 <0.001**		
DCP(ng/ml)	53(34.9 – 63.3)	28(22 – 44)	23(19 – 24)	48.367	<0.001**
Pairwise	P_1 <0.001**	P_2 0.001**	P_3 <0.001**		
AFP (ng/dl)	450 (200 – 600)	28 (22 – 44)	2.5(2 – 8.9)	72.409	<0.001**
Pairwise	P_1 0.002*	P_2 <0.001**	P_3 <0.001**		

*p≤0.001 is statistically highly significant, LSD Fisher least significant difference, p1 difference between HCC group and cirrhosis group, p2 difference between cirrhosis and control groups, p3 difference between HCC and control groups IQR interquartile range KW Kruskal Wallis test *p<0.05 is statistically significant

Table (4):Performance of FGF-19, DCP and AFP in diagnosis of HCC among studied participants:

	Cutoff	AUCs	Sensitivity	Specificity	PPV	NPV	Accuracy	p
AFP	≥48ng/ml	0.793	71.4%	74.3%	58.1%	83.9%	73.3%	<0.001**
FGF-19	≥238.2pg/ml	0.857	82.9%	80%	67.4%	90.3%	81%	<0.001**
DCP	≥31.5ng/ml	0.902	85.7%	88.6%	78.9%	92.5%	87.6%	<0.001**
Double markers								
FGF-19, DCP	Either is positive		94.3%	67.1%	58.9%	95.9%	76.2%	<0.001**
FGF-19+AFP	Either is positive		94.3%	72.9%	63.5%	96.2%	80%	<0.001**
DCP+AFP	Either is positive		97.1%	80%	70.8%	98.2%	85.7%	<0.001**
Triple markers								
DCP, FGF-19, AFP	Either is positive		97.1%	67.1%	59.6%	97.9%	76.2%	<0.001**

AUC area under curve PPV positive predictive value NPV negative predictive value **p≤0.001 is statistically highly significant

Table (5): Performance of FGF-19, DCP and AFP in diagnosis of small HCC (<2cm) among studied participants:

	Cutoff	AUCs	Sensitivity	Specificity	PPV	NPV	Accuracy	P
AFP	≥31.4ng/ml	0.82	82.2%	70%	52.3%	92.5%	75.3%	<0.001**
DCP	≥27.3ng/ml	0.845	82.2%	71.4%	53.5%	92.6%	75.3%	<0.001**
FGF-19	≥230.539 Pg/ml	0.899	82.5%	80%	62.2%	93.3%	81.4%	<0.001**
Double markers								
FGF-19, DCP	Either is positive		100%	65.7%	52.9%	100%	75.3%	<0.001**
FGF-19+AFP	Either is positive		96.3%	64.3%	51%	97.8%	75.3%	<0.001**
DCP+AFP	Either is positive		96.3%	72.9%	57.8%	98.1%	79.4%	<0.001**
Triple markers								
DCP, FGF-19, AFP	Either is positive		100%	60%	49.1%	100%	71.1%	<0.001**

AUC area under curve PPV positive predictive value NPV negative predictive value *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (6): Correlation between FGF-19 and baseline data among studied patients:

	FGF-19	
	R	p
Age (year)	0.372	<0.001**
Albumin (g/dl)	0.12	0.322
Hemoglobin (g/dl)	0.105	0.389
Total bilirubin (mg/dl)	0.017	0.889
AST (U/L)	-0.16	0.185
ALT (U/L)	-0.11	0.36
Urea (mg/dl)	-0.011	0.929
Creatinine (mg/dl)	0.071	0.558
WBC (10^3/mm^3)	-0.163	0.178
Platelet(10^3/mm^3)	0.028	0.816
INR	-0.054	0.659
AFP	**0.285**	**0.017***
DCP	**0.39**	**0.001****

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (7): Correlation between DCP and baseline data among studied patients:

	DCP	
	R	**p**
Age (year)	0.314	<0.001**
Albumin (g/dl)	0.077	0.526
Hemoglobin (g/dl)	0.046	0.708
Total bilirubin (mg/dl)	-0.03	0.805
AST (U/L)	-0.08	0.51
ALT (U/L)	-0.074	0.545
Urea (mg/dl)	-0.181	0.134
Creatinine (mg/dl)	-0.089	0.462
WBC (10^3/mm^3)	-0.017	0.889
Platelet(10^3/mm^3)	0.031	0.8
INR	0.007	0.954
AFP	**0.562**	**<0.001****
FGF-19	**0.39**	**0.001****

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant.

DISCUSSION

In our study, in the HCC group, hemoglobin levels were significantly lower in both HCC and Cirrhosis groups compared to the Control group. Median values for platelet count, exhibit significant differences among the groups.

This is in line with the findings of **Al-Sayed et al. [7],** who evaluated the serum level of Des-gamma carboxy prothrombin as a biomarker for the early diagnosis of hepatocellular carcinoma following chronic active hepatitis as well as infection with the hepatitis C virus (HCV). According to their study, there was a noteworthy distinction between the three groups under investigation in terms of hematological data. Specifically, patients with cirrhotic active hepatitis post virus C and patients with HCC on top of cirrhotic active hepatitis post virus C exhibited a considerable decline in TLC, Hb, and platelets in comparison to control group . In contrast to patients with cirrhotic active hepatitis post virus C, patients with HCC exhibited decreased levels of TLC, Hb, and platelets.

The findings of **Gad et al. [8],** who revealed that individuals with cirrhosis and HCC had noticeably reduced platelet counts, were consistent with this. WBC differences between the cirrhosis, HCC, and control groups were statistically not significant.

In our study, median values for albumin (2.28 - 2.66 - 3.8), total bilirubin (9 – 1.8 -1), AST (168 – 79- 33), and INR (2.5 – 1.5 - 1) all exhibit significant differences among the groups (P1, P2, and P3 all < 0.001).

Regarding to liver function tests, **Al-Sayed et al. [7]** reported that, comparing patients with cirrhotic active hepatitis post virus C and patients with HCC on top of cirrhotic active hepatitis post virus C to control group, there were significant increases in ALT, AST, total bilirubin, and INR and significant decreases in albumin. In contrast to group II, patients in group III exhibited lower levels of albumin and greater levels of ALT, AST, total bilirubin, and INR.

This result was in line with a study by **Anber et al. [9],** which found that the HCC patients they looked at had higher serum levels of AST and ALT. The difference between serum AST and ALT increases with the progression of the disease. Moreover, prothrombin time lengthening and decreased blood albumin levels are observed in HCC. According to his arguments, the development of HCC with low serum albumin concentration and prolonged prothrombin time may be indicated by the fast deterioration that occurs in cirrhotic individuals with decreased liver synthetic functions

In our study, In the HCC group, FGF-19 levels were significantly higher; median (288.88pg/ml) compared to both the Cirrhosi; median (230pg/ml) and Control groups; median (201 pg/ml) (P1 < 0.007 and P2 < 0.002).

This is in line with the findings of **Mohamed et al. [10],** who measured blood FGF-19 concentrations in HCC cases and evaluated the diagnostic utility of this method for HCC identification. They found that the HCC group had considerably higher serum FGF-19 levels than the cirrhosis and control groups.

Maeda et al. [11] found greater serum levels of FGF-19 in their HCC group (214.5 pg/mL) in comparison to the control group (78.8 pg/mL, P =

0.002) and the cirrhosis group (100.1 pg/mL, P < 0.001). These findings are consistent with our findings. In their investigation, however, no statistically significant distinction was found between the cirrhotic cases and controls.

Sun et al. [12] found that FGF-19 levels were greater in the HCC and diabetes-HCC groups compared to the control and diabetes groups (220.5, 185.1, 115.8, and 70.4 pg/mL, respectively, P < 0.001). These results are in line with our own findings. All of these findings suggest that FGF-19 might be involved in the etiology of HCC.

Despite the fact that the liver produces bile acid from cholesterol, enterohepatic circulation strictly controls the amount of bile acid synthesized in the liver as well as its secretion. On the other hand, hepatocyte injury is caused by cholestasis and liver dysfunction, which also raise the concentration of bile acid in the blood and bile **[13].** Normal hepatocytes, like HCC cells, secrete FGF19 in an autocrine manner to shield them from the harmful effects of bile acid. Given that FGF19 suppresses the manufacture of bile acid by down regulating cholesterol 7 alpha-hydroxylase (Cyp7a), patients with CLD may have a slight increase in serum FGF19 levels, which could have the unintended consequence of raising serum bile acid levels **[14].**

In our study, DCP and AFP levels are significantly elevated in both HCC and Cirrhosis groups compared to the Control group; for DCP (median was 53ng/ml, 28 ng/ml, 23 ng/ml) respectively, for AFP (median was 450 ng/ml, 28ng/ml, 2.5ng/ml) respectively.

This is consistent with the findings of **Al-Sayed et al. [7],** who observed that, in comparison to control group, patients with cirrhotic active hepatitis post virus C and patients with HCC on top of cirrhotic active hepatitis post virus C had significantly higher levels of alpha feto protein (AFP) and des-gamma carboxyprothrombin (DCP). In contrast to group II, patients in group III displayed greater levels of AFP.

El-Derany [15] found that a greater serum AFP level was linked to the development of HCC in NASH patients. According to **Choi et al. [16],** there was no discernible change in the control group, but the level of DCP and AFP-L3 in HCC patients started to rise six months and a year, respectively, before diagnosis. According to **Li et al. [17],** patients with HCC had significant increases in AFP, AFP-L3, and AFP-L3/AFP three years prior to the diagnosis of HCC.

FGF-19 and age, alfa fetoprotein, and DCP showed statistically significant positive correlations in our investigation. FGF-19 and other indicators showed a statistically non-significant connection.

Sun et al. [12] found a positive correlation (P < 0.05) between FGF-19 and AFP in patients with HCC, which is consistent with the findings of the current study.

A statistically significant positive association was seen in our investigation between DCP and FGF-19, alfa fetoprotein, and age. Between DCP and other metrics, there is a statistically insignificant association.

According to **Al-Sayed et al. [7],** there is a substantial correlation between aggressive tumor behavior and poor liver function and increased DCP levels.

A cutoff value of ≥48ng/ml is the most effective for predicting HCC, with an area under curve of 0.793, sensitivity of 71.4%, specificity of 74.3%, positive predictive value of 58.1%, negative predictive value of 83.9%, and overall accuracy of 73.3% observed.

According to **Loglio et al. [18],** AFP levels more than 7 ng/mL demonstrated excellent specificity (99.6%) in Caucasian patients with HBV compensatory cirrhosis who had long-term NUC therapy, indicating the emergence of HCC within a year.

AFP level was shown to be a potential noninvasive prognostic measure for HCC patients in a meta-analysis involving 29 studies and 4726 HCC patients. Additionally, AFP Slope > 7.5 ng/mL per month was linked to HCC recurrence following liver transplantation **[19].**

The best FGF-19 cutoff value for HCC prediction in the current investigation is ≥238.2 pg/ml, with an area under the curve of 0.857, sensitivity of 82.9%, specificity of 80%, positive predictive value of 67.4%, negative predictive value of 90.3%, and overall accuracy of 81%.

In terms of predicting small HCC, 230.539 pg/ml is the optimal cutoff value for FGF-19, with an area under the curve of 0.899, sensitivity of 82.5%, specificity of 80%, positive predictive value of 62.2%, negative predictive value of 93.3%, and overall accuracy of 81.4%.

AUC of 0.795, sensitivity of 53.2%, specificity of 95.1%, PPV of 95.9%, and NPV of 48.7% were found for the 200 pg/mL FGF-19 cut-off point in the Maeda et al. (2019) study using ROC curve analysis. The outcome was similar to that of AFP (AUC = 0.827).

In the **Mohamed et al. [10]** trial, FGF-19 performed better as a diagnostic tool for HCC detection at a cut-off > 180 pg/mL, with an AUC of 0.98, 100% sensitivity, 90% specificity, 90% PPV, and 100% NPV. Probably as a result of the bigger sample size.

With an area under curve of 0.902, sensitivity of 85.7%, specificity of 88.6%, positive predictive value of 78.9%, negative predictive value of 92.5%, and overall accuracy of 87.6%, the optimal cutoff value of DCP for the prediction of HCC is ≥31.5ng/ml.

According to our research, ≥27.3 ng/ml is the accepted DCP cutoff value for predicting small HCC nodules, with an area under the curve of 0.854, sensitivity of 82.2%, specificity of 71.4%, positive predictive value of 53.5%, negative predictive value of 92.6%, and overall accuracy of 75.3%.

According to **Al-Sayed et al. [7],** DCP has a higher sensitivity and specificity than AFP for differentiating between the controlled group and the HCC group (83.7%, 90.33% - 66%, 89.49%), as well as 83.6%, 85% - 65%, and 79.5%) for differentiating between the cirrhotic and HCC groups.

Ji et al. [20] reported that in a different multicentric investigation conducted in China, the sensitivity and specificity for DCP and AFP were (82.6, 78.5%–90.7%, 69%). The sensitivity and specificity of DCP varied from 52 to 85% and 81 to 97%, respectively, in three comprehensive meta-analyses involving populations infected with HCV **[21].**

In this study, considering presence of FGF≥238.2 pg/ml and/or AFP≥48 pg/ml and/or DCP≥31.4 ng/ml, sensitivity is raised to 97.1% and specificity became 67.1%, PPV 59.6%, NPV 97.9% and overall accuracy 76.2%

Considering presence of AFP≥48 pg/ml and/or DCP≥31.4 ng/ml, sensitivity is raised to 97.1% and specificity became 80%, PPV 70.8%, NPV 98.2% and overall accuracy 85.7%

Considering presence of FGF≥238.2 pg/ml and/or AFP≥48 pg/ml, sensitivity is 94.3% and specificity became 72.9%, PPV 63.5%, NPV 96.2% and overall accuracy 80%.

In a study by **Maeda et al. [11]**, it was found that the sensitivity of AFP and DCP markers for detecting Hepatocellular Carcinoma (HCC) at union for international cancer control (UICC) stage I was relatively low but increased as the disease progressed. In contrast, the sensitivity of FGF19 remained consistently around 50% across different stages, making it notably more sensitive than AFP and DCP at stage I. When FGF19 measurement was added to AFP and DCP tests, it significantly improved HCC detection sensitivity. Notably, in 26% of cases where AFP and DCP were negative, FGF19 could detect 14.1% of these cases. Additionally, 21.7% of small HCC cases negative for AFP and DCP showed elevated serum FGF19 levels. It's important to note that while AFP and DCP are specific to HCC, FGF19 elevation can also be observed in various other cancer types.

According to **Al-Sayed et al. [7],** DCP has more accuracy and sensitivity than AFP. In addition to DCP's excellent diagnostic performance, they discovered that DCP was more effective than AFP at differentiating HCC from liver cirrhosis and had a high capacity for doing so when AFP was negative. **Ji et al. [20]** have demonstrated that DCP is more accurate than AFP in the diagnosis of HCC and in the diagnosis of individuals with AFP negative for HCC.

DCP is more appropriate and effective than AFP for HCC surveillance, as evidenced by its elevated positive proportions, which are comparable to or even better than the majority of HCC results **[22].**

CONCLUSION

Compared to non-HCC patients, HCC patients had considerably increased serum levels of FGF19 and DCP. The serum level of FGF19 & DCP correlated with disease progression to HCC. FGF19 & DCP can be identified as promising potential biomarkers that may offer early detection of HCC. FGF19 showed the best diagnostic performance amongst other markers in the study for detection of small HCC. It has been demonstrated that the combination of AFP with DCP and FGF19 is a sensitive, quick, and easily accessible technique for enhancing HCC early detection.

CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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