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Serum Fibroblast Growth Factor 19 As A Predictor and Follow Up of Hepatocellular Carcinoma

Said Abdelbaky Gad, Ahmed I. Elagrody
Internal Medicine Department Faculty of Medicine, Zagazig University
Corresponding author: Said Abd Elbaky Gad Shams El Deen**, Mobile:** (+20)01227517689**,**
Email saidabdelbaky12345@gmail.com

ABSTRACT

Background: Abnormal autocrine fibroblast growth factor 19 (FGF19) productions have been observed in several types of cancers, including hepatocellular carcinoma (HCC), which is considered 3rd cause of cancer deaths worldwide with gradually increased incidence. **Objective:** To investigate the role of FGF 19 in prediction, diagnosis and follow up of HCC together with alpha feto protein (αFP). **Patients and methods:** This study was carried in Internal Medicine Department and Clinical Pathology Department, Faculty of Medicine Zagazig University Egypt in the period from October 2017 to October 2020. The study included 150 patients (111 males and 39 females) classified into 3 groups: 50 healthy volunteers as a control, 50 patients with liver cirrhosis documented by examination and investigation and 50 Patients with HCC with variable sizes. All participants in the study were subjected for the following after written consent and approval by their search ethics committee of Zagazig University.

Result: The median of FGF19 level between control, liver cirrhosis and HCC was 4, 6 and 10 87 pg/ml respectively with higher sensitivity for detection of small HCC with high significance of α Fp between HCC > cirrhosis > control.

Conclusion: FGF19 can be used successfully as a novel biomarker for HCC diagnosis and follow up after treatment together with already existing biomarker α FP.

Keywords: α FP, HCC, FGF 19.

INTRODUCTION

Liver cirrhosis represents the end stage of several chronic liver injuries. It is characterized by degeneration, regeneration by nodules with loss of lobular architecture, which results in decrease of liver cell mass, portal hypertension and porto-systemic shunt opening. Hepatocellular carcinoma (HCC) represent the 5th common cancer worldwide and 3rd cause of death between cancers, which represent the most serious complication following chronic infection by hepatitis (C) virus and hepatitis (B) virus [(1)]. Inspite of the advances in imaging diagnosis and therapeutic advances in treatment modalities, the 5th year survival rate of HCC still about 20 % [(2)].

Tumor makers are widely used as a diagnostic follow up after treatment and prognosis. In HCC α fetoprotein (α FP) is used for diagnosis, follow up of HCC but with different variable changes so it cannot used alone as a biomarker of HCC serum fibroblast growth factor 19 (FGF19) is autocrine factor signals through FGF receptor tyrosine kinase to regulate wide range of biological processes. Dysregulation between FGF and FGFR promote developmental of some diseases including cancers. FGF19 secreted from ileum negatively regulate bile duct acid synthesis in the liver. It has been also demonstrated that over expression of FGF19 and FGFR4 is associated with unfavorable prognosis of HCC. In this study, we aimed to investigate serum level of FGF19 by sandwich enzyme linked immunosorbent assay (ELIZA) in HCC patients and to evaluate its sensitivity and specificity together with α F protein in diagnosis, follow up after treatment of HCC [(3)].

Fibroblast growth factor 19 (FGF19) is a circulating hormone that actively participates in governing bile acid synthesis, glycogenesis, and lipid metabolism [(4)]. In human, there is a negative correlation between FGF19 and cardiovascular risk factors [(5)] and FGF19 as an independent factor of the development of coronary artery disease [(6)].

Aim of the work was to investigate the role of FGF 19 in prediction, diagnosis and follow up of HCC together with alpha feto protein (αFP).

PATIENTS AND METHODS

This study was conducted in Internal Medicine Department and Clinical Pathology Department, Faculty of Medicine Zagazig University Egypt in the period from October 2017 to October 2020. The study included 150 patients (111 males and 39 females) classified into 3 groups:

- 50 healthy volunteers as a control.
- 50 patients with liver cirrhosis documented by examination and investigation.
- 50 patients with HCC with variable sizes.

All participants in the study were subjected for the following:

1- Full history taking.
2- General & local examination.
3- Routine laboratory investigates as CBC, PT, INR, Liver function tests, kidney function tests.
4- Specific laboratory investigations as FGF19, AFP [(6, 7)].

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Ethical approval:

A written consent from each partiocipant and approval was obtained by the Research Ethics Committee of Zagazig University were obtained.

Diagnosis of liver cirrhosis:

- Diagnosis of liver cirrhosis is based on laboratory investigations, clinical examination and or histological examination. HCC is diagnosed based on contrast enhanced imaging and or histological analysis.
- Measurement of FGF19 and αFP measurement of FGF19 in patients and control were determined by using sandowish ELIZA technique. α Fetoprotein is determined by chemilumen- scence enzyme immune assay and was collected one month before treatment.
- Also Child pugh scoring system classification was done and included:
  - **Child A**: 30 patients with CLD and 9 patients with HCC.
  - **Child B**: 10 patients with CLD and 18 patients with HCC.
  - **Child C:** 10 patients with CLD and 23 patients with HCC.
- there were 20 patients with HBV and 80 patients with HCV.
- There were 24 females with CLD and HCC, 46 males with CLD and HCC.

Statistical analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures were coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis.

According to the type of data, qualitative were represented as numbers and percentages. Quantitative continues group was represented as mean ± SD. The following tests were used to test differences for significance. Difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups by t-test or Mann Whitney. ROC curve for cutoff and validity by sensitivity and specificity. P value was set at ≤ 0.05 for significant results & < 0.001 for high significant result.

RESULTS

Table (1): Age distribution among studied group

		N	Mean	SD	F	P
Age	**Control**	**50**	**56.8000**	**6.38557**	**22.411**	**0.00****
	CLD	**50**	**57.0000**	**6.65475**		
	HCC	**50**	**63.3600***	**2.84827**		

* Significant

HCC group were significantly older than other groups as Age was distributed as 56.8 ± 6.3, 57.0 ± 6.65 and 63.36 ± 2.84 years respectively among Control, CLD and HCC.

Table (2): Sex distribution among studied group

			Group			Total	X^2	P
			Control	CLD	HCC			
Sex	**Male**	**N**	**35**	**35**	**41**	**111**	**2.49**	**0.28**
		%	**70.0%**	**70.0%**	**82.0%**	**74.0%**		
	Female	**N**	**15**	**15**	**9**	**39**		
		%	**30.0%**	**30.0%**	**18.0%**	**26.0%**		
Total		**N**	**50**	**50**	**50**	**150**		
		%	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

There was no significant difference among groups regarding sex distribution and males were majority among all groups.

Table (3):- CHILD class between CLD and HCC groups

			CLD	HCC	Total	X^2	P
CHILD	**A**	**N**	**30**	**9**	**39**	**124.07**	**0.00****
		%	**60.0%**	**18.0%**	**26.0%**		
	B	**N**	**10**	**18**	**28**		
		%	**20.0%**	**36.0%**	**18.7%**		
	C	**N**	**10**	**23**	**33**		
		%	**20.0%**	**46.0%**	**22.0%**		
Total		**N**	**50**	**50**	**100**		
		%	**100.0%**	**100.0%**	**100.0%**		

HCC group was significantly associated with Class C and B more than CLD group as it was significantly associated with CHILD A.

Table (4): AFP distribution among groups

		N	Mean	SD	Median	Minimum	Maximum	Kruskal Walis	P-Value
AFP	**Control**	**50**	**3.5600**	**2.31199**	**4.0**	**1.50**	**8.50**	**11.894**	**0.00****
	CLD	**50**	**6.4400**	**3.40564**	**6.0**	**3.80**	**15.20**		
	HCC	**50**	**1087.5220**	**2219.49769**	**1087**	**5.50**	**8000.00**		

HCC was significantly higher than control and CLD without significant difference between CLD and control groups.

Table (5): FGF 19 distribution among studied groups

		N	Mean	SD	F	P- Value
FGF19	**Control**	**50**	**69.7000**	**17.47914**	**326.984**	**0.00****
	CLD	**50**	**125.3000**	**34.42842**		
	HCC	**50**	**236.9000**	**42.83869**		
	Total	**150**	**143.9667**	**77.19942**		

HCC group was significantly higher regarding FGF19 than other groups and CLD group was significantly higher than control group.

Table (6): Size of tumor among HCC group only

		N	%
Tumor size	**<2 cm**	**28**	**56.0**
	>2 cm	**22**	**44.0**
	Total	**50**	**100.0**

56% were small tumor and 44% were large.

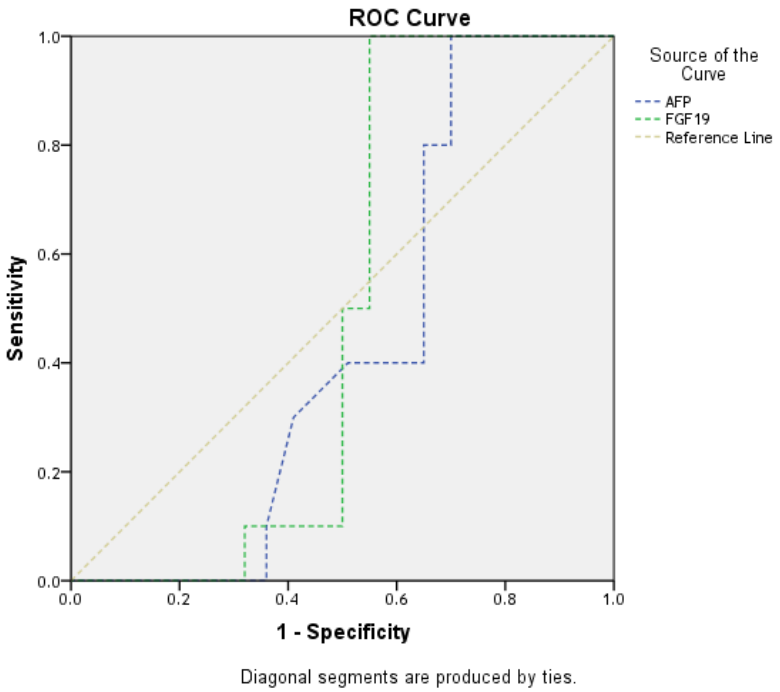
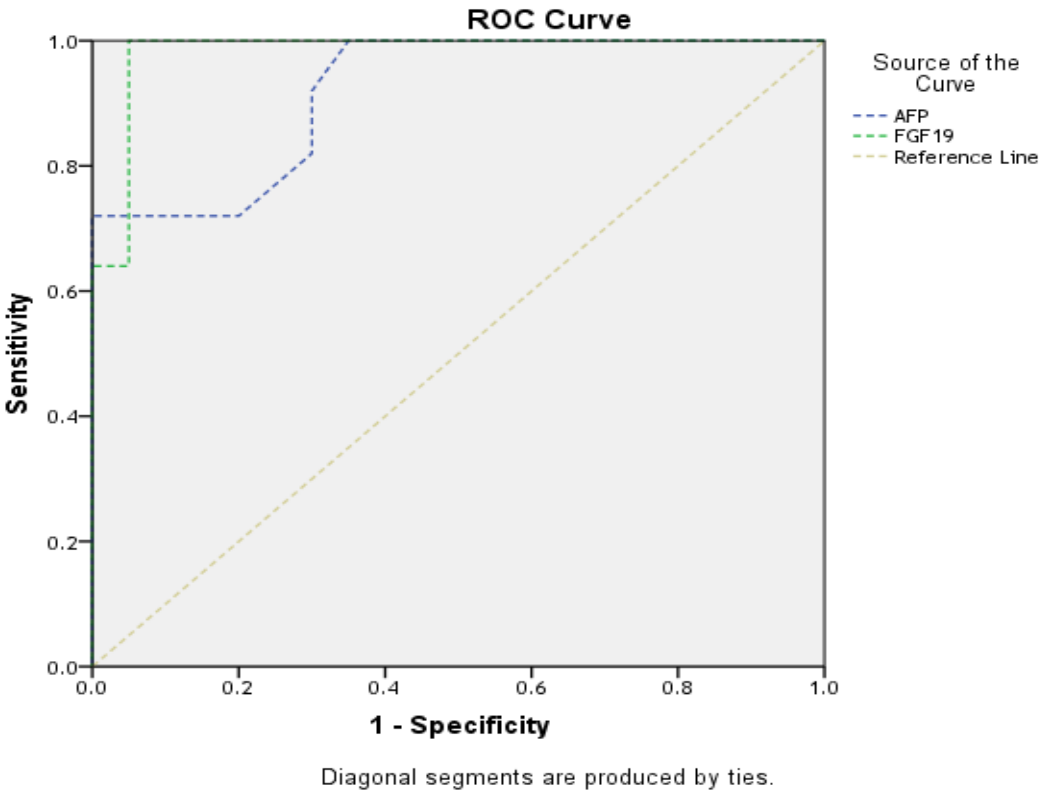


Figure (1): ROC curve for detection of cutoff regarding CLD

Table (7): Table of ROC curve for detection of cutoff regarding CLD

Area Under the Curve						Sensitivity	Specificity
Test Result Variable(s)	Area	Cutoff	P	95% Confidence Interval			
				Lower Bound	Upper Bound		
AFP	**0.441**	**>4.85**	**0.240**	**0.351**	**0.531**	**78.5%**	**37.5%**
FGF19	**0.493**	**>112**	**0.889**	**0.399**	**0.587**	**55.5%**	**50.8%**

Non-significant area under curve with cutoff > 4.85 and >112 respectively and weak validity for detection of CLD, with AFP sensitivity and specificity with FGF19 sensitivity and specificity.



ROC Curve for cutoffs regarding HCC

Table (8): Table of ROC curve for detection of cutoffs regarding HCC

Area Under the Curve					
Test Result Variable	Area	Cutoff	P	95% Confidence Interval	
				Lower Bound	Upper Bound
AFP	0.919	>7.5	0.00**	0.875	0.963
FGF 19	0.982	>204	0.00**	0.965	0.999

Significant AUC with cutoffs > 7.5 and > 204 for AFP and FGF19 respectively

Table (9): Validity of FGF 19

	Sensitivity	Specificity
AFP For all tumor	75.5%	67.5%
FGF 19 for all tumor	85.8%	70.0%
AFP & FGF 19 for all tumor	92.2%	67.5%
AFP For small tumor	53.3%	62.0%
FGF 19 for small tumor	67.5%	73.3%
AFP & FGF 19 for small tumor	84.5%	64.5%

This table showed that FGF19 had validity higher than AFP especially at small tumor and showed that combination between AFP and FGF19 increase validity.

DISCUSSION

HCC represents the fifth most common cancer worldwide and the third most frequent cause of mortality among oncological malignancies [(1)]. HCC as a grave endangering disease, early diagnosis and follow up of diagnosed patients to minimize the prevalence, complications and improve life quality of patients with this fatal outcome, these measures introduce different laboratory and/ or radiological modalities in the diagnosis of the diseases [(7)]. The ideal biomarkers should have high sensitivity and specificity for early detection of HCC. FGF19 is abnormal autocrine growth factor secreted in many types of M cells including HCC [(3)].

In our study, we decided to study the role of FGF 19, as novel noninvasive biomarkers for prediction, detection and follow up of HCC in combination with α-FP at the same time. Our study

showed that FGF19 is highly significant with regard to CLD and HCC with significance in HCC group than CLD group, which is in direct agreement with the result obtained by **Takahiro *et al.* [8]** that showed the same results. There is significant difference in FGF19 in patients with larger size of masses, which is in accordance with study done by **Sun *et al.* [9]** that showed marked increase in serum level of FGF19 as size of the tumor increase.

FGF19 showed sensitivity and specificity under the ROC curve for diagnosis of CLD but not AFP with cutoff value > 112 and > 4.85 respectively, which are nearly similar to the results obtained by **Kanda *et al.* [10]** that showed significant AUC with cutoffs > 75 and > 204 respectively for AFP and FGF19. Another study by **Lin *et al.* [11]** showed that FGF19 has higher validity for diagnosis of small tumor than AFP and both increase validity, which is in agreement with our study, which showed the same results.

Our study had showed high significance of AFP in HCC than control and CLD. **Kang *et al.* [12]** demonstrated that a unique molecular subtype of FGF19 is associated with poor prognosis in liver cancer. AFP had no significant difference between CLD and control. Another study by **Toyoda *et al.*[13]** showed significant difference between HCC > CLD > control as regards liver enzyme, platelets, albumin and this is in agreement of our studies, besides our study showed no sex predilection but older age groups showed significant difference [13].

Child Pugh scoring system classification showed significant difference in HCC prevalence from child A < B < C, which is in close association with a study done by **Zhu *et al.* [14].**

In summary, from the previous studies, our study results and other similar studies, we can conclude that FGF19 can be used as a novel biomarkers in detection, diagnosis and follow up HCC especially small HCC and this validity can be increased by conjunction with use of AFP.

CONCLUSION

FGF19 can be used successfully as a novel biomarker for HCC diagnosis and follow up after treatment together with already existing biomarker α FP.

RECOMMENDATIONS

Other novel biomarkers as hepatocyte growth factor could increase the specificity and sensitivity for diagnosis of HCC in combination with FGF19 and AFP.

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