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Serum fibroblast growth factor 19 and calcium channel α2δ1 subunit as diagnostic biomarkers for hepatocellular carcinoma

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Abstract

Background: *Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths and ranks as the fifth most common cancer. Detecting HCC early is crucial for improving patient outcomes. In this study, we evaluated the diagnostic potential of Fibroblast Growth Factor 19 (FGF-19) and Voltage-gated Calcium Channel α2δ1 subunit (VGCC α2δ1) in HCC.* ***Patients and methods:*** *In this prospective study, serum FGF-19 and VGCC α2δ1 levels were compared among 44 HCC patients, 26 patients with cirrhosis but without HCC, and 15 healthy controls. Receiver operating characteristic curve (ROC) analysis was used to evaluate the diagnostic potential of FGF-19 and VGCC α2δ1 in HCC, as well as their complementary role with AFP. The study also investigated the correlation between these levels and clinicopathological characteristics.* ***Results****: Serum FGF-19 levels were significantly higher in HCC patients compared to patients with cirrhosis and healthy controls. Additionally, FGF-19 levels were significantly elevated in cirrhotic patients compared to healthy controls. VGCC α2δ1 levels were significantly higher in both HCC and cirrhotic patients compared to healthy controls, with no significant difference between the HCC and cirrhosis groups. The diagnostic performance of FGF-19 was superior to that of VGCC α2δ1 in HCC diagnosis, with FGF-19 demonstrating 95.5% sensitivity, 76.9% specificity, and 88.5% accuracy, while VGCC α2δ1 showed 25% sensitivity, 100% specificity, and 53% accuracy. A strong positive correlation was found between FGF-19 and VGCC α2δ1 with AFP. The combination of VGCC α2δ1, FGF-19, and AFP resulted in a sensitivity of 21%, specificity of 100%, and accuracy of 63%, which did not show superior diagnostic performance* compared to FGF-19 *alone.* ***Conclusion:*** *FGF-19 is an excellent positive and a good negative test. VGCC α2δ1 is very poor positive and good negative test. Their combined use with AFP may improve the diagnostic efficiency of HCC.*

Introduction

Significant efforts have been made to detect HCC early. HCC research includes the discovery of novel, reliable and non-invasive blood proteins as diagnostic biomarkers for HCC[1]. Fibroblast Growth Factor 19 (FGF-19) is one of the original members of the endocrine FGF subfamily[2].Due to its involvement in a number of physiological processes that impact bile acid secretion, glucose and lipid metabolism, cell proliferation, differentiation, and motility, it has drawn a lot of attention[3-5]. FGF-19 is expressed in the terminal ileum in response to the bile-acid-stimulated intestinal Farnesoid X receptor[2], and then, through the portal circulation to the liver, it attaches to its receptor, FGF receptor 4 (FGFR4), and a cofactor known as β-klotho. This action initiates the transcription of various genes that negatively regulate bile acid synthesis[6]. Furthermore, it has been shown that autocrine FGF-19 secretion has aided in the advancement of cancers, including HCC through mTOR dependent mechanisms[7-11]. It promotes tumor cell survival and has antiapoptotic impacts through the FGFR4-glycogen synthase kinase (GSK) 3β-Nrf2 signaling pathway[12]. Voltage-gated calcium channels (VGCC) are involved in a number of vital physiological processes. In addition to hormone release, VGCC activation is required for the release of neurotransmitters at brain synapses[13].A trans-membrane protein called VGCC α2/δ1 subunit creates glycosyl-phosphatidylinositol (GPI) anchored protein[14] which, by enhancing the rate and voltage-dependent calcium channel gating, can alter the function of calcium channels[15]. The α2/δ1 subunit regulates calcium influx into liver tumor beginning cells through L and N-type voltage-gated calcium channels, and it is a functioning hepatic cancer stem cell and a hallmark of tumor-initiating cells[16], moreover, is connected to extracellular signaling[17]. The purpose of this study is to assess the diagnostic value of serum FGF-19 and VGCC α2/δ1 subunit as potential biomarkers for detecting HCC.

Participants and Methods

This study involved 44 patients diagnosed with heap-tocellular carcinoma, 26 patients with cirrhosis, and 15 healthy controls. A comprehensive history was collected from all cases in the study, followed by a detailed clinical examination. Abdominal ultrasonography was used for radiological assessment. Triphasic pelvi-abdominal computed tomography (CT) was used for diagnosis of HCC according to AASLD criteria[18].For laboratory assessment, about 10 millimeters of venous blood samples were collected into three tubes. Sodium citrate tube for INR and EDTA tube for complete blood counts evaluated by cell dyne. Silica-Based tube was used for evaluating liver

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functions, including levels of serum albumin, bilirubin, and liver transaminases using autoanalyser Roche Cobas Integra-800. ELISA determined Alfa fetoprotein level (AFP) along with hepatic virological markers. The remaining blood samples were separated, and the collected serum was preserved at -80°C for further analysis of FGF-19 and VGCC α2/δ1 subunit levels using enzyme-linked immunosorbent assays (ELISAs).

Measurement of Serum FGF-19 and VGCC α2/δ1 subunit levels

The sample and ELISA reagent were added into each well, incubated for 1 hour at 37°C, then the plate was washed 5 times then substrate solution A and B were added and incubated for 10 minutes at 37°C after that stop solution was added and color developed then Optical Density (OD) value was read within 10 minutes. VGCC α2/δ1 subunit assay principle: It's an enzyme-linked immunosorbent assay. The plate has been pre-coated with human CACNA2D1 antibody. CACNA2D1 present in the sample was added and binds to antibodies coated on the wells. Then biotinylated human CACNA2D1 antibody was added and bound to CACNA2D1 in the sample. Then streptavidin-HRP was added and bound to the biotinylated CACNA2D1 antibody. After incubation unbound streptavidin-HRP was washed away. Substrate solution was then added and color developed in proportion to the amount of human CACNA2D1. The reaction was terminated by addition of acidic stop solution and absorbance was measured at 450 nm. Kits code No. E4572Hu. They were provided from Bioassay Technology Laboratory (BT LAB)^{R}. Standard curve range is 15-3000ng/L. FGF-19 assay principle: It's an enzyme-linked immunosorbent assay. The plate has been pre-coated with human FGF19 antibody. FGF19 present in the sample was added and bound to antibodies coated on the wells. Then biotinylated human FGF19 antibody was added and bound to FGF19 in the sample. Then streptavidin-HRP was added and bound to the biotinylated FGF19 antibody. After incubation unbound streptavidin-HRP was washed away. Substrate solution was then added and color developed in proportion to the amount of human FGF19. The reaction was terminated by addition of acidic stop solution and absorbance was measured at 450 nm. Kits code No. E2198Hu. They were provided from Bioassay Technology Laboratory (BT LAB)^{R}. Standard curve range is 2-600ng/L.

Ethics approval and consent to participate.

This study was performed with the approval of the Mansoura Faculty of Medicine Institutional Review Board (Code: MD.21.08.509). All patients and/or their legal guardian(s) provided written informed consent before participation. None of the human participants in this study are minors. All methods were carried out following the guidelines and regulations of the Declaration of Helsinki.

Statistical analysis

Data were fed to the computer and analyzed using IBM Statistical Package for the Social Science (SPSS) software package version 25.0. A statistical significance threshold was established at $P < 0.05$. Categorical (qualitative) data were described using frequencies and percentages. Metric (quantitative) data were described using median (minimum and maximum) for non-parametric data and mean ± standard deviation (SD) for parametric data after testing normality using Kolmogorov-Smirnov test. Data were considered normally distributed if $p>0.05$, and not if $p <0.05$.

Results

Table 1 shows the clinical and laboratory parameters among the three groups. The male sex was more predominant in the HCC group compared to the cirrhosis group (P value = 0.019), with no significant difference versus the healthy control group. Additionally, the cirrhosis group had a male sex predominance compared to the healthy group. There were no significant differences in age, total bilirubin, direct bilirubin, serum albumin, INR, hemoglobin, platelets count and VGCCα2δ1 subunit between the HCC group and the cirrhosis group. However, both groups showed significant differences in these parameters compared to the control group (P value <0.001). Both AFP and FGF-19 was significantly higher in HCC versus cirrhotic and control groups (P value <0.001) however no significant difference concerning AFP level between cirrhosis group and control. **Table 1** comparisons of the clinical and laboratory parameters between the three groups. **Table 2** shows a correlation between tumor markers and clinical/laboratory parameters. A strong positive correlation was found between FGF-19 and AFP with a medium strength positive correlation between VGCC α2δ1 and both AFP and FGF-19. FGF showed a significant positive correlation with age, serum bilirubin, INR, liver enzymes, and BCLC stage of HCC, and a significant negative correlation with serum albumin. VGCCα2δ1 subunit showed a significant positive correlation with age, serum bilirubin, INR, liver enzymes, creatinine and CTP score and a significant negative correlation with serum albumin, hemoglobin and platelets count. In addition, AFP showed a significant positive correlation with age, serum bilirubin, INR, liver enzymes, WBCs count and serum creatinine and a significant negative correlation with serum albumin.

The validity of the study biomarkers in differentiating between the study groups.

The validity of the study biomarkers in differentiating between the three study groups was demonstrated in **tables 3 & 4**, **figures 1 & 2**. The three biomarkers were found to be statistically significant discriminators between the cirrhosis group and the HCC group compared to the control group. Additionally, FGF and AFP significantly differentiate the HCC group from the cirrhosis group, while VGCC α2δ1 was not able to differentiate between HCC and cirrhosis. In differentiation between the HCC group and cirrhotic group, the ROC curve showed that VGCC α2δ1 had a sensitivity of 25% and specificity of 100% with an accuracy of 53%, **table 4** and an AUC of >501.2, **table 3**. FGF-19 at a cut-off >78.2 ng/dL, **table 3** had a sensitivity of 95.5%, specificity of 76%, and accuracy of 87% with an AUC of 0.92, **table 4**. AFP at a cut-off >12.96 ng/dL had a sensitivity of 77%, specificity of 96%, and accuracy of 84%, **table 4**. with an AUC of 0.91, **table 3**. Additionally, when VGCC α2δ1, FGF-19, and AFP were combined, the sensitivity was 21%, specificity was 100%, and accuracy was 63%. **Table 5** shows the results of binary logistic regression, which was performed to ascertain the effects of male sex, early satiety, significant weight loss, AST >27, ALT >38, AFP >12.96, and FGF >78.2 on the likelihood that cirrhotic participants will exhibit

HCC. In univariate analysis, all these predictor variables were found to be statistically significant. However, only four risk factors were included in the multivariate analysis. The three biomarkers were excluded from the multivariate analysis due to VGCC having 100% specificity and insufficient cases for the other two markers (only 1 case had AFP>12.96 in the cirrhosis group, and only 2 cases had FGF-19<78.2 in the HCC group). The model was statistically significant ($\chi 2$ [5] = 41.881, P<0.001). Out of the 5 predictor variables, only male sex and serum ALT >38 IU/L were identified as statistically significant independent predictors of HCC. Male participants with serum ALT>38 IU/L have 9.4 and 22.5 times higher odds of developing HCC, respectively.

Table 1: Comparisons of the clinical and laboratory parameters between the three groups

Characteristic	Group			
	Control N=15	***Cirrhosis N=26***	***HCC N=44***	
Categorical				**p-value**
▪ ***Male sex***	13 (86.7%) a	15 (57.7%) b	38 (86.4%) a	*__0.019__
▪ ***Current smoking***	5 (33.3%)	3 (11.5%)	11 (25%)	*0.236
Quantitative				**p-value**
▪ ***Age (years)[mean ± SD]***	36.9 ± 5.7 a	62.3 ± 6.3 b	63.3 ± 7 b	**<0.001**
Quantitative median (Q1-Q3)				**P-value**
▪ ***Total bilirubin (mg/dl)***	0.8 (0.7-0.9) a	1.9 (1.3-3.3) b	1.4 (1-3.6) b	**<0.001**
▪ ***Direct bilirubin (mg/dl)***	0.3(0.2-0.3) a	0.7(0.5-1.7) b	0.7(0.4-1.8) b	**<0.001**
▪ ***Serum albumin (g/dl)***	4 (3.9-4.2) a	3.1(2.6-3.5) b	3.3(2.73-3.7) b	**<0.001**
▪ ***INR***	1 (0.9-1.1) a	1.33 (1.2-1.5) b	1.28(1.1-1.5) b	**<0.001**
▪ ***ALT (IU/L)***	35(22-40) a, b	20(16-31.3) a	44.5(26.5-66.3) b	**<0.001**
▪ ***AST (IU/L)***	32(26-35) a	29(23-51) a	68.5(34-106.8) b	**<0.001**
▪ ***Serum creatinine (mg/dl)***	0.8(0.7-0.9)	0.87(0.7-1.1)	0.9(0.7-1.2)	0.175
▪ ***Hemoglobin level (g/dl)***	13.5 (12.9-13.8) a	9.6 (8.6-12.1) b	11.5 (9.2-12.7) b	**<0.001**
▪ ***Platelet count (*103 / µl)***	212(178-290) a	98 (50.5-136) b	145(80-192.5) b	**<0.001**
▪ ***WBC count (*103 / µl)***	5(4.1-5.6)	4.66(3.95-7.13)	6.4(4.33-8.28)	0.147
▪ ***AFP (ng/ml)***	2.22(1.53-2.98) a	3.92(2.2-6.8) a	67(13.4-260) b	**<0.001**
▪ ***FGF-19 (ng/dl)***	28(20.5-34.2) a	66.2(60.9-79.5) b	129.25(89.3-171.5) c	**<0.001**
▪ ***VGCCα2δ1 subunit (ng/dl)***	34(17-53) a	212 (136.9-294.2) b	250.5(148.8-634.5) b	**<0.001**

Categorical data: *N (%),* ***test of significance****: Chi-square test or *Fisher's exact test,* ***Age data****: mean ± SD,* ***test of significance****: one-way ANOVA,* ***all other quantitative data:*** *median (Q1-Q3),* ***test of significance:*** *Kruskal-Wallis Htest,* ***Posh-hoc tests for pairwise comparisons:*** *presented in letters (similar letters= insignificant difference, and different letters= significant difference).*

Table 2: Correlation between tumor markers and some clinical/laboratory parameters

Parameter	AFP		FGF-19		VGCCα2δ1	
	r_s	p-value	r_s	p-value	r_s	p-value
AFP	-	-	0.635	<0.001	0.340	**0.001**
FGF-19	0.635	<0.001	-	-	0.472	**<0.001**
VGCC α2δ1	0.340	0.001	0.472	<0.001	-	-
Age	0.386	<0.001	0.454	<0.001	0.512	**<0.001**
Total bilirubin	0.301	0.005	0.315	0.003	0.489	**<0.001**
Direct bilirubin	0.348	0.001	0.369	0.001	0.492	**<0.001**
Serum albumin	-0.273	0.012	-0.330	0.002	-0.444	**<0.001**
INR	0.235	0.031	0.479	<0.001	0.409	**<0.001**
ALT	0.415	<0.001	0.307	0.004	0.219	**0.045**
AST	0.497	<0.001	0.422	<0.001	0.303	**0.005**
Serum creatinine	0.232	0.033	0.124	0.259	0.246	**0.023**
Hemoglobin	-0.200	0.067	-0.213	0.050	-0.421	**<0.001**
Platelet count	-0.024	0.828	-0.159	0.146	-0.404	**<0.001**
WBCs count	0.231	0.033	0.093	0.400	-0.025	**0.819**
CTP score (cirrhotic groups)	0.032	0.795	0.032	0.792	0.237	**0.048**

BCLC stage (HCC group)	0.127	0.412	0.336	0.026	0.201	**0.191**
Milan criteria (HCC group) *	-0.066	0.672	-0.118	0.445	-0.039	**0.801**
PVT (HCC group) *	0.253	0.097	0.258	0.090	0.180	**0.243**

Table 3: Cutoff levels of the three biomarkers

Biomarker	Cutoff	AUC	95% CI	p-value
Cirrhosis vs. control				
AFP	>3.11	0.792	0.637 to 0.903	**<0.0001**
VGCC α2δ1	>74	0.897	0.762 to 0.970	**<0.0001**
FGF	>44.1	0.962	0.850 to 0.997	**<0.0001**
HCC vs. control				
AFP	>3.11	0.989	0.918 to 1.000	**<0.0001**
VGCC α2δ1	>74	0.973	0.893 to 0.998	**<0.0001**
FGF	>44.1	1.000	0.939 to 1.000	**<0.0001**
HCC vs. cirrhosis				
AFP	>12.96	0.911	0.817 to 0.966	**<0.0001**
VGCC α2δ1	>501.2	0.584	0.460 to 0.701	0.2243
FGF	>78.2	0.922	0.832 to 0.972	**<0.0001**

AUC: *area under the ROC curve.* ***CI:*** *confidence interval.*

Table 4: Diagnostic performance of the biomarkers

Biomarker	Sensitivity	specificity	PPV	NPV	Accuracy	F1 score	MCC
Cirrhosis vs. control							
▪ ***VGCC***	0.85	1.00	1.00	0.79	0.90	0.92	0.82
▪ ***FGF-19***	0.96	1.00	1.00	0.94	0.98	0.98	0.94
▪ ***AFP***	0.58	0.93	0.94	0.56	0.71	0.713	0.50
▪ ***AFP + FGF + VGCC α2δ1***	0.38	1.00	1.00	0.48	0.60	0.56	0.43
HCC vs. control							
▪ ***VGCC***	0.889	1.000	1.00	0.75	0.92	0.94	0.82
▪ ***FGF-19***	1.00	1.00	1.00	1.00	1.00	1.00	1.00
▪ ***AFP***	0.98	0.938	0.98	0.93	0.97	0.98	0.91
▪ ***AFP + FGF + VGCC α2δ1***	0.72	1.00	1.00	0.29	0.75	0.84	0.45
HCC vs. Cirrhosis							
▪ ***VGCC***	0.25	1.00	1.00	0.44	0.53	0.40	0.33
▪ ***FGF-19***	0.95	0.76	0.88	0.91	0.87	0.91	0.75
▪ ***AFP***	0.77	0.96	0.9714	0.7143	0.84	0.86	0.71
▪ ***AFP + FGF + VGCC α2δ1***	0.21	1.00	1.00	0.59	0.63	0.35	0.35

PPV: *positive predictive value,* ***NPV:*** *negative predictive value,* ***MCC:*** *Matthews's correlation coefficient*

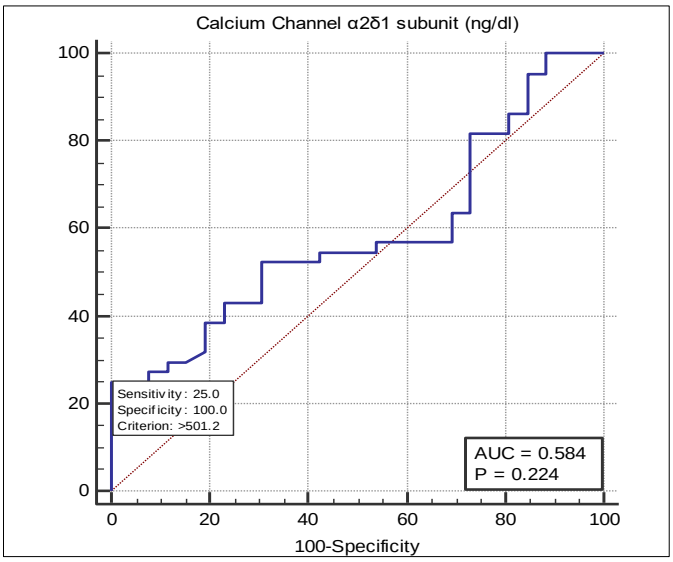

Figure 1: Calcium channel α2δ1 subunit in HCC Vs Cirrhosis

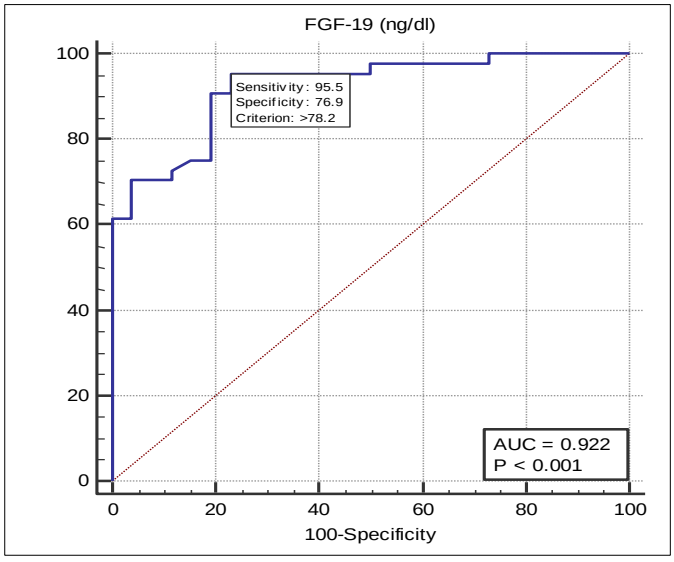

Figure 2: FGF-19 in HCC Vs Cirrhosis

Table 5: Predictors of HCC.

Risk factor	Univariate			Multivariate		
	p-value	COR	95% CI	p-value	AOR	95% CI
Male sex	**0.009**	r(1) 4.6	r(1) 1.45 – 14.8	**0.016**	r(1) 9.4	r(1) 1.5 – 58.2
Early satiety	**0.009**	r(1) 4.6	r(1) 1.47 – 14.4	0.055	r(1) 4.6	r(1) 0.97 – 22.3
AST >27 (IU/L)	**0.001**	r(1) 7.8	r(1) 2.33 – 26	0.487	r(1) 1.7	r(1) 0.36 – 8.35
ALT >38 (IU/L)	**0.001**	r(1) 15.8	r(1) 3.3 – 75.2	**0.006**	r(1) 22.5	r(1) 2.4 – 211
AFP >12.96 (ng/ml)	**<0.001**	r(1) 85	r(1) 10.2 – 708	-	-	-
FGF-19>78.2 (pg/ml)	**<0.001**	r(1) 70	r(1) 13 – 378	-	-	-

COR: *crude odds ratio,* ***AOR:*** *Adjusted odds ratio,* ***CI:*** *confidence interval,* ***r(1):*** *reference category,* ***Test of significance:*** *binary logistic regression (Backward elimination).*

Discussion

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths globally and the fifth most common cancer[19]. Surveillance for HCC in patients with cirrhosis typically involves ultrasound (U/S) every 6-8 months with or without alpha-fetoprotein (AFP) testing. However, U/S has limited sensitivity (46%), especially for detecting small lesions, dropping to 33% in obese patients with a BMI over 30[20,21]. AFP also has a sensitivity of around 60%[22]. While CT and MRI have higher specificity (94%) and sensitivity (69% and 84%, respectively), they are not recommended for routine surveillance due to cost and variability[22,23]. Therefore, there is a need for a new non-invasive tool with high sensitivity and specificity at a low cost for early detection of HCC[24]. This study aims to evaluate the accuracy of serum FGF-19 and the Calcium Channel α2δ1 subunit in diagnosing HCC. Our study revealed that VGCC α2δ1 levels were not statistically significantly different between the cirrhotic group and the HCC group. In contrast, Badr et al. reported a significantly higher level of VGCC α2δ1 in patients with HCC compared to those with cirrhosis and the normal control group. In our study, a VGCC α2δ1 level >501.2 ng/dl had a sensitivity of 25% and specificity of 100%, with a positive predictive value (PPV) of 100%, negative predictive value (NPP) of 44%, and an accuracy of 53% for distinguishing between HCC and cirrhosis. However, in a previous study, VGCC α2δ1 showed 100% sensitivity, 96% specificity, 98% PPV, 100% NPV, 98.7% accuracy at a cut-off point of 14.22 ng/dL, and an area under the curve (AUC) of 0.977[25]. This difference in sensitivity can be explained by the different cut-off levels. Also, different patients' HCC stages may add some explanation. Badr et al.'s study included only patients with advanced HCC who were not amenable for surgical or loco-regional therapy, while our study included different tumor stages. In this study, FGF-19 levels were found to be significantly higher in the HCC group compared to the cirrhotic and control groups. Consistent with our findings, Maeda et al. also reported elevated serum levels of FGF-19 in their HCC patients. However, they did not observe a statistically significant difference between the cirrhotic cases and controls in their study[26]. Similarly, Li et al. and Mohamed et al. reported significantly higher serum FGF-19 levels in HCC patients compared to controls[27,28]. Li et al. also noted a significant increase in FGF-19 mRNA expression in HCC tissues compared to paired peri-tumoral tissues, suggesting a potential mechanistic link between FGF-19 and hepatic cancer stem cells[27]. In our study, FGF-19 showed superior diagnostic performance with a cut-off > 44.1 ng/dL, achieving an AUC of 0.962, sensitivity of 96%, specificity of 100%, PPV of 100%, and NPV of 93% in distinguishing between cirrhosis and control groups. Additionally, at a cut-off > 44.1 ng/dL, FGF-19 demonstrated perfect sensitivity and specificity of 100%, PPV of 100%, and NPV of 100% in discriminating between HCC and control groups. At a cut-off > 78.2 ng/dL, FGF-19 had an AUC of 0.922, sensitivity of 95.5%, specificity of 76.9%, PPV of 87.5%, NPV of 90.9%, and accuracy of 88.5% in distinguishing HCC from cirrhotic patients without HCC. Maeda et al. also found that FGF had a sensitivity of 53.2%, specificity of 95.1%, PPV of 95.9%, and NPVof 48.7% for diagnosing HCC[26]. When VGCC α2δ1, FGF-19, and AFP were combined, the sensitivity was 21%, specificity was 100%, and accuracy was 63%. This indicates that the combination of these markers does not improve the diagnostic accuracy for diagnosing HCC compared to individual markers. In contrast Maeda et al found that, the combined use of FGF19 with AFP increases the diagnostic accuracy of HCC [26]. Our study showed a significant positive correlation between FGF-19 and AFP. This finding aligns with previous research by Sun et al. and Mohamed GA et al., who also observed a positive association between FGF-19 and AFP in HCC patients[28,29]. However, Maeda et al. reported no significant relationship between serum FGF-19 levels and AFP[26]. We found a positive correlation between age, bilirubin, INR, liver enzymes, VGCC α2δ1 subunit, and FGF-19. Conversely, albumin and hemoglobin showed a negative correlation with FGF-19. In contrast, Mohamed G et al. in their study found no correlation between FGF-19 and age, bilirubin, liver enzymes, and hemoglobin. However, they found a positive correlation with AFP and INR, while it was negatively correlated with albumin[28]. Our study found that AFP, VGCC α2δ1, and FGF-19 biomarkers are significant in distinguishing cirrhosis and HCC from control groups. However, VGCC was not effective in differentiating HCC from cirrhosis. In distinguishing HCC from cirrhosis, AFP was a reliable test, VGCC α2δ1 was weak, FGF-19 was excellent, and the combination of all three biomarkers was moderate. The current study has some limitations due to the relatively small sample size and being a single-center study. Further multicenter studies with larger numbers of patients may be necessary to validate these results.

Conclusion

This study showed that AFP is a good positive and a good negative test, VGCC α2δ1 is a very poor positive and poor

negative test, FGF-19 is an excellent positive and a good negative test for discrimination HCC from cirrhosis.

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