Alpha-L-Fucosidase Versus Alpha-Fetoprotein: A Comparative Study for Diagnosing Hepatocellular Carcinoma in Post-Viral Cirrhotic Patients

Original Article

Sherif Ahmed Megahed Ahmed, Sameh Mohamed Faheem Ghaly, Moamen Abd-elfattah Shabaan and Marwa Ahmed Mohamed

Department of Internal Medicine, Hepatology and Gastroenterology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, particularly in patients with viral cirrhosis. Alpha-fetoprotein (AFP) is widely used for HCC diagnosis; however, it suffers from limited sensitivity and specificity, especially in early-stage HCC. Alpha-L-fucosidase (AFU) has emerged as a potential biomarker for HCC detection.

Aim of the Work: To evaluate AFU diagnostic performance compared to AFP in Egyptian patients with HCC post-viral cirrhosis.

Patients and Methods: A cross-sectional case-control study was carried out on 90 participants divided into three groups: HCC patients with viral cirrhosis (*n*=30), cirrhosis-only patients (*n*=30), and healthy controls (*n*=30). Serum AFP and AFU levels were measured using ELISA.

Results: AFU levels were considerably higher in HCC patients (129.87±32.99 U/ml) compared to cirrhotic (33.43±14.82 U/ml, *P-value* <0.001) and healthy controls (3.18±1.20 U/ml, *P-value* <0.001). AFP levels were also elevated in HCC patients (4431.21±11438.90 ng/ml) versus cirrhotic (883.83±973.62 ng/ml, *P-value* <0.05) and healthy controls (*P-value* <0.001). AFU demonstrated 100% sensitivity and 90% specificity at a cutoff >52 U/ml, with an accuracy of 99.4%. AFP showed 96.67% sensitivity and specificity at a cutoff >10.5 ng/ml, with 97.6% accuracy.

Conclusion: AFU is a highly sensitive and complementary biomarker to AFP for HCC diagnosis in cirrhotic patients. Combining AFU and AFP may improve early detection of HCC, particularly in AFP-negative cases.

Key Words: Alpha-L-fucosidase, alpha-fetoprotein, biomarkers, cirrhosis, hepatocellular carcinoma.

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Corresponding Author: Sherif Ahmed Megahed Ahmed, Internal Medicine, Hepatology and Gastroenterology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt., **Tel.:** +201207157339, **E-mail**: sherifmegahed1001@gmail.com

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INTRODUCTION

Hepatocellular carcinoma (HCC) ranks as the sixth most prevalent malignancy and the third foremost cause of cancer-related death globally[1]. The prevalence of HCC is increasing, presenting a considerable risk to world health[2]. Epidemiological studies have shown a robust correlation between HCC and persistent infections with HBV and HCV[3].

A substantial proportion of HCC patients are diagnosed at advanced stages, often accompanied by underlying liver dysfunction[4]. These patients typically have a poor prognosis, highlighting the critical need for early detection to improve survival rates[5]. Tumor markers serve as valuable tools for early diagnosis and screening[6].

Alpha-fetoprotein (AFP) is the most commonly used biomarker for detecting HCC in clinical practice. However, AFP has limited sensitivity and specificity, particularly in early-stage HCC[7]. Many HCC patients do not exhibit elevated AFP levels, while some individuals with benign hepatic conditions may have elevated AFP, leading to false positives[8].

Identifying alternative biomarkers is crucial for the early diagnosis of HCC in high-risk groups. Enhanced diagnostic instruments has the capacity to improve patient

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outcomes. Thus, the advancement and use of additional biomarkers have emerged as a priority for researchers, laboratory medicine, and clinical practice[5].

Alpha-L-fucosidase (AFU), a lysosomal enzyme present in all human cells, facilitates the breakdown of sugars that contain L-fucose[9]. AFU has been proposed as a potential tumor marker for the diagnosis of HCC. Multiple studies have shown markedly increased blood AFU activity in HCC patients compared to those with benign hepatic conditions[9].

This study aims to evaluate the effectiveness of AFU as a diagnostic marker compared to AFP in Egyptian patients with HCC due to viral cirrhosis.

PATIENTS AND METHODS

Study Design and Population

This study was designed as a cross-sectional case-control investigation conducted at Ain Shams University Hospitals from January 2022 to June 2022. Ninety participants, aged 21 to 75 years, were enlisted and divided into three groups. Group A included 30 patients diagnosed with hepatic cirrhosis and HCC. Group B included 30 patients with liver cirrhosis without hepatocellular carcinoma, and Group C included 30 healthy individuals serving as controls to determine normal biomarker levels.

ETHICAL CONSIDERATION

The research was conducted under approval from the Institutional Review Board at Ain Shams Faculty of Medicine (Approval no: MS 735/2021).

Exclusion Criteria

Participants were excluded if they were younger than 18 years, had liver cirrhosis due to non-viral causes, or were diagnosed with malignancies other than HCC. Additionally, individuals with significant organ dysfunction, such as CKD, IHD, DM, or hyperthyroidism, were excluded.

Data Collection and Procedures

The clinical evaluation included comprehensive history-taking and an exhaustive physical examination. Laboratory investigations encompassed CBC, renal function assessments (blood urea nitrogen, serum creatinine, sodium, and potassium), and hepatic function evaluations (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, total protein, albumin, total bilirubin, and direct bilirubin). Coagulation profiles, including prothrombin time, INR, and PTT, were assessed. Viral indicators, such as hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCAb), were evaluated by the ELISA technique.

Radiological imaging included pelvi-abdominal ultrasound to identify cirrhosis and hepatic focal lesions. Triphasic CT was used to confirm the diagnosis of HCC. Biomarker analysis measured serum AFP and AFU levels, with AFP determined using the ELISA method.

Statistical Analysis

Data management and statistical analysis were performed using SPSS version 26 (IBM, Armonk, New York, United States). Quantitative data were presented as mean ± standard deviation (SD). Comparisons between two groups used the Student's t-test, while comparisons among three groups employed one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Non-parametric data were reported as median (range) and analyzed using Tukey's test. Qualitative data were expressed as frequencies and percentages and analyzed using the Chi-square test. A *p-value* below 0.05 was considered statistically significant, a *p-value* below 0.01 was deemed extremely significant, and a *p-value* over 0.05 was classified as non-significant.

RESULTS

Age substantially differed among the studied groups ($P < 0.001$). Post hoc analysis showed that Group A (59.1 ± 5.6 years) had a considerably higher mean age compared to Group B (55.4 ± 4.0 years, $P = 0.042$) and Group C (38.4 ± 7.4 years, $P < 0.001$). Additionally, Group B was considerably older than Group C ($P < 0.001$). Regarding age groups, all participants in Group A (100%) and most in Group B (96.67%) were over 50 years, while almost all participants in Group C (96.67%) were under 50 years ($P < 0.001$).

There were no significant differences in BMI across the groups ($P = 0.573$), with similar mean values observed in Group A (22.4 ± 2.6), Group B (23.0 ± 2.4), and Group C (22.8 ± 1.6).

Gender distribution did not considerably differ among the groups ($P = 0.621$). Males predominated in Groups A and B (73.33% in both), whereas Group C included a slightly higher proportion of females (36.67%). Smoking status considerably differed among the groups ($P < 0.001$). Non-smokers constituted 100% of Group C, compared to 46.67% and 50% in Groups A and B, respectively. Current and ex-smokers were only observed in Groups A and B, with Group A having a higher proportion of ex-smokers (20%) compared to Group B (10%). DM considerably differed among the groups ($P < 0.001$). Groups A (53.33%) and B (56.67%) had similar proportions of diabetic patients, while none of the participants in Group C had DM.

HTN also considerably differed among the groups ($P < 0.001$). HTN was present in 53.33% of Group A and 33.33% of Group B but was absent in Group C. Non-hypertensive individuals constituted 100% of Group C, compared to 46.67% in Group A and 66.67% in Group B. (Table 1)

Table 1: Demographic data in the studied groups.

								ANOVA		TUKEY'S Test		
		Group A		Group B		Group C		F	*P-value*	A&B	A&C	B&C
Age	Range	52-74		49-66		25-52		107.792	<0.001*	0.042*	<0.001*	<0.001*
	Mean ±SD	59.100±5.598		55.400±3.997		38.367±7.402						
BMI	Range	18-26.5		19-26.8		19.9-26		0.561	0.573			
	Mean ±SD	22.400±2.559		22.997±2.407		22.797±1.570						
Chi-Square		N	%	N	%	N	%	X^2	*P-value*	A&B	A&C	B&C
Age group	<50 Years	0	0.00	1	3.33	29	96.67	81.300	<0.001*	-	-	-
	>50 Years	30	100.00	29	96.67	1	3.33					
Gender	Male	22	73.33	22	73.33	19	63.33	0.952	0.621	-	-	-
	Female	8	26.67	8	26.67	11	36.67					
Smoking	No	14	46.67	15	50.00	30	100.00					
	Current	10	33.33	12	40.00	0	0.00	25.442	<0.001*	-	-	-
	Ex-Smoker	6	20.00	3	10.00	0	0.00					
DM	No	14	46.67	13	43.33	30	100.00	26.124	<0.001*	-	-	-
	Yes	16	53.33	17	56.67	0	0.00					
HTN	No	14	46.67	20	66.67	30	100.00	21.202	<0.001*	-	-	-
	Yes	16	53.33	10	33.33	0	0.00					

ANOVA: Analysis of Variance, X^2: Chi-Square Test.

Hemoglobin and platelet counts were markedly decreased in Groups A (HCC with cirrhosis) and B (cirrhosis alone) compared to Group C (healthy controls) ($P < 0.001$), with Group A displaying the lowest platelet levels. Group A exhibited substantially increased levels of total and direct bilirubin compared to Groups B and C ($P < 0.001$). Similarly, elevated AST and ALT levels were seen in Groups A and B, with Group A displaying the highest values. Albumin levels were markedly reduced, whereas INR values were elevated in Groups A and B compared to Group C ($P < 0.001$).

The prevalence of HCV antibodies was much higher in Groups A (96.67%) and B (93.33%) compared to Group C (0%; $P < 0.001$). Other markers, such as WBC count, creatinine, sodium, and potassium, showed no significant differences across the groups. BUN levels were elevated in Group A compared to Group C ($P = 0.009$), but no significant difference was seen between Groups A and B. (Table 2)

Table 2: Comparison between the studied groups as regard laboratory investigation.

					ANOVA		TUKEY'S Test		
		Group A	Group B	Group C	F	*P-value*	A&B	A&C	B&C
WBCs	Range	3-11.5	2-11.1	4.1-10.9	0.373	0.690			
	Mean ±SD	6.443±2.163	6.510±2.333	6.880±1.799					
Hb	Range	8.2-12.8	7.9-12.2	10.5-14.6	38.039	<0.001*	0.472	<0.001*	<0.001*
	Mean ±SD	10.417±1.234	10.067±1.152	12.473±1.073					
PLTs	Range	29-115	56-189	130-422	99.756	<0.001*	0.081	<0.001*	<0.001*
	Mean ±SD	74.100±22.536	106.600±29.038	270.867±93.204					
BUN	Range	6-58	4-55	5-32	5.010	0.009*	0.770	0.009*	0.057
	Mean ±SD	21.600±12.458	19.733±11.638	13.433±6.191					
Creat.	Range	0.3-2.2	0.2-1.7	0.2-1.2	1.898	0.156			
	Mean ±SD	0.883±0.443	0.810±0.367	0.700±0.270					
Na	Range	130-148	127-148	132-146	0.790	0.457			
	Mean ±SD	138.833±4.662	137.633±5.980	139.200±4.358					
K	Range	3.1-5.2	3.2-5.2	3.4-5	0.271	0.764			
	Mean ±SD	4.167±0.624	4.097±0.588	4.203±0.492					
Total Bilirubin	Range	1-12.5	0.6-4.2	0.5-1.7	15.782	<0.001*	<0.001*	<0.001*	0.358
	Mean ±SD	3.493±2.980	1.620±0.861	0.980±0.327					
Direct Bilirubin	Range	0.3-9.7	0.1-2.1	0-0.9	13.535	<0.001*	0.001*	<0.001*	0.426
	Mean ±SD	2.110±2.231	0.823±0.523	0.393±0.230					
AST	Range	18-139	12-111	13-36	14.180	<0.001*	0.127	<0.001*	0.004*
	Mean ±SD	47.167±26.819	37.200±20.174	20.433±5.679					
ALT	Range	9-135	7-96	5-30	12.436	<0.001*	0.870	<0.001*	<0.001*
	Mean ±SD	37.333±23.830	34.767±23.680	14.167±6.204					
Albumin	Range	1.8-3.8	1.6-3.6	3.5-5.2	113.512	<0.001*	0.157	<0.001*	<0.001*
	Mean ±SD	2.750±0.509	2.510±0.481	4.303±0.511					
INR	Range	1-2.1	0.9-2.5	0.9-1.3	18.311	<0.001*	0.907	<0.001*	<0.001*
	Mean ±SD	1.477±0.294	1.447±0.354	1.090±0.124					
Chi-Square		N %	N %	N %	X^2	*P-value*	A&B	A&C	B&C
HBsAg	No	27 90.00	28 93.33	30 100.00	2.965	0.227	-	-	-
	Yes	3 10.00	2 6.67	0 0.00					
HCV Ab	No	1 3.33	2 6.67	30 100.00	77.799	<0.001*	-	-	-
	Yes	29 96.67	28 93.33	0 0.00					

*: Significant *p-value*.

AFU levels considerably differed among the three groups ($P < 0.001$). Group A (HCC with cirrhosis) had the highest AFU levels (129.87 ± 33.00 µl U/ml), which were considerably greater than those in Group B (cirrhosis only, 33.43 ± 14.82 µl U/ml) and Group C (healthy controls, 3.18 ± 1.20 µl U/ml) based on post hoc analysis ($P < 0.001$ for all comparisons). Additionally, AFU levels in Group B were considerably higher than in Group C ($P < 0.001$). (Table 3)

Table 3: Comparison between the three groups regarding the α-L-fucosidase (AFU) by (µl U/ml).

AFU (µl U/ml)				ANOVA		TUKEY'S Test		
	Group A	Group B	Group C	F	*P-value*	A&B	A&C	B&C
Range	55-180	15-73	0.9-5.5	300.790	<0.001*	<0.001*	<0.001*	<0.001*
Mean±SD	129.867±32.997	33.433±14.818	3.177±1.199					

AFU: Alpha-L-Fucosidase, SD: standard deviation.

The comparison of liver condition between Groups A (HCC with cirrhosis) and B (cirrhosis only) revealed no statistically significant differences in the MELD score (16.43 ± 4.81 vs. 14.40 ± 4.15, $P = 0.085$) or the Child score (8.57 ± 2.98 vs. 9.23 ± 1.94, $P = 0.309$). However, the distribution of Child grades showed a significant difference between the two groups ($P = 0.027$). Group A had an increased proportion of patients in Child Grade A (40%) compared to Group B (10%), while Group B had a greater proportion in Child Grade C (50%) compared to Group A (33.33%). (Table 4)

Table 4: Comparison between Group (A) & (B) regarding liver condition (MELD Score, Child Score, Child Grade, PVT).

						T-Test	
		Group A		Group B		t	*P-value*
MELD Score	Range	9-29		8-24		1.753	0.085
	Mean±SD	16.433±4.812		14.400±4.149			
Child Score	Range	5-14		5-12		-1.027	0.309
	Mean±SD	8.567±2.979		9.233±1.942			
Chi-Square		N	%	N	%	X^2	*P-value*
Child Grade	Child A	12	40.00	3	10.00		
	Child B	8	26.67	12	40.00	7.200	0.027*
	Child C	10	33.33	15	50.00		

MELD Score: Model for End-Stage Liver Disease Score, PVT: Portal Vein Thrombosis, X^2: Chi-Square Test.

In Group A, AFU levels were considerably higher in hypertensive patients (142.00 ± 30.18 µl U/ml) compared to non-hypertensive patients (116.00 ± 31.46 µl U/ml; $P = 0.029$). AFU levels also showed significant differences based on the number and size of focal lesions. Patients with multiple focal lesions had higher AFU levels (158.27 ± 18.90 µl U/ml) compared to those with a single lesion (113.42 ± 27.88 µl U/ml; $P < 0.001$). Similarly, patients with focal lesions >3 cm had higher AFU levels (150.50 ± 32.40 µl U/ml) than those with lesions <3 cm (116.11 ± 26.03 µl U/ml; $P = 0.003$).

No notable variations in AFU levels were observed based on sex ($P = 0.816$), diabetes status ($P = 0.482$), HBsAg positivity ($P = 0.412$), HCV antibody status ($P = 0.565$), portal vein thrombosis ($P = 0.314$), smoking status ($P = 0.317$), or Child grade ($P = 0.500$).

Table 5: Correlation between AFU and other clinical parameters in group A.

Group A		AFU (µl U/ml)		T-Test or ANOVA	
		N	Mean±SD	T or F	*P-value*
Gender	Male	22	129.000±34.027	-0.235	0.816
	Female	8	132.250±32.070		
DM	No	14	134.500±30.993	0.713	0.482
	Yes	16	125.813±35.142		
HTN	No	14	116.000±31.457	-2.308	0.029*
	Yes	16	142.000±30.182		
HBsAg	No	27	128.185±34.357	-0.833	0.412
	Yes	3	145.000±7.810		
HCV Ab	No	1	149.000±0.000	0.583	0.565
	Yes	29	129.207±33.379		
PVT	No	8	119.625±30.626	-1.026	0.314
	Yes	22	133.591±33.711		
No. of Focal Lesion	Single	19	113.421±27.877	-4.727	<0.001*
	Multiple	11	158.273±18.900		
Size of Focal Lesion	<3 cm	18	116.111±26.025	-3.215	0.003*
	>3 cm	12	150.500±32.399		
Smoking	No	14	139.643±31.436	1.200	0.317
	Current	10	119.700±37.962		
	Ex-Smoker	6	124.000±25.219		
Child Grade	Child A	12	124.333±34.217	0.711	0.500
	Child B	8	141.750±28.034		
	Child C	10	127.000±35.926		

AFU: Alpha-L-Fucosidase, DM: Diabetes Mellitus, HTN: Hypertension, HBsAg: Hepatitis B Surface Antigen, HCV Ab: Hepatitis C Virus Antibody, PVT: Portal Vein Thrombosis.

In Group A, AFP levels were considerably higher in patients with multiple focal lesions (11,259.46 ± 17,497.25 ng/ml) compared to those with a single lesion (883.83 ± 973.62 ng/ml; $P = 0.014$). AFP levels were also considerably elevated in patients with focal lesions >3 cm (10,322.21 ± 16,995.97 ng/ml) compared to those with lesions <3 cm (932.23 ± 978.04 ng/ml; $P = 0.026$).

No notable variations in AFP levels were observed based on gender ($P = 0.843$), diabetes status ($P = 0.855$), hypertension ($P = 0.954$), HBsAg positivity ($P = 0.230$), HCV antibody status ($P = 0.707$), portal vein thrombosis ($P = 0.307$), smoking status ($P = 0.557$), or Child grade ($P = 0.326$). (Table 6)

Table 6: Correlation between AFP and other clinical parameters in group A.

Group A		AFP (ng/ml)		T-Test or ANOVA	
		N	Mean±SD	T or F	*P-value*
Gender	Male	22	4431.214±11438.904	-0.200	0.843
	Female	8	5395.000±12394.240		
DM	No	14	5107.607±11031.784	0.184	0.855
	Yes	16	4321.263±12225.298		
HTN	No	14	4555.157±13123.419	-0.058	0.954
	Yes	16	4804.656±10293.073		
HBsAg	No	27	3837.656±10365.861	-1.227	0.230
	Yes	3	12343.333±20488.110		
HCV Ab	No	1	330.000±0.000	-0.380	0.707
	Yes	29	4838.507±11663.343		
PVT	No	8	1075.438±874.768	-1.040	0.307
	Yes	22	6001.964±13239.271		
No. of Focal Lesion	Single	19	883.826±973.620	-2.612	0.014*
	Multiple	11	11259.455±17497.254		
Size of Focal Lesion	<3 cm	18	932.233±978.037	-2.359	0.026*
	>3 cm	12	10322.208±16995.967		
Smoking	No	14	6998.857±15506.157	0.599	0.557
	Current	10	3582.570±7720.192		
	Ex-Smoker	6	1139.500±884.664		
Child Grade	Child A	12	901.042±787.353	1.169	0.326
	Child B	8	8336.025±14063.671		
	Child C	10	6314.600±15392.084		

AFP: Alpha-Fetoprotein, DM: Diabetes Mellitus, HTN: Hypertension, HBsAg: Hepatitis B Surface Antigen, HCV Ab: Hepatitis C Virus Antibody, PVT: Portal Vein Thrombosis.

AFU revealed significant positive correlations with the size of focal lesions ($P = 0.002$) but did not considerably correlate with AFP ($P = 0.073$), age ($P = 0.414$), BMI ($P = 0.225$), WBCs ($P = 0.845$), Hb ($P = 0.168$), platelets ($P = 0.180$), or other biochemical variables such as total bilirubin ($P = 0.695$) and ALT ($P = 0.637$).

AFP, on the other hand, revealed significant positive correlations with the size of focal lesions ($P < 0.001$), total bilirubin ($P = 0.030$), and MELD score ($P = 0.003$). No significant correlations were observed between AFP and parameters like direct bilirubin ($P = 0.052$), BUN ($P = 0.009$), WBCs ($P = 0.493$), or BMI ($P = 0.730$). (Table 7)

Table 7: Correlation between the two markers and other parameters in group (A).

Group A	AFU (µl U/ml)		AFP (ng/ml)	
	r	*P-value*	R	*P-value*
AFP	0.332	0.073		
Age	0.155	0.414	0.110	0.563
BMI	-0.228	0.225	0.066	0.730
WBCs	0.037	0.845	-0.130	0.493
Hb	-0.258	0.168	0.129	0.498
PLTs	0.382	0.18	0.042	0.827
BUN	0.246	0.190	0.468	0.009*
Creat.	0.283	0.129	0.323	0.082
Na	-0.019	0.920	-0.341	0.065
K	-0.088	0.643	0.093	0.623
Total Bilirubin	0.075	0.695	0.397	0.030*
Direct Bilirubin	0.104	0.583	0.358	0.052*
AST	-0.030	0.877	-0.042	0.825
ALT	-0.090	0.637	0.115	0.544
Albumin	-0.065	0.731	-0.226	0.229
INR	-0.004	0.985	0.040	0.835
Child Score	-0.006	0.974	0.186	0.324
MELD Score	0.194	0.303	0.527	0.003*

r: correlation coefficient, *: Significant *P-value*.

ROC curve analysis was conducted for AFU and AFP to differentiate between HCC patients (Group A) and cirrhotic patients without HCC (Group B). AFU revealed excellent diagnostic performance with a cutoff >52 µl U/ml, achieving a sensitivity of 100.0%, specificity of 90.0%, PPV of 90.9%, NPV of 100.0%, and an overall accuracy of 99.4%. Similarly, AFP demonstrated a very good ability to distinguish between the groups, with a cutoff >10.5 ng/ml yielding a sensitivity of 96.67%, specificity of 96.67%, PPV of 96.67%, NPV of 96.67%, and an accuracy of 97.6%.

DISCUSSION

HCC is a leading cause of cancer-related mortality worldwide, with increasing incidence driven by risk factors such as chronic hepatitis B and C, non-alcoholic steatohepatitis, and alcohol abuse. Current surveillance methods, including ultrasound and AFP, are limited by AFP's low sensitivity and specificity, particularly in early-stage HCC[10-14]. Advances in biomarkers like AFP-L3, Des-γ-carboxyprothrombin, and glypican-3 have shown potential for improving diagnosis and prognosis. AFU, a lysosomal enzyme overexpressed in HCC, has demonstrated the ability to detect up to 85% of cases earlier than ultrasonography[15-18]. This study evaluates the diagnostic performance of AFU versus AFP in post-viral cirrhotic Egyptian patients.

In the current study, the age of patients in the cirrhosis and HCC groups was considerably higher than that of the healthy control group. This can be attributed to the relatively younger age of the healthy controls, whereas the mean age of HCC patients (59.1 ± 5.6 years) was within the sixth decade, compounded by underlying liver cirrhosis. These findings align with previous reports indicating that HCC commonly affects individuals in their fifth or sixth decades[19].

Additionally, males were more frequently affected than females in both the HCC and cirrhosis groups ($P = 0.621$), likely due to the relatively small sample size. This observation is consistent with prior studies showing a higher prevalence of HCC in males, largely due to the greater burden of risk factors, particularly chronic viral hepatitis, in men[1].

The study also highlights that chronic viral infection is a predominant risk factor for HCC in this cohort of Egyptian patients. HCV infection was identified in 29 patients (96.67%), while HBV infection was present in one patient (3.33%). These findings underscore the ongoing burden of HCV in Egypt and the risk of HCC in individuals with HCV-related chronic liver disease, even in the era of effective direct-acting antiviral agents (DAAs), as noted by ***Villani et al.***[20].

In the studied HCC patients, 10 individuals (33.3%) were diabetic, and 6 (20%) were both diabetic and hypertensive. Collectively, more than half of the HCC patients had diabetes, reflecting the role of DM in the development of liver cirrhosis and its predisposition to HCC as an expected complication of cirrhosis, consistent with the findings of ***Li et al.***[21].

Previous studies have demonstrated that serum AFU activity is considerably elevated ($p < 0.001$) in patients with HCC compared to both healthy controls and cirrhotic patients[22]. Similarly, this study found a highly significant increase in serum AFP levels in HCC patients compared to cirrhotic and healthy controls. These results align with reports identifying elevated AFP levels as a diagnostic marker for HCC, especially when combined with imaging modalities like triphasic CT or dynamic MRI. Guidelines have also recommended combining serum AFP measurements with abdominal ultrasound for screening cirrhotic patients for early HCC detection[19, 23].

No correlation was observed between AFU levels and laboratory data, including Child's score. These findings are consistent with Montaser et al.[24], who reported that AFU activity levels did not vary considerably with Child's classification ($p > 0.05$) in HCC patients. Similarly, ***Mossad et al.***[25] concluded that AFU levels were influenced by the presence of HCC rather than liver function, and ***Malaguarnera et al.***[26] found no correlation between AFU levels and ALT activity.

AFU showed no significant correlation with serum AFP in this study, although AFU demonstrated 100% sensitivity and 90% specificity at a cutoff value >52 µl U/ml, while AFP showed 96.6% sensitivity and 96.67% specificity at a cutoff >10.5 ng/ml. These results are consistent with findings from ***Mossad et al.***[25] and ***Malaguarnera et al.***[26], who also reported no correlation between AFU and AFP. Additionally, the findings align with ***Yuling et al.***[5], who noted that AFU had higher pooled sensitivity (0.72) than AFP (0.61) but lower specificity (0.78 vs. 0.90). This supports the multimarker approach for diagnosing HCC, particularly in cirrhotic patients with normal or low AFP levels.

Studies evaluating the diagnostic accuracy of AFU have shown high sensitivity (82%) and specificity ranging from 70.7% to 85.4%[27]. In an Egyptian cohort, a comparative study found AFU to have higher sensitivity (81.8%) than AFP (68.2%) but lower specificity (55% vs. 75%). When combined, AFP and AFU achieved a sensitivity of 88.6%[28]. However, AFU levels have also been found to be elevated in other tumors, limiting its specificity for HCC[29,30].

This study is limited by its relatively small sample size, which may impact the generalizability of the findings. Additionally, the cross-sectional design does not allow for assessing the longitudinal utility of AFU as a biomarker for early HCC detection. Furthermore, the study did not evaluate the performance of AFU in combination with other emerging biomarkers, which could provide a more comprehensive diagnostic approach. Lastly, the study is restricted to a single-center Egyptian cohort, limiting its applicability to broader, diverse populations.

CONCLUSION

This study demonstrates that serum AFU levels are considerably elevated in HCC patients compared to cirrhotic and healthy controls, highlighting its potential as a diagnostic marker. While AFP remains the standard tumor marker, AFU shows promise as a complementary biomarker, particularly for cases with normal or low AFP levels. Combining AFU with AFP may enhance the diagnostic accuracy for HCC, but further large-scale, multicenter studies are needed to validate these findings and explore their clinical application in routine surveillance and early detection programs.

CONFLICT OF INTERESTS

There is no conflicts of interest.

DECLARATION OF CONFLICTING INTERESTS

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of

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دور إنزيم ألفا-إل-فوكسيداز كعلامة تشخيصية مقارنة مع ألفا فيتو بروتين في مرضى سرطان الكبد بعد التليف الفيروسي

شريف أحمد مجاهد أحمد، سامح محمد فهيم غالي، مؤمن عبد الفتاح شعبان و مروة أحمد محمد

قسم الباطنة العامة، أمراض الكبد والجهاز الهضمي، كلية الطب، جامعة عين شمس، القاهرة، مصر

الخلفية: يُعتبر سرطان الكبد الأولي من الأسباب الرئيسية للوفيات المرتبطة بالسرطان على مستوى العالم، خاصة في المرضى الذين يعانون من تليف الكبد الفيروسي. يُستخدم ألفا فيتو بروتين بشكل واسع في تشخيص سرطان الكبد، ولكنه يعاني من محدودية الحساسية والدقة، خصوصاً في المراحل المبكرة من المرض. ظهر إنزيم ألفا-إل-فوكسيداز كعلامة بيولوجية محتملة للكشف عن سرطان الكبد.

هدف الدراسة: تهدف هذه الدراسة إلى تقييم الأداء التشخيصي لإنزيم ألفا-إل-فوكسيداز مقارنة مع ألفا فيتو بروتين في المرضى المصريين المصابين بسرطان الكبد بعد التليف الفيروسي.

المرضى وطرق البحث: تم إجراء دراسة مقطعية على ٩٠ مشاركاً تم تقسيمهم إلى ثلاث مجموعات: مرضى سرطان الكبد مع تليف الكبد الفيروسي (عددهم ٣٠)، مرضى التليف الكبد الفيروسي فقط (عددهم ٣٠)، وأفراد أصحاء كمجموعة ضابطة (عددهم ٣٠). تم قياس مستويات ألفا فيتو بروتين وألفا-إل-فوكسيداز في المصل باستخدام تقنية الـ ELISA، وتم إجراء تحليل إحصائي شمل تحليل منحنى ROC لتقييم الحساسية والدقة التنبؤية لكلتا العلامتين.

النتائج: كانت مستويات إنزيم ألفا-إل-فوكسيداز مرتفعة بشكل ملحوظ لدى مرضى سرطان الكبد (١٢٩,٨٧±٣٢,٩٩ وحدة/مل) مقارنة بمرضى التليف (٣٣,٤٣±١٤,٨٢ وحدة/مل) والأصحاء (٣,١٨±١,٢٠ وحدة/مل). كما كانت مستويات ألفا فيتو بروتين مرتفعة لدى مرضى سرطان الكبد (٤٤٣١,٢١±١١٤٣٨,٩٠ نانوغرام/مل) مقارنة بمرضى التليف (٨٨٣,٨٣±٩٧٣,٦٢ نانوغرام/مل) والأصحاء. أظهر إنزيم ألفا-إل-فوكسيداز حساسية بنسبة ١٠٠٪ ودقة بنسبة ٩٠٪ عند عتبة >٥٢ وحدة/مل، مع دقة إجمالية بلغت ٩٩,٤٪. وأظهر ألفا فيتو بروتين حساسية ودقة بنسبة ٩٦,٦٧٪ عند عتبة >١٠,٥ نانوغرام/مل، مع دقة إجمالية بلغت ٩٧,٦٪.

الاستنتاج: يُعتبر إنزيم ألفا-إل-فوكسيداز علامة بيولوجية حساسة للغاية ومكملة لألفا فيتو بروتين في تشخيص سرطان الكبد لدى مرضى التليف. قد يُساهم الجمع بين ألفا-إل-فوكسيداز وألفا فيتو بروتين في تحسين الكشف المبكر عن سرطان الكبد، خاصة في الحالات التي تكون فيها مستويات ألفا فيتو بروتين طبيعية.