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Original article

The Association of Aldo-Keto Reductase Family 1 Member B10 with Hepatocellular Carcinoma

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Abstract:

Background: A lack of effective diagnosis methods for preclinical HCC has resulted in a low rate of early detection. Aldo-keto reductase family 1 member B10 (AKR1B10) is associated with several cancer types. Objective: Studying the association of AKR1B10 with HCC and the probability of its clinical utility for prognosis of HCC after treatment. **Methods:** A cross sectional study was conducted on 120 subjects who were divided into: group I; included 40 patients with HCC, group II; included 40 patients with CLD and group III; included 40 apparently healthy subjects. All patients were subjected to complete history taking thorough clinical examination. Complete blood picture, liver enzymes, serum bilirubin, S. albumin, INR, S. creatinine, S. AFP and S. AKR1B10 by ELISA- were done. AKR1B10 was done before and one month after HCC ablation. Pelvi-abdominal ultrasonography, multislice CT scan and/or dynamic MRI- were done. Patients with HCC were treated by TACE and RFA. **Results:** There is a statistically significant decrease of AKR1B10 after treatment, in improved and failed cases. ROC curve analysis for AKR1B10 before treatment is good in differentiating between HCC and CLD groups (AUC=0.728) at a cut off level of 2834.5. There is a statistically significant decrease of AFP from before to after treatment detected for HCC group. **Conclusion:** AKR1B10 is good for diagnosis of HCC and could be used as a novel screening method and its diagnostic efficacy for HCC is more when combined with AFP.

Keywords: Hepatocellular carcinoma; Alpha-fetoprotein; Aldo-Keto Reductase Family 1 Member B10 (AKR1B10); Radiofrequency Ablation

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common tumor worldwide and the second most common cause of cancer-related death [(1)].

Most cases of HCC develop in patients with chronic liver disease (70%-90%). Alpha-fetoprotein (AFP)- together with hepatic ultrasonography- is the most common marker used in clinical practice to detect HCC in cirrhotic patients and has been considered the gold-standard serum marker for screening patients at high risk for HCC, as well as for the diagnosis and monitoring of responses to HCC treatment for over 40 years [(2)].

Its sensitivity decreases to about 40% for the detection of small tumors [(3)]. Significant increase in serum AFP level (20–200 ng/mL) is detected in a considerable number of patients with chronic liver disease, including 15%–58% of patients with chronic hepatitis and 11%–47% with cirrhosis [(4)]. An ideal serum biomarker should be both sensitive, specific for HCC detection at an early stage, easy to test and non-invasive [(5)].

Identification of a biochemical marker with better sensitivity and/or specificity than AFP could be extremely helpful in improving early diagnosis of HCC. Aldo-Keto Reductase Family 1 Member B10 (AKR1B10)- is overexpressed in several types of tumor tissue, including HCC tissue. AKR1B10 is mainly expressed in the cytoplasm and can be secreted through a lysosome-mediated non-classical pathway and regulated by lysosome exocytosis signaling [(6)].

Aldo-keto Reductase Family 1 Member B10 (AKR1B10) modulates cell growth and survival by regulating lipid synthesis and eliminating carbonyl compounds [(7)]. These are key steps involved in the proliferation and development of tumors through the regulation of the retinoic acid signaling pathway [(8)]. AKR1B10 can exert its regulatory role in the initiation and development of HCC, suggesting it is involved in the molecular signaling pathways that lead to the development of HCC [(9)]. However, this role of AKR1B10 is not well understood.

The expression of AKR1B10 in patients with HCC is negatively associated with the degree of tumor differentiation; enhanced expression of AKR1B10 was identified in well-differentiated, low-grade HCC tissues and down regulated expression of AKR1B10 was identified in poorly differentiated, high-grade HCC tissues [(10)]. Patients with low AKR1B10 expression appear to be associated with a poorer prognosis compared with those with positive expression following surgical resection of HCC tumors [(6)].

Aim of the Work

The aim of this work was to study the association of Aldo-keto Reductase Family 1 Member B10 (AKR1B10) with Hepatocellular carcinoma (HCC) and the probability of its clinical utility for prognosis of HCC after treatment of HCC with radiofrequency ablation and trans arterial embolization, in comparison to alpha fetoprotein (AFP).

Patients and methods

This study is a cross sectional study with short term follow up of group I, conducted on 120 subjects who were attending outpatient clinics and department of Hepatology, Gastroenterology and Infectious diseases in Benha University Hospital and Liver and Cardiac Research Center of Kafr Elsheikh, within the period of August 2022 to February 2023. The study design was approved by the ethical committee of Benha University Hospitals, Benha University {M.S.3.7.2022}. An informed written consent was obtained from all patients participating in this study after explaining the study measures in detail. The subjects included in this study were divided into 3 groups: group I; which included 40 patients with hepatocellular carcinoma (HCC), group II; which included 40 patients with chronic liver disease and group III; which included 40 apparently healthy subjects. Patients more

than 18 years old with naive HCC were enrolled while patients younger than 18 years old, HCC with any intervention before, with severe comorbidities or other malignancies- were excluded from the study.

All patients were subjected to complete history taking and thorough clinical examination. The laboratory investigations included; complete blood picture, liver enzymes, serum bilirubin (total & direct) (mg/dl), and serum albumin (g/dl), international normalized ratio (INR), serum creatinine (mg/dl) and blood urea(mg/dl), serum alpha –fetoprotein (AFP) (ng/dl) by enzyme-linked immune sorbent assay (ELISA) and serum AKR1B10 (ng/ml) by the enzyme linked immune sorbent assay (ELISA). The patients with HCC who had intervention with radiofrequency ablation and transarterial chemoembolization (TACE)- were evaluated with AKR1B10 before and one month after the intervention. Imaging investigations included pelviabdominal ultrasonography (US), abdominal multislice CT scan and/or dynamic Magnetic Resonance Imaging (MRI) a characteristic classical pattern of early arterial enhancement followed by contrast medium "washout" in late venous phase [(11,12).] Staging of HCC was based on BCLC classification **[(13).]** Patients with HCC were treated by radiofrequency ablation (RFA) for early stage (BCLC A= Single nodule or 3 nodules < 3 cm, Child Pugh A-B, Performance status: 0) **[(14)]** and TACE for intermediate stage (BCLC B = Multinodular, Child Pugh A-B, Performance status: 0) **[(15).]**

Statistical Analysis

Data analysis was performed by SPSS software, version 25 (SPSS Inc., PASW statistics for windows version 25. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using median (interquartile range) for non-normally distributed data and mean± Standard deviation for normally distributed data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (≤0.05) level. Chi-Square, Fischer exact test were used to compare qualitative data between groups as appropriate. Kruskal Wallis and Mann Whitney U test were used to compare between 2 studied groups and more than 2 studied groups, respectively for non-normally distributed data. Wilcoxon signed Rank test was used to compare between more than 2 studied periods. One Way ANOVA test was used to compare more than 2 independent groups with Post Hoc Tukey test to detect pair-wise comparison. The Spearman's rank-order correlation is used to determine the strength and direction of a linear relationship between two non-normally distributed continuous variables and / or ordinal variables. Receiver operating characteristics curve (ROC curve) was used to calculate validity (sensitivity & specificity) of continuous variables with calculation of best cut off point. Predictive values and accuracy are assessed using cross tabulation. The level of significance was taken at P value <0.05 is significant, otherwise is non-significant. The p-value is a statistical measure for the probability that the results observed in a study could have occurred by chance.

Results

There were statistically significant differences between studied cases as regard ascites, hepatic encephalopathy grade and child score. GI in letters bleeding and portal vein thrombosis were statistically significantly higher among HCC cases than CLD group (P=0.002 and P<0.001 respectively). There was a statistically significant difference is detected between HCC & CLD groups for Spleen and Portal vein size /mm (P<0.05) with higher values were detected among HCC group than CLD group. There was a statistically significant difference was detected between HCC & healthy groups

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for Spleen and Portal vein size /mm (P<0.05) with higher values detected among HCC group than healthy group. There was a statistically significant difference detected between CLD & healthy groups for Spleen and Portal vein size /mm (P<0.05) with higher values detected among CLD group than healthy group, (Table 1).

As regard the laboratory investigations of the studied cases. there was a statistically significant difference between studied groups as regard ALT, AST, albumin, total bilirubin, direct bilirubin and INR (P<0.001). There was a statistically significant difference detected between HCC & CLD groups for ALT, AST, total bilirubin, direct bilirubin and INR (P<0.05) with higher values were detected among HCC group than CLD group. ALT, AST, albumin, total bilirubin, direct bilirubin and INR values- were higher among HCC group than healthy group (P<0.05) except for albumin which was lower among cases than control group. There was a statistically significant difference detected between CLD & healthy groups for AST, albumin, total bilirubin, direct bilirubin and INR (P<0.05) with higher values detected among CLD group than healthy group except for albumin which was lower among cases than control group.

Serum creatinine level and TLC count were statistically higher in HCC group than in CLD group (P<0.05), while platelet count was higher among CLD group than HCC group.

The hemoglobin level and platelet count were statistically lower among HCC group than control group. The hemoglobin level and platelet count values were statistically lower among CLD group than healthy group (P<0.05), while total leucocytic count was higher among cases than control group (Table 2).

Table (3) demonstrates that, a statistically significant higher median AKR1B10 before treatment among HCC than CLD and healthy group and within group significance showed statistically significant different between each pair. A statistically significant decrease of AKR1B10 from before to after treatment was detected for HCC group. Also, there was statistically significant higher median AFP before treatment among HCC than CLD and healthy group and within group significance showed statistically significant different between each pair. A statistically significant decrease of AFP from before to after treatment is detected for HCC group.

Table (1): Clinical characteristics, GIT bleeding and portal vein thrombosis between studied groups (I and II).

	HCC group (N=40) n(%)	**CLD group (N=40) n(%)**	**Test of significance (Overall)**
Ascites			
No ascites	15(30)	19(47.5)	χ^2=12.42
Mild or moderate	17(34)	19(47.5)	p=0.002*
Tense ascites	18(36)	2(5.0)	
Hepatic encephalopathy			
No HE	21(42.0)	30(75.0)	χ^2=9.86
Grade 1 or 2 HE	23(46.0)	8(20.0)	p=0.007*
Grade 3 or 4 HE	6(12.0)	2(5.0)	
Child			
Grade A	7(14)	10(25)	χ^2=12.46
Grade B	23(46)	27(67.5)	p=0.002*
Grade C	20(40)	3(7.5)	
GI bleeding	27(54.0)	9(22.5)	χ2=9.19 P=0.002*
PV thrombosis	12(24)	4(10)	χ2FET=35.1 P<0.001*

χ^2=Chi-Square test, FET: Fischer exact test *statistically significant Abbreviations; **HCC:** hepatocellular carcinoma.**CLD**: chronic liver disease **HE:** hepatic encephalopathy **GI:** gastro intestinal **PV:** portal vein

Table (2): Comparison of the laboratory investigations between studied groups.

	HCC group (N=40)	CLD group (N=40)	Healthy group (N=40)	Test of significance (Overall)	Within group significance
ALT(U/L)	87.5(61.75-106.25)	30(18.25-41)	22(21-25)	KW=73.94 P<0.001*	P1<0.001* P2<0.001* P3=0.053
AST(U/L)	101.5(88.5-136.75)	48.5(37.25-69.88)	24(21-26)	KW=104.18 P<0.001*	P1<0.001* P2<0.001* P3<0.001*
Albumin	2.62±0.44	2.68±0.41	4.09±0.31	F=182.89 P<0.001*	P1=0.496 P2=0.001* P3=0.001*
total bilirubin	3.7(1.7-7.7)	1.93(1.12-2.47)	1(0.9-1.1)	KW=55.28 P<0.001*	P1<0.001* P2<0.001* P3<0.001*
direct bilirubin	1.2(0.463-4.5)	0.8(0.25-1.0)	0.3(0.25-0.35)	KW=39.88 P<0.001*	P1<0.001* P2<0.001* P3=0.001*
INR	1.88±0.56	1.61±0.37	1.16±0.089	F=35.02 P<0.001*	P1=0.002* P2=0.001* P3=0.001*
Urea(mg/dl)	30(24-37.5)	29.5(25-34.5)	28(23.25-31)	KW=1.50 P=0.472	P1=0.880 P2=0.286 P3=0.286
Creatinine(mg/dl)	1.28±0.39	1.09±0.16	1.09±0.15	F=7.28 P<0.001*	P1=0.001* P2=0.002* P3=0.893
HB(gm/dl)	9.45±1.44	9.54±1.82	12.46±0.91	F=59.36 P<0.001*	P1=0.786 P2=0.001* P3=0.001*
TLC	7.3(5.33-8.7)	6.25(4.9-7.1)	4.7(4.4-5.2)	KW=29.45 P<0.001*	P1=0.025* P2<0.001* P3<0.001*
PLT	80.5(62-97)	86(64.75-109.25)	274.5(235.75-304.25)	KW=82.78 P<0.001*	P1=0.421 P2<0.001* P3<0.001*

Parameters described as mean ± SD, number (%), KW: Kruskal Wallis test, F: One Way ANOVA test, p1: difference between HCC & Chronic liver disease, p2: difference between HCC & healthy group, p3: difference between CLD & healthy group.Abbreviations: **ALT :** Alanine Transaminase. **AST:** Aspartate Transaminase. INR**:** International Normalized Ratio .**HB:** Hemoglobin .**TLC:** Total Leucocytic Count .**PLT**: Platelets

Table (3): Comparison of Aldo-Keto Reductase Family 1 Member B10 and alpha fetoprotein between studied groups.

AKR1B10	HCC group (N=40)	CLD group (N=40)	Healthy group (N=40)	Test of significance (Overall)	Within group significance
Before	3920 (2077.75-5045.25)	2086 (1092-3320.5)	820 (469.5-1095.5)	KW=57.39 P<0.001*	P1<0.001* P2<0.001* P3<0.001*
After	2174(1989.75-2999)	NA	NA		
Wilcoxon signed rank test	Z=4.78 P<0.001*				
Alpha Fetoprotein					
Before	3118(1472.5-8325.25)	15.0(12-19.0)	13.5(11-17)	KW=87.53 P<0.001*	P1<0.001* P2<0.001* P3<0.001*
After	79(43.5-428)	NA	NA		
Wilcoxon signed rank test	Z=4.78 P<0.001*				

Parameters described as median (IQR), p1: difference between HCC & Chronic liver disease, p2: difference between HCC & healthy group, p3: difference between CLD & healthy group, NA: Not applicable.

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Thirty cases of HCC group received treatment, 83.3% of them showed improvement by CT after treatment, 15 patients received treatment by radiofrequency and 15 patients received TACE but 6 cases died and 4 cases were missed. There was no statistically significant difference between failed and improved cases as regard AKR1B10 pre-treatment. Median AKR1B10 after treatment illustrates statistically significant higher value among failed than improved cases. For failed cases; statistically significant decrease of AKR1B10 after treatment from 4019 to 3522. For improved cases, a statistically significant decrease from 4980 to 2125 after treatment (Table 4).

There is statistically significant negative correlation between AKR1B10 and the following; spleen size (r=-0.44), AFP before (r=-0.586) and AFP after treatment (r=-0.765) , AST (r=-0.346), Child score (r=-0.742), total bilirubin (r=-0.772), direct bilirubin (-0.764) and INR (r=-0.640). While statistically significant positive correlation is detected with albumin (r=0.557). Also, there was a non-statistically significant correlation between AKR1B10 before treatment with laboratory findings among chronic liver disease cases. There was statistically significant positive correlation between AKR1B10 before treatment and body mass index among healthy group (r=0.322) (Table 5).

Table (6) and figures (1-2)- illustrates that area under Receiver Operating Characteristic (ROC) curve for AKR1B10 before treatment is good in differentiating between HCC & CLD groups (AUC=0.728) with the best detected cut off point is 2834.5, yielding sensitivity of 72%, specificity 62.5% and total accuracy is 67.8%. Area under curve for AKR1B10 before treatment in differentiating between HCC & control groups is excellent (AUC=0.911) with the best detected cut off point is 1452, yielding sensitivity of 80%, specificity of 97.5% and total accuracy of 87.8%. Area under curve for AKR1B10 in differentiating between CLD & healthy groups is excellent (AUC=0.856) with the best detected cut off point is 1086, yielding sensitivity of 77.5%, specificity of 75% and total accuracy of 67.8%.

Table (4): Comparison of AKR1B10 among treated cases pre and post treatment.

	Response of AKR1B10 to treatment		test of significance
	Failed treatment	Improved treatment	(Mann Whitney U test)
AKR1B10 pre	4019(1350-5001)	4980(2613-7502)	Z=1.75 P=0.08
AKR1B10 after	3522(1012-3711)	2125(1251-3412)	Z=2.03 P=0.05*
Wilcoxon signed rank test	Z=2.02 P=0.04*	Z=4.37 P<0.001*	

parameters described as median (interquartile range), *statistically significant.

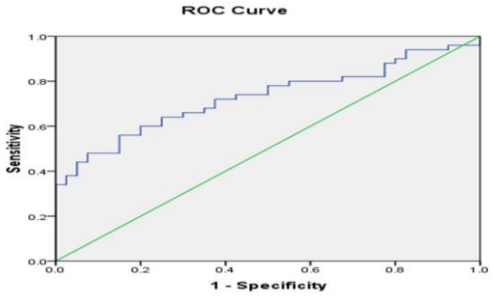

Figure (1): Roc curve of AKR1B10 before treatment to differentiatie between HCC &CLD.

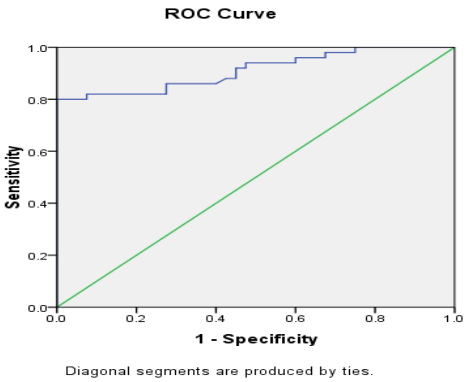

Figure (2): Roc curve of AKR1B10 before treatment to differentiatie between HCC &control.

Table (5): Correlation between AKR1B10 before and after treatment with laboratory findings among cases with hepatocellular carcinoma, AKR1B10 before treatment with laboratory findings among cases with chronic liver disease and healthy group.

		Hepatocellular Carcinoma Group		**Chronic Liver Disease Group**		**Healthy Group**
		AKR1B10 Before	AKR1B10AFTER	AKR1B10		AKR1B10
1.	**UREA**	r -.198	.345	r .096	R	.094
		p .168	.062	p .554	P	.563
2.	**CREAT**	r -.214	-.033	r .192	R	.161
		p .135	.865	p .236	P	.321
3.	**HB**	r .184	-.109	r .261	R	.047
		p .202	.565	p .104	P	.776
4.	**TLC**	r -.160	-.135	r -.112	R	.094
		p .266	.476	p .491	P	.564
5.	**PLT**	r -.173	.203	r -.216	R	-.027
		p .230	.282	p .182	P	.867
6.	**GIT.BLEEDING**	r -.135	-.131	r .150		
		p .350	.489	p .354		
7.	**SPLEEN**	r **-.440****	-.084	r .024	R	.198
		p **.001**	.660	p .885	P	.221
8.	**PV**	r -.145	-.273	r .030	R	.232
		p .316	.144	p .853	P	.149
9.	**AFP**	r **-.586****	-.204	r -.149	R	-.099
		p **.001**	.280	p .359	P	.543
10.	**AFP.AFTER**	r **-.765****	.267			
		p **.001**	.154			
11.	**BMI**	r -.004	-.007	r .001	**R**	**.322***
		p .979	.972	p .996	**P**	**.042**
12.	**ALT**	r -.094	-.198	r .176	R	.027
		p .517	.295	p .277	P	.867
13.	**AST**	r **-.346***	.089	r .164	R	.008
		p **.014**	.642	p .311	P	.961
14.	**Albumin**	r **.557****	-.152	r .097	R	.118
		p **.001**	.421	p .551	P	.469
15.	**CHILD**	r **-.742****	-.200	r -.093		
		p **.001**	.288	p .567		
16.	**Age**	r **-.012**	.217	r -.075	R	-.019
		p **.932**	.249	p .647	P	.906
17.	**Total bilirubin**	r **-.772****	-.269	r -.143	R	.162
		p **.001**	.151	p .379	P	.318
18.	**Direct bilirubin**	r **-.764****	-.221	r -.097	R	.186
		p **.001**	.241	p .558	P	.251
19.	**INR**	r **-.640****	-.318	r -.164	R	-.247
		p **.001**	.087	p .312	P	.125

r:Spearman correlation coefficient , *statistically significant Abb: **PV:** portal vein, **AFP:** Alpha Feto-Protein, **BMI:** Body Mass Index

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Table (6): Diagnostic performance of AKR1B10 in differentiating between studied groups.

	AUC (95%CI)	P value	Cut off point	Sensitivity %	specificity%	PPV%	NPV%	Accuracy%
differentiation between HCC &CLD								
AKR1B10	0.728 (0.624-0.832)	<0.001*	2834.5	72.0	62.5	70.6	64.1	67.8
differentiate between HCC &Control								
AKR1B10	0.911 (0.851-0.971)	<0.001*	1452	80.0	97.5	97.6	79.6	87.8
Between CLD & healthy								
AKR1B10	0.856 (0.774-0.938)	<0.001*	1086	77.5	75.0	75.6	76.9	67.8

AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value

Discussion

Most patients with hepatocellular carcinoma (HCC) are diagnosed at an advanced stage. A lack of effective diagnosis methods for preclinical HCC has resulted in a low rate of early detection. Aldo-keto reductase family 1 member B10 (AKR1B10) is associated with several cancer types. However- to the best of our knowledge- the diagnostic value of AKR1B10 in early-stage HCC is poorly understood [16].

The aim of this work was to study the association of Aldo-keto Reductase Family 1 Member B10 (AKR1B10) with hepatocellular carcinoma (HCC) and the probability of its clinical utility for prognosis of HCC after treatment with radiofrequency ablation and trans arterial embolization, in comparison to alpha fetoprotein (AFP) [17].

In the present study, considering our suggested biomarker, there was a statistically significant higher median of AKR1B10 before treatment among HCC than other groups (CLD and healthy group) (P1<0.001), and within group significance shows statistically significant difference between each pair. A statistically significant decrease of AKR1B10 from before to after treatment is detected for HCC group (P<0.001). This was in accordance with Zhu et al who reported that the level of serum AKR1B10 was significantly higher in HCC patients than in health donors [18].

Also, Liu et al reported that patients with HCC had greater levels of AKR1B10 than the control group, and this was statistically significant difference (p 0.001) [19].

Similarly, Han et al, agreed that AKR1B10 level showed significantly (p< 005) higher levels among early and intermediate stages of HCC than the late and terminal stages of HCC [16].

Also, Wu et al disclosed in their study, there is a significant association between AKR1B10 levels and hepatocellular carcinoma and AKR1B10 level was higher among HCC patients than CLD and controls (p <0.05) [20].

In agreement to our results, Wang et al reported that AKR1B10 was found with a significant (p< 005) increase in HCC group [21].

The present study demonstrated that there was no statistically significant difference (P=0.08) in pre-treatment AKR1B10 levels in treated cases (including failed and improved cases). But after treatment, the median AKR1B10 value was statistically significantly higher among failed than improved cases (3522, 2125 respectively) (P=0.05). In failed cases, there is statistically significant decrease of AKR1B10 value after treatment (from 4019 to 3522 respectively) P=0.04). In improved cases there was a statistically significant decrease from 4980 to 2125 after treatment P<0.001).

Similarly, Schmitz et al revealed that in HCC patients treated with surgical resection (n = 92) or liver transplantation (n = 76), AKR1B10 overexpression was

significantly associated with lower tumor classification, underlying viral hepatitis and cirrhosis [6]

Similarly, Wang et al revealed that additional reports of associations between favorable HCC prognosis following surgical resection and higher AKR1B10 expression, are consistent with a dynamic role for this enzyme at different stages of HCC development and progression [22].

This study, there was a statistically significant negative correlation between AKR1B10 and the following: spleen size, AFP before and after treatment, AST, Child score, total bilirubin, direct bilirubin, and INR while, statistically significant positive correlation was detected with albumin P <0.001.

This came in the same line with, Sato, S., et al have demonstrated that; of the 627 differently expressed genes, the most abundantly expressed gene in patients with elevated AFP (hepatocellular carcinoma cases) was AKR1B10, which was originally isolated as an overexpressed gene in human HCC. The qRT-PCR and immunohistochemical studies confirmed a proportional correlation between AKR1B10 expression and serum AFP [9].

ROC curve analysis of AKR1B10 before treatment in differentiating between HCC and control groups is excellent (AUC=0.911) with the best detected cut off point is 1452 yielding sensitivity of 80%, specificity of 97.5% and total accuracy of 87.8%. Area under curve for AKR1B10 before treatment in differentiating between CLD and healthy groups is excellent (AUC=0.856) with the best detected cut off point is 1086 yielding sensitivity of 77.5%, specificity of 75% and total accuracy of 67.8%. Similarly, European Association for the Study of the Liver reported that elevated levels of serum AKR1B10 were identified in patients with HCC compared with patients with other liver disorders [11]. Compared with advanced and terminal stage HCC, a significant increase in AKR1B10 levels was primarily detected in early and intermediate stage HCC. The sensitivity (81.0%) and specificity (60.9%) for HCC diagnosis with AKR1B10. Conversely, a prominent increase in AFP was observed in advanced and terminal stage HCC. Furthermore, concurrent measurement of serum AKR1B10 and AFP significantly increased sensitivity and negative predictive value for HCC diagnosis [16].

Also , conducted a recent meta-analysis which comprised 12 different cohorts from 11 studies including 2747 HCC patients and 2053 controls, showed that the pooled specificity and the pooled sensitivity of AKR1B10 for the diagnosis of HCC were 0.78 (95% CI: 0.69–0.85) and 0.85 (95% CI: 0.77–0.90), respectively. The pooled sensitivity and specificity of serum AKR1B10 for the diagnosis of HCC were 0.80 (95% CI: 0.70–0.86) and 0.87 (95% CI: 0.77–0.93), respectively. The pooled sensitivity and specificity of AKR1B10 in malignant tumor tissue for the diagnosis of HCC were 0.78 (95% CI: 0.61–0.89) and 0.82 (95% CI: 0.69–0.90), respectively [21].

In 2022, Wang et al reported in their study that, the pooled sensitivity and specificity of AKR1B10 to distinguish HCC from benign liver disease were 0.71 (95% CI: 0.62–0.78) and 0.84 (95% CI: 0.77–0.89), respectively. The sensitivity and specificity of AKR1B10 combined with alpha fetoprotein (AFP) in the diagnosis of HCC were 0.84 (95% CI: 0.79–0.88) and 0.88 (95% CI: 0.73–0.95), respectively. The pooled sensitivity and specificity of AKR1B10 in malignant tumor tissue for the diagnosis of early-stage HCC were 0.85 (95% CI: 0.62–0.95) and 0.88 (95% CI: 0.81–0.93), respectively. A meta-analysis of five studies including 798 patients demonstrated that high AKR1B10 expression in liver malignant tumor was associated with better overall survival in patients with HCC after hepatectomy [22].

Thus, concluded that; AKR1B10 exhibits a great clinical value in the diagnosis of HCC, especially for early-stage HCC, with good diagnostic accuracy. Furthermore, AKR1B10 expression can predict the

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prognosis of HCC patients after hepatic resection [23].

Also, Wu et al have demonstrated that; distinct expression patterns of AKR1B10 were significantly associated with the metastatic incidence and survival rates of HCC patients. Patients with negative staining in primary tumors had better prognostic outcomes. Thus, they concluded that; AKR1B10, acts as potential prognostic biomarkers of HCC [20]

The reported that as an independent risk factor, AKR1B10 can exert its regulatory role in the initiation and development of HCC, suggesting it is involved in the molecular signaling pathways that lead to the development of HCC [9].

Also, Schmitz et al revealed that the expression of AKR1B10 in patients with HCC is negatively associated with the degree of tumor differentiation; enhanced expression of AKR1B10 was identified in well-differentiated, low-grade HCC tissues and downregulated expression of AKR1B10 was identified in poorly differentiated, high-grade HCC tissues. Patients with low AKR1B10 expression appear to be associated with a poorer prognosis compared with those with positive expression following surgical resection of HCC tumors [6].

Limitations:

A limitation of the current study was the relatively small number of subjects. In addition, whether the association between serum AKR1B10 levels and tissue AKR1B10 expression in patients with HCC was linearly dependent or not- was not investigated. In this regard, a prospective large sample analysis of the association between serum AKR1B10 levels and HCC tissues expression should be performed in multicenter studies. Furthermore, AKR1B10 expression was not exclusively revealed in malignant tumors; a low to moderate expression was also observed in the normal human tissues or non-neoplastic conditions. Therefore, further studies are required to characterize the specific role of AKR1B10 in liver cancer screening.

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Conclusion

In conclusion, the current study demonstrated that AKR1B10 has a high diagnostic value for HCC and could be used as a novel screening method. In addition, AKR1B10 has excellent diagnostic efficacy when combined with AFP to diagnose HCC.

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