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Osteopontin and Human Aldehyde Dehydrogenase (ALDH) as a Tumor Marker for Detection of Hepatocellular Carcinoma

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Abstract

Background/Aim: *Hepatocellular carcinoma (HCC) is a global health problem because of its increasing prevalence worldwide and its poor prognosis. In Egypt HCC incidence has increased sharply and nearly doubled over the last decade. The outcome of HCC depends mainly on its early diagnosis; therefore, new and specific markers for HCC are critically needed. Osteopontin (OPN) is a glycoprotein that over expressed in HCC and known to be an independent predictor of poor prognosis. Aldehyde dehydrogenase (ALDH) is a polymorphic enzyme responsible for the oxidation of aldehydes to carboxylic acids, which leave the liver and are metabolized by the body's muscle and heart. ALDH1 and ALDH2 are the most important enzymes for aldehyde oxidation. These enzymes are found in many tissues of the body but are at the highest concentration in the liver. The aim was to assess the value of OPN in Egyptian patients with HCC.*

Methods: *This study included 50 patients with HCC, 50 patients with liver cirrhosis and 50 healthy controls. For all groups, clinical data and image findings were studied; serum alpha-fetoprotein & ALHD & OPN levels were detected by enzyme immunoassay (EIA) kit. Tumor characteristics were assessed including size, number and site.*

Results: *Our data showed that ALDH was more sensitive and specific than AFP, ALDH had 74% sensitivity and 82% specificity, P- value (0.000) but AFP had 66% sensitivity and 64% specificity, P-value (0.003). However, serum OPN was significantly higher in HCC patients compared to cirrhotic patients and controls. The sensitivity and specificity in diagnosis of HCC were 92.5% and 85% respectively at cutoff of 239 ng/ml with 91.1% accuracy.*

Conclusion: *OPN could be a useful diagnostic & prognostic marker for detection of HCC more than ALDH or AFP.*

Keywords: Hepatocellular carcinoma, ALDH, Osteopontin, Alpha-fetoprotein.

Introduction

Hepatocellular carcinoma (HCC) accounts for 90% of primary liver neoplasms representing one of the most common cancers and is responsible for up to 1 million deaths annually worldwide **(Ghouri *et al.*, 2017).** Generally leading to death with 6-20 months. The disease is often clinically silent until it is well advanced, or tumor diameter exceeds to 10 cm. Hepatocellular carcinoma frequently arises in the setting of cirrhosis, appearing 20-30 years following the initial insult to

the liver. However, 25% of patients have no history or risk factor for the development of cirrhosis. HCC with more than 250000 new cases annually and a 5year survival rate of less than 5% is the five leading causes of cancer death in the word **(Balogh *et al.*, 2016).** Hepatitis C virus (HCV) is considered the most common etiology of chronic liver disease (CLD) in Egypt, where prevalence of antibodies to HCV (anti-HCV) is approximately 10-fold greater than in the United States and Europe **(Mohamed *et al.*, 2014).** Egypt has the highest prevalence of HCV worldwide and has rising rates of hepatocellular carcinoma (HCC). Egypt's unique nature of liver disease presents questions regarding the distribution of HBV and HCV in the etiology of **HCC (Abdelmoez *et al.*, 2019). (Lehman and Wilson 2009)** reported prevalence for HBV and HCV to be 6.7% and 13.9% among healthy populations, and 25.9% and 78.5% among HCC cases. Detection and characterization of all hepatic focal lesions are critical especially in patients with liver cirrhosis, as those patients are at high risk to develop hepatocellular carcinoma **(Lau *et al.*, 2016).** Serum α-fetoprotein (AFP) is the only marker that has been widely used for screening and diagnosis of HCCs. However, development of false-negative or false-positive rates with (AFP) was as high as 30%-40% for patients with small hepatocellular carcinomas **(Negm *et al.*, 2017).** Liver biopsy is the traditional gold standard method to establish the diagnosis and to determine the extent of inflammatory changes and the extent of fibrosis and cirrhosis. However, this procedure has many disadvantages, it is invasive, coasty and difficult to standardize **(sharma *et al.*, 2014).** Patients with chronic HCV are often anxious regarding undergoing a liver biopsy. Biopsy results show significant variability up to 40% for fibrosis diagnosis which can lead to a wrong diagnosis, indeed the result depends on the representatively of the punctured sample **(Trifan and Stanciu 2012).** That is why there has been increasing interest in noninvasive assessment of liver fibrosis by the use of surrogate serum markers **(Stasi and Milani, 2016).** The utility of OPN in early HCC detection may be relevant to many reports suggesting that beside its important role in metastasis, OPN expression is also critical for tumor growth of human HCC, and that down-regulation of OPN suppresses growth of HCC via induction of apoptosis **(Wu *et al.*, 2012; Sanyal *et al.*, 2010).** OPN attracted attention as a promising biomarker for HCC diagnosis in patients with virus-related cirrhosis with better sensitivity than AFP in differentiating HCC cases from cirrhosis and controls **(Kim *et al.*, 2006; Shang *et al.*, 2012).** Besides these features, a number of biological markers including cytokines and growth. Aldehyde dehydrogenase is a polymorphic enzyme responsible for the oxidation of aldehydes to carboxylic acids, which leave the liver and are metabolized by the body's muscle and heart. There are three different classes of these enzymes in mammals: class 1 (low Km, cytosolic), class 2 (low Km, mitochondrial), and class 3 (high Km, such as those expressed in tumors, stomach, and cornea).ALDH1 and ALDH2 are the most important enzymes for aldehyde oxidation, and both are tetrameric enzymes composed of 54kDA subunits. These enzymes are found in many tissues of the body but are at the highest concentration in the liver **(Mohamed *et al.*, 2015).** So the aim of this study is to evaluate the diagnostic and prognostic value of ALDH and Osteopontin levels in patients with hepatocellular carcinoma Patients.

Subject & Methods

The current study was Prospective study consisted of three groups, where group (I) included sixty patients with HCC. While patients with cancers other than HCC or metastatic liver cancer were excluded. Group (II) included sixty patients with liver cirrhosis and without any evidence of HCC and sixty healthy adults were recruited as controls (Group III). All patients included in this study had the procedure thoroughly explained to them. HCC was diagnosed by abdominal US and confirmed by triphasic CT scan. The clinical/ pathological data of the patients were recorded, including age, sex, viral infections {Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV)}, alcohol intakes, biochemical liver function test results, and AFP levels

Tumor characteristics were detected by abdominal US with or without CT scan (including tumor size, number, site, halo sign and neovascularization).

Blood Sampling and Biochemical Assays

Fasting venous blood samples (10 ml) were collected by trained laboratory technicians. A portion of blood was allowed to clot and then centrifuged at 3500g for 5 min to separate the serum used for assessment of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and g-glutamyl transpeptidase (GGT), total bilirubin, direct bilirubin, albumin, creatinine and glucose concentrations were assayed using Beckman CX4 chemistry analyzer (NY, USA, supplied by the Eastern Co. For Eng. & Trade-Giza, Egypt). Viral infection status (HCV Ab and HBsAg) were measured using Abbott, Axyam (USA, Supplied by Al kamal company). Serum aliquots were stored at -80°C until assayed and thawed immediately before the measurements levels. Serum AFP, ALDH and Osteopontin levels were determined using an enzyme-linked binding protein assay kit. All assays were performed in duplicate according to the manufacturer's instructions.

Statistical Analysis

Statistical package (SPSS, version 20.0) was used for data management. Descriptive statistics was presented as mean ± standard deviations for continuous variables, number and percentage for categorical variables (frequency distribution). Unpaired student t-test (two sided) was used to test the significance of difference between the mean value of studied groups and chi-square test was used for comparison of categorical variables. The diagnostic value for each marker was assessed using sensitivity, specificity, positive (PPV) and negative (NPV) predictive values. Receiver operating characteristic curves (ROC) were constructed to assess the validity of the markers in predicting HCC by calculating the area under the curve (AUC). The significance level was set at $P<0.05$.

Results

The demographic data of the studied groups were summarized in Table 1 where there was comparison between the cirrhosis group and hepatocellular group regarding residence , occupation and etiology of the diseases . HCC group included 60 patients, their ages ranged from 48 to 89 years with mean value 60.9 ± 9, they were 43(71.5%) males and 17 (28.5%) females, including 36(60%) Urban, 24(40%) Rural, with 14 (35%) Farmer and 46 (65%) Non- farmer with etiological factors of 33(55%) as a result of smoking, 3(2.5%) ,alcohol consumption, 54(90%) HCV which is the most relevant oncogenic agent for HCC development and 6 (5%) dHBV. Finally, there were no statistically significant differences in the mean values of ages or gender in all studied groups ($P > 0.05$). On the other hand, according to Liver Cirrhosis group included 60 patients, their ages ranged from 34 to 80 years with mean value 56.5 ± 9.3 (P. value= 0.08), they were 27 (45%) males and 33(55%) females (P. value=0.01*), including 39(65%) Urban and 21 (35%) Rural (P. value= 0.54), with 12 (20%) Farmer and 48(80%) Non- farmer (P. value= 0.186), with associated risk factors of 24 (40%) for smokers (P. value= 0.2), 6 (5%) alcohol consumption (P. value= 0.72), 54 (90%) HCV which well established as the major risk factor for HCC (P. value= 0.54). Table 2 showed the Radiological examination of studied groups (Control, LC and HCC patients) Sonar and Computed tomography. The comparison between the studied groups regarding the biochemical parameters were presented in table 3 which showed a significance difference in all parameters in the studied groups.

As regards ALDH and osteopontin values were higher in HCC cases than liver cirrhotics groups (P1=0.000). In the receiver operating curve (ROC) (table4), the area under curve (AUC) for AFP was 0.65% when we use > 18.9 ng/mL as a cutoff point, with a sensitivity of 66% and a specificity of 64%. For Osteopontin the cutoff point that gives an AUC equal 0.917 was 239ng/ml with a sensitivity of 92.5% and a specificity of 85%.

Table1. *Demographic Features of the studied patient groups:*

Characteristics	HCC Patients (n = 60)	Liver Cirrhosis (n = 60)	P. value
Age (years)			
Range	**48- 89**	**34- 80**	**0.08**
Mean ± SD	**60.9 ± 9**	**56.5 ± 9.3**	
Gender			
Male	**43(71.5%)**	**27 (45%)**	**0.01***
Female	**17 (28.5%)**	**33(55%)**	
Residence			
Urban	**36(60%)**	**39(65%)**	**0.54**
Rural	**24(40%)**	**21 (35%)**	
Occupation			
Farmer	**14 (35%)**	**12 (20%)**	**0.186**
Non- farmer	**46 (65%)**	**48(80%)**	
Etiology			
Smoking	**33(55%)**	**24 (40%)**	**0.2**
Alcohol	**3(2.5%)**	**6 (5%)**	**0.72**
HCV	**54(90%)**	**54 (90%)**	**0.54**
HBV	**6 (5%)**	**0 (0%)**	**0.44**

Table2. *Radiological examination of studied groups (Control, LC and HCC patients) Sonar and Computed tomography.*

Parameters	Control group N (%)	LC group N (%)	HCC group N (%)
Liver:			
-Normal liver	60(100%)	0(0%)	0(0%)
-Bright liver	0(0%)	0(0%)	0(0%)
-Coarse liver	0(0%)	60(100%)	60(100%)
Focal lesion	0(0%)	0(0%)	60(100%)
Ascites:			
No	60(100%)	36(60%)	48(80%)
Mild	0(0%)	14(23.3%)	4(6.7%)
Mod	0(0%)	6(10%)	6(10%)
Severe	0(0%)	4(6.7%)	2(3.3%)
PVT:			
Yes	0(0%)	6(10%)	6(10%)
No	60(100%)	54(90%)	54(90%)
Splenomegaly:			
Yes	0(0%)	6(10%)	14(23.3%)
No	60(100%)	54(90%)	46(76.7%)
Hepatomegaly:			
Yes	0(0%)	8(13.3%)	6(10%)
No	60(100%)	52(86.7%)	54(90%)
Hypertension:			
Yes	0(0%)	6(10%)	0(0%)
No	60(100%)	54(90%)	60(100%)

*p-value < 0.05 significant, PVT (portal vein thrombosis).

Table3. *Biochemical parameters of the studied groups*

Parameter	Control group Mean ±SD	LC group Mean ±SD	HCC group Mean ±SD	P-value
ALT(IU/L)	20.33 ± 7.11	57.11 ± 12.71	67.22 ± 13.44	0 .005 [a, b]
AST(IU/L)	23.00± 9.66	87.33 ± 17.11	99.55 ± 16.00	0.000 [a, b]
Albumin(g/dl)	3.9 ± 0.5	2.77±0.4	2.55 ± 0.56	0.000 [a, b]
T.BIL (mg/dl)	0.66 ± 0.17	5.55 ± 2.22	6.33 ± 1.22	0.003 [a, b]
Glucose(mg/dl)	90.2 ± 13.2	133.3 ± 11.23	111.7 ± 6.03	0.000 [a, b]
Creatinine(mg/dl)	0.66 ± 0.17	1.76 ± 0.22	2.17 ± 0.55	0.005 [a, b]
AFP (ng/dl)	4.7 ± 2.55	177.1± 25.0	586.2 ± 33.4	0.000 [a, b]
ALDH	67± 11.23	95± 14.7	107±18.8	0.000 [a, b]
Osteopontin	133±12.7	234±27.5	447±45.8	0.000 [a, b]
ALT: alanine aminotransferase, **AST:** aspartate aminotransferase, **T.BIL**: total bilirubin, **AFP**: alpha-fetoprotein, **P-value** <0.05 considered significant. [a] Significant difference from control group. [b] Significant difference from LC group				

Table4. *Sensitivity and specificity of diagnostic values of AFP, ALDH and Osteopontin levels detection of HCC in different subjected cases.*

Biomarker	Cut-off value	AUC	sensitivity	Specificity
AFP	18.9 ng/ml	0.65	66%	64%
ALDH	87 ng/ml	0.76	74%	82%
Osteopontin	239 ng/ml	0.917	92.5%	85%

Discussion

Egypt has the highest prevalence of HCV worldwide and has rising rates of hepatocellular carcinoma (HCC). Egypt's unique nature of liver disease presents questions regarding the distribution of HBV and HCV in the etiology of **HCC (Abdelmoez *et al.*, 2019).** Our results showed a significant increase in AST, ALT, serum bilirubin in HCC group in comparison with the control group, as there was a statistically significant increase in ALT in HCC patients group and Cirrhosis group comparing to control group, these results agreed with Al-Jumaily & Khaleel (2012) who reported significant alteration in liver functions in patient groups (cirrhotic and HCC groups) when compared to control subjects **(Giannini *et al.*, 2005).** These data could be related to the fact that aminotransferases are typically elevated in all liver disorders appearing to be more sensitive and specific tests for acute than chronic hepatocellular damage **(zekri *et al.*, 2010).** Also agreed with Mohamed *et al.*, (2014) who found that there was no significant difference between HCC patients group and Cirrhosis group in the mean alanine transaminase (ALT) **(Mohamed *et al.*, 2014).** High ALT levels are associated with inflammation of liver and individuals who have ALT levels are more likely to have damage to the liver that causing regeneration **(Lewis, 2016).** While regarding to AST, these results show a statistically significant increase in AST (Aspartate transaminase) in HCC patients group and Cirrhosis group comparing to control group, these results agreed with Negm *et al.*, (2017) who reported a significant elevation in AST in HCC and cirrhotic groups in comparison with control group **(Negm *et al.*, 2017).** Also agreed with Mohamed *et al.*, (2014) who found that there was no significant difference between HCC patients group and Cirrhosis group in the mean aspartate transaminase (AST) **(Mohamed *et al.*, 2014).** Regarding to serum bilirubin, these results show a statistically significant increase in serum bilirubin observed in both HCC and cirrhotic group when compared to control group, these results agreed with Negm *et al.*, (2017) who reported a

significant elevation in serum bilirubin in HCC and cirrhotic groups in comparison with control group **(Negm *et al*., 2017).** In contrast, our results showed a significant decrease in serum albumin in both HCC and cirrhotic group when compared to control group, these results agreed with Al-Jumaily & Khaleel (2012) who reported significant decrease in albumin in HCC and cirrhotic groups in comparison with control group **(Giannini *et al*., 2005).** Liver function tests are a helpful screening tool which is an effective modality to detect hepatic dysfunction. Since the liver performs a variety of functions so no single test is sufficient to provide complete estimate of function of liver **(Thapa and Walia, 2007).** The results also showed a statistically significant increases in the mean values of fasting and blood glucose levels in cirrhosis group as well as HCC group when compared to control group, but there was no statistically significant difference in its mean values in cirrhosis group when compared to HCC group.

This study also showed that, there were statistically significant increases in the mean values of serum creatinine in cirrhotic group and HCC group when compared to control group, in contrast there was no statistically significant difference in its mean value in cirrhotic group when compared to HCC group. Many changes in kidney function are strongly linked with increased mortality, extending to those with chronic liver disease. Chronic liver disease is associated with primary and secondary kidney disease and impacts markedly on survival, these results agreed with Slack *et al*., (2010) who reported a significant elevation in blood glucose and creatinine levels in HCC and cirrhotic groups in comparison with control group **(Slack *et al*., 2010).** The results also showed a statistically significant increase in the mean values of AFP in HCC and cirrhosis group compared to control group, these results agreed with El Shafie *et al*., (2012) who reported that the serum levels of AFP are significantly elevated in chronic liver diseases and more elevated in HCC cases **(Allazouny *et al*., 2017).** and contrast with Trevisani et al., (2001) who reported that not all tumors secrete AFP and serum concentrations are normal in up to 40% of small HCC **(Trevisani *et al*., 2001).** While according to ALDH, this study showed a statistically significant increase in the mean values of ALDH in HCC group and cirrhosis group compared to control group.

Finally according to OPN levels, this study showed a statistically significant increase in the mean values of OPN in HCC group and cirrhosis group compared to control group, these results agreed with some studies who reported that plasma levels of OPN were significantly higher in HCC plasma than in cirrhosis, chronic hepatitis C and healthy controls **(Salem *et al*., 2013).** Suggesting the use of circulatory OPN as a complement diagnostic biomarker for AFP. In contrast to Zekri *et al*., (2011) who reported that OPN levels in HCC patients were not significantly higher than that those with chronic liver diseases **(Zekri *et al*., 2011).** Also, in another study, it was found that the mean OPN level in HCC patients was not significantly different from HCV or other chronic liver disease patients while it was significantly higher in these diseases than control group **(Abdel-Hamid *et al*., 2014).** When evaluating OPN, ALDH and AFP in diagnosis of HCC, it was demonstrated that OPN at an optimal cut-off value 239 ng/ml had a better performance than ALDH at a cut-off value 87 ng/ml and AFP at a cut-off value > 18.9 ng/ml for HCC diagnosis. The sensitivity and specificity of OPN for HCC diagnosis were 92.5%and 85% comparing to ALDH whose sensitivity and specificity for HCC diagnosis were 74% and 82% vs. AFP whose sensitivity and specificity for HCC diagnosis were 70% and 73% with an area under the ROC curve of 0.917 in comparison to 0.76 vs. 0.65 for OPN in comparison to ALDH vs. AFP, respectively.

This is in agreement with Shang *et al*., (2012) who found that OPN at an optimal cut-off of 91 ng/ml had a better performance than AFP at a cut-off of 20 ng/ml for early HCC diagnosis. The sensitivity and specificity for early HCC diagnosis were 74% and 66% vs. 53% and 93% with an area under the ROC curve of 0.76 vs. 0.71 for OPN vs. AFP, respectively **(shang *et al*., 2012).**

Conclusion

In this study, we concluded that serum OPN and ALDH had a better diagnostic performance than AFP for detection of HCC in Egyptian patients, while the sensitivity and specificity of serum OPN was more than the sensitivity and specificity of ALDH so, OPN may be considered as a promising HCC biomarker for diagnosis, particularly for those with negative AFP.

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