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Original article

Serum Level of Cluster of Differentiation 166 in Diagnosis of Hepatocellular Carcinoma

Marwa Shabaan [a], Amany H. Lashin [a], Shuzan A. Mohamed [b], Hany R. Elkholy [a]

[a] Department of hepatology, gastroentrology and infectious disease, Benha faculty of medicine, Banha University, Egypt. [b] Department of Medical Biochemistry and Molecular Biology, Benha faculty of medicine, Banha University, Egypt.

Correspondence to: Marwa Shabaan, Department of hepatology, gastroentrology and infectious disease, Benha faculty of medicine, Banha University, Egypt

Email:

marwashaaban40@gmail.com

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Abstract:

Background: Hepatocellular carcinoma is a worldwide health problem . It is considered the second most common cause of cancer-associated fatalities and it is the fifth major cause of cancer all over the world. Cluster of differentiation 166 is a cell surface member of the immunoglobulin super- family that plays an important role in many biological activities. The distribution of CD166 in specific cell and tissue offer their involvement in the maintenance and development of tissue architecture, in neurogenesis and in tumor progression . **Aim and objectives :** to evaluate the diagnostic value of serum-CD166 in patients with HCC. **Methods:** This study was conducted on 90 subjects attending Department of Hepatology , Gastroenterology and Infectious Diseases in Benha University Hospitals as a cross sectional study. Subjects were classified into three groups; Group I : included 35 patients with HCC, Group II: included 35 patients with liver cirrhosis, Group III: included 20 apparently healthy subjects served as a control group. Human CD166 and alpha fetoprotein were assessed in all groups , all laboratory investigations were done . **Results:** Serum CD166 concentrations were much higher in HCC than in cirrhosis and healthy individuals . A positive correlation was found between serum CD166 and AFP. The area under the ROC curve for serum-CD166 was 0.951, while in AFP (AUC-ROC, 0.943) , with a cut-off of 1357ng/ml (sensitivity: 94.3%, specificity: 97.1%) for CD166 . **Conclusion :** Serum CD166 may represent a potential diagnostic marker for HCC .

Key words : Hepatocellular carcinoma (HCC) , Alpha-fetoprotein (AFP) , Cluster of differentiation 166 (CD166) .

Introduction

Hepatocellular carcinomna (HCC) is the fifth most common tumor worldwide and the second most common cause of cancer-related deaths (1). It is one of the most common aggressive malignancies worldwide; accounting for about two thirds of all primary liver cancer cases (2). Most cases of HCC develop on top of chronic liver disease (70%-90%) (3).

The global distribution of HCC is variable because it is most prevalent in areas with widespread chronic hepatitis B virus (HBV) infection. Additionally, the western world is complaining from rising HCC prevalence as a result of migration from HBV-endemic regions, hepatitis C virus (HCV) infection, alcoholic cirrhosis and non-alcoholic steato hepatitis associated with the obesity epidemics ***(4).***

In Egypt, liver cancer counts for 11.75% of the malignancies of the digestive organs and 1.68% of the total malignancies. HCC forms 70.48% of all liver tumors among Egyptians and it is considered the main complication of cirrhosis, and represents a growing incidence in Egypt, which may be due to a shift in the relative importance of (HBV) and HCV as primary risk factors, and advancements in screening programs and diagnostic materials ***(5) .***

Cluster of differentiation 166 (CD166)is a cell surface member of the immunoglobulin super- family that is over-expressed in several types of epithelial tumors. It was considered as a valuable prognostic marker of disease progression and poor survival (6 & 7) .

The anti-apoptotic role of CD166 in liver cancer cells and the function of CD166 on liver tumorigenesis relied on Yes associated protein (YAP) (8) . YAP is an onco-protein that plays important roles in the maintenance of the transformative phenotype of liver cancer cells (9) . YAP is primarily located in the nucleus, and it is difficult to be detected in the serum. Serum indicators that reflect YAP function in liver cancers are not clear. The transmembrane protein Jag-1 is a downstream target of YAP in liver cancer cells (10) .

The aim of this work was to study the clinical usefulness of serum CD-166 as a diagnostic marker for hepatocellular carcinoma.

Study subjects:

This study was conducted as a case control study on 70 patients who were recruited from Hepatology, Gastroenterology and Infectious Diseases

Department, Benha University Hospitals, in addition to 20 apparently healthy subjects serving as healthy control in period from September 2018 to April 2019 . Subjects included in this study were classified into the following groups , ***Group I :*** included 35 patients with hepatocellular carcinoma (29 males and 6females) , diagnosed by ultrasonography (U/S) and confirmed by Triphasic Computed Tomography . ***Group II:*** (23males and 12 females) included 35 patients with liver cirrhosis diagnosed by clinical, laboratory and U/S assessment. The mean age of patients with HCC was 56.5±8.8 years compared to 57.8±9.2 years in LC group . ***Group III:*** included 20 (14males and 6 females) apparently healthy subjects served as a control group.

The study protocol was approved by the Ethical Committee of Faculty of Medicine, Benha University. An informed written concent was obtained from all patients participating in this study after explaining the study measures in details.

Methods :

Venous blood samples (~ 6 ml) were taken using sterile syringes under aseptic conditions. The collected samples were collected and divided as follow : Part 1: (0.5 ml) on EDTA for complete blood count (CBC). CBC including the differential count was done automatically , Part 2: (0.9 ml) was put on 0.1 ml tri-sodium citrate solution (3.8%) in a ratio of 9:1 for determination of prothrombin time (sec.), concentration and INR , Part 3: (~ 4.5 ml) were left to clot for half an hour and then centrifuged for 15 minutes at 1000 ×g. Hyperlipidemic and hemolyzed samples were excluded. Sera were used for biochemical investigations ,

1. Fasting blood glucose (mg/dl) *(Trinder, 1969).*

2. Liver biochemical tests: Including:

- Serum alanine aminotransferase ,Serum aspartate aminotransferase
- Serum bilirubin (total bilirubin and direct bilirubin)
- Serum albumin

3.Kidney function tests:Serum creatinine (mg/dl) andbloodurea.

The analysis of serum AST, ALT, albumin, total bilirubin, direct bilirubin, were performed on Biosystem A15 autoanalyzer.

4. Serum AFP Assay:

Immunospec AFP Quantitative Test Kit is based on a solid phase enzyme-linked immunosorbent assay. It was performed on Das plate washer serial Number 934 and

the result was obtained by Das plate reader serial Number 20067 .The assay system utilizes one anti-AFP antibody for solid phase (microtiter wells) immobilization and another mouse monoclonal anti-AFP antibody in the antibody-enzyme (horseradish peroxidase) conjugate solution.

5. Serum CD166 Assay:

This assay employs an in-vitro double-antibody sandwich enzyme - linked immune-sorbent assay (ELISA) for quantitative detection of the level of Human serum CD166 by using commercially kit Human ALCAM/CD166 Picokine ELISA kit **(Boster biological Technology, Pleasanton CA, USA) .**

Statistical analysis :

The collected data was revised, coded and tabulated using Statistical package for Social Science **(IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).** Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

The clinical data were expressed as Mean and standard deviation $(\pm SD)$. for quantitative data, Frequency and distribution for qualitative data. Quantitative data were compared using independent Student's t-test. On the other hand, qualitative data were compared using chi square test and fisher exact test (FET). Logistic regression OR (Odds Ratio) of regression: It is the expected (B) in regression, it was done to quantify how much is the predicted outcome among individuals with the independent variables compared with the cirrhotic and control groups. p value is significant if <0.05 at confidence interval 95% .

The ROC curve is a fundamental tool for diagnostic test evaluation.

In a ROC curve the true positive rate (Sensitivity) is plotted in function of the false positive rate (100-Specificity) for different cut-off points of a parameter. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. The area under the ROC curve (AUC) is a measure of how well a parameter can distinguish between two diagnostic groups (diseased/normal).

The diagnostic performance of a test, or the accuray of a test to discriminate diseased cases from normal cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis. ROC curves can also be used to compare the diagnostic performance

of two or more laboratory or diagnostic tests

Results :

This study conducted on 90 subjects attending Department of Hepatology , Gastroentrology and Infectious Diseases in Benha University Hospital as a cross sectional study in the period from September 2018 to April 2019. All subjects divided into 3 goups including 35 patients with hepatocellular carcinoma (group I) , 35 patients with liver cirrhosis (group II) and 20 apparently healthy subjects as control (group III) .

An informed written concent was obtained from all patients participating in this study after explaining the study measures in details.

Table (1) Shows that Smoking was significantly associated with HCC when compared to cirrhotic group . No significant differences were found between HCC and LC groups regarding other Socio demographic data .

Table (2) Shows that HCC showed significantly higher AFP concentration when compared to LC group . Otherwise , no significant differences were found in CBC , FBG , creatinine and liver function tests among studied cases .

Table (3) shows that CD166 level was significantly higher in LC and HCC when compared to control groups . Moreover, it was significantly higher in HCC when compared to LC groups .

Table (4) shows that ROC curve of serum AFP show AUC=0.943 , cut off value of 42.6 , sensitivity 88.6% , specificity 91.4% , PPV 91,2 and NPV88.9 , while for serum CD166 show AUC=0.951 , cut off values1357, sensitivity 94.3% , specificity 97.1% , PPV 97.1 and NPV94.4 . Comparing AUCs, revealed that combined AFP+CD166 was significantly better than each marker alone.

Table (5) shows that serum CD166 level was significantly higher in patients with higher child class . Child class C patients had the highest concentration (11144) and Child class B patients had the lowest (9771)

Table (1): Socio demographic data of the studied groups **:**

		LC N=35		HCC N=35		Test	*p*
		N	%	N	%		
Age (years)	**mean±SD**	57.8±9.2		56.5±8.8		ANOVA	0.322
Gender	**Males**	23	65.7%	29	82.9%	chi square test	0.250
	Females	12	34.3%	6	17.1%		
Occupation	**Farmer**	27	77.1	25	71.4	chi square test	0.584
	Non Farmer	8	22.9	10	28.6		
Residence	**Rural**	24	68.6	22	62.9	chi square test	0.615
	Urban	11	31.4	13	37.1		
Marital status	**Single**	3	8.6	2	5.7	Fisher exact test.	0.643
	Married	32	91.4	33	94.3		
History of Smoking		4	11.4	11	31.4	chi square test	0.041

SD, standard deviation

Table (2): Laboratory investigations of the studied cases **:**

		LC N=35	HCC N=35	Test	*P*
HB (g/dL)	**mean±SD**	9.9±1.8	10.2±2.8	T test	0.153
WBCs (X10^9/L)	**mean±SD**	5.5±1.2	12.1±3.5	T test	0.077
platelets (x10^9/L)	**mean±SD**	88.6±20.2	103.8±31.8	T test	0.362
FBG (mg/dL)	**mean±SD**	119±27.8	104.9±67.9	T test	0.260
Creatinine (mg/dL)	**mean±SD**	1.2±0.7	1.2±.6	T test	0.838
ALT (I/U)	**mean±SD**	45.6±10.9	49.6±12.5	T test	0.597
AST (I/U)	**mean±SD**	57.5±18.2	64.8±12.9	T test	0.349
Bilirubin (mg/dL)	**Median**	2.6	2.2	Mann Whitney test	0.101
	Range	0.6-6.8	0.5-16.6		
Albumin (g/dL)	**mean±SD**	2.7±0.9	2.8±0.6	T test	0.729
INR	**mean±SD**	1.5±0.4	1.6±0.4	T test	0.172
PT (seconds)	**mean±SD**	15.8±2.6	16.7±3.1	T test	0.148
AFP (ng/mL)	**Median**	6.8	263.2	Mann Whitney test	**<0.001**
	Range	0.1-62.3	2-13588		

SD, standard deviation

Table (3): Comparison of Serum CD166 concentration among studied groups :

CD166 (ng/mL)	Normal N=20	LC N=35	HCC N=35	P^1	P^2	P^3	P^4
Median	166.2	780	7147	**<0.001^K**	**<0.001^M**	**<0.001^M**	**<0.001^M**
Minimum	75	275	376				
maximum	390	1430	11144				

p1, comparison between control, LC and HCC; p2, comparison of LC versus control; p3, comparison of HCC versus control; p4, comparison between LC and HCC; M, Mann Whitney test; K, Kuskal Wallis test .

Table (4): Area under ROC curve and performance criteria of serum AFP, CD166, combined markers for discrimination between HCC and LC cases :

	Discrimination between LC and HCC		
	AFP	**CD166**	**AFP+CD166**
AUC	0.943	0.951	1
95% CI	0.882-1	0.885-1	1-1
P^1	<0.001	<0.001	<0.001
Cut off	42.6	1357	-
Sensitivity (%)	88.6	94.3	100
Specificity (%)	91.4	97.1	100
PPV (%)	91.2	97.1	100
NPV (%)	88.9	94.4	100
Accuracy	90.0	95.7	100
P^2	-	0.988	0.937
P^3	-	-	0.948

ROC, receiver operating characteristic curve; AUC, area under ROC curve; PPV, positive predictive value; NPV, negative predictive value; p1, comparison of AUCs versus AFP AUC; p2, comparison of AUCs versus CD166 AUC.

Table (5): Comparison of CD166 level according to Child classes in LC and HCC groups :

		LC and HCC N=70			
		Median	**Minimum**	**Maximum**	***p***
Child	**A**	6630	939.2	9771	**0.021^K**
	B	803.2	281.2	7743	
	C	1217.2	275	11144	

K, Kruskal Wallis test.

Discussion:

Hepatocellular carcinoma (HCC) is a worldwide health problem. It is considered the second most common cause of cancer associated fatalities and it is the fifth major cause of cancer all over the world. This variance between occurrence and fatality

ensures that it is an aggressive tumor with poor prognosis. Incidence of HCC is rapidly growing in the west due to increased epidemic of its risk factors like alcohol, fatty liver and viral hepatitis (12).

Cluster of differentiation 166 (CD166), also known as activated leukocyte cell adhesion molecule (ALCAM) **(7)**, It is a 110 kD type I transmembrane glycoprotein that is a member of the immunoglobulin superfamily of proteins. In humans it is encoded by the ALCAM gene. It was first described as a CD6 ligand on leukocytes **(14).**

CD166 plays an important role in many biological activities, including T-cell activation and proliferation, angiogenesis, hematopoiesis and axon fasciculation **(15).** The distribution of CD166 in specific cell and tissue offer their involvement in the maintenance and development of tissue architecture, in neurogenesis, immune responses and in tumor progression **(16).**

The aim of our work was to study the clinical usefulness of serum CD-166 as adiagnostic marker for hepatocellular carcinoma and correlate its level with AFP, the current marker of HCC.

In the current study, HCC commonly presented in males (82.9%) more than females (17.1%) with a male to female ratio 4.8:1 . Male predominance for HCC development was reported by (17) in 2002 . This also was nearly in agreement with previous study in 2014(18) who reported that male to female ratio of 3.1:1 among HCC patients.

In the current study, the mean age of patients with HCC was 56.5±8.8 years, ranging from 35 to 74 years. This result agreed with (19)who reported in a study including 41 HCC patients that, the mean age of HCC patients was 57.95 ± 8.41 years (19) and (20) in 2007 who documented that the mean age was 56.28 years for the HCC patients. Also, previous study in 2002 stated that the incidence of HCC increases progressively with advancing age, however, in areas with high risk the mean age is definitely younger (21).

In the current study, Cigarette smoking was observed in patients with HCC (31.4%) more than those of liver cirrhosis(11.4%) . This finding come in agreement with a study in 2010**,** who reported that , cigarette smoking may increase the risk of HCC among HCV seropositive (25) . Although, previous study in 2008 reported that 46.3% of HCC cases were smokers (19), other study in 2006 reported that smoking yields chemicals with oncogenic potential that

increase the risk of HCC (26), however, the role of smoking was not clear in his study.

The results of AFP in our study showed a statistical significant difference between LC and HCC groups, serum AFP was significantly higher in HCC group when compared to liver cirrhosis group . These results are agreed with those of previous studies who referred to that the increase in selective transcriptional activation in AFP gene in the malignant hepatocytes resulting in increased secretion of AFP during the development of HCC to inhibit immune response of liver cancer cells. (27), (30) , (31)

According CD166 and its relation to hepatocellular carcinoma the present study did Comparison of CD166 concentration among studied groups and found that CD166 level was significantly higher in LC and HCC when compared to control groups. Moreover, it was significantly higher in HCC when compared to LC groups.

In the current study, median serum CD166 level was significantly higher in HCC patients (7147pg/ml) than cirrhotic patients (780pg/ml) and both were significantly higher than controls (166.2pg/ml) . This is in agreement with study conducted by a study in 2015 hat reported higher levels of CD166 in HCC patients (32).

Child classes showed significantly different levels of CD166, the highest concentration was associated with Child C, while the lowest concentration was associated with Child B.

In the current study ROC curve of serum CD166, AFP, combination of both markers was conducted for discrimination between HCC cases and LC groups.

ROC curve of serum AFP show AUC=0.943 , cut off value of 42.6 , sensitivity 88.6% , specificity 91.4% , PPV 91,2 and NPV88.9 , while for serum CD166 show AUC=0.951 , cut off value 1357, sensitivity 94.3% , specificity 97.1% , PPV 97.1 and NPV94.4 .

Combination of both markers revealed AUC (AUC = 1), with sensitivity 100% , specificity100% , PPV 100% and NPV100% .

Excellent AUCs for AFP as well as for CD166 were found (AUC=0.943, 0.951 respectively). Combination of both markers revealed perfect AUC (AUC = 1), with increased sensitivity, specificity, PPV and NPV than single marker .

This was in agreement with study in 2015 that identified the cut-off value of serum CD166 for the prediction of HCC. However, serum CD166 measurements are not standardized (32), and the cut-off value

of serum CD166 in the present study may not be applicable to other analytic methods. The optimal cut-off of serum CD166 should be re-determined after the measurement method is standardized.

CD166 showed an AUC of 0.986 with 100% sensitivity and 89.41% specificity. One study also determined serum CD166 levels in HBV (n=48), HCV (n=40), cirrhosis (n=41), gastric (n=21), breast (n=25) and lung (n=21) cancer patients and found it exclusively elevated levels in HCC patients. Since no ROC curve analysis was performed, these findings require re-evaluation (33).

Our study has some limitations as the small number of patients in some of the univariate analyses might lead to insignificant findings in the statistical analyses, so larger studies should be considered to clarify diagnostic value of serum CD166 in liver damage.

Finally we can conclude that CD166 was better diagnostic marker for HCC .

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