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Original paper

Soluble CD25 as a predictor of hepatocellular carcinoma compared with alpha-fetoprotein

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Abstract

Aim of the study: We aimed to evaluate soluble CD25 (sCD25) as a marker for hepatocellular carcinoma (HCC) diagnosis.

Material and methods: Eighty-eight subjects were enrolled in our study in the years 2017-2018. They were divided into three groups as follows: group 1 – HCC group (n = 44) patients, represented by BCLC stage A (n = 16) patients, stage B (n = 14) patients and stage C (n = 14) patients for each stage. All HCC patients were on top of cirrhosis. Group 2 – group of cirrhotic patients without HCC (n = 32); 50% of them were Child-Turcotte-Pugh class A (n = 16) while class B was represented only by 43.7% (n = 14) of patients. Group 3 – control group (n = 12) of healthy subjects.

Results: The levels of sCD25 and AFP were higher in HCC patients than cirrhotic and control groups without a statistically significant difference between the three groups (p-value > 0.05). For HCC presence, sensitivity and specificity of sCD25 were 86.4% and 29.5% respectively at a cut-off value of 1.1×10^3 pg/ml (AUC = 0.619, p-value = 0.054, PPV = 33.2%, NPV = 68.44%). For early detection of HCC, sCD25 had a sensitivity of 70.5% and a specificity of 30.9% at a cut-off value of 1.575×10^3 pg/ml (AUC = 0.577, p-value = 0.251, PPV = 58.5%, NPV = 43.1%), while the sensitivity and specificity of AFP were 75% and 62.5% respectively at a cut-off value of 9.5 ng/ml (AUC = 0.828, p = 0.000, PPV = 73.4%, NPV = 64.4%) in the same settings.

Conclusions: sCD25 seems to offer no better detection rate of HCC compared to AFP with lower sensitivity and specificity.

Key words: hepatocellular carcinoma, alpha-fetoprotein, HCC markers, soluble CD25.

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Introduction

Hepatocellular carcinoma (HCC) is reported as the most frequently detected primary liver malignancy [1]. It is the 5th most common cancer in males and the 9th most common in females worldwide [2]. There is a high prevalence of both hepatitis C virus (HCV) and hepatitis B virus (HBV) infections in Egypt, which resulted in an increasing HCC incidence rate in the past ten years [3]. HCC has many risk factors. In most cases, it occurs as a complication of chronic liver disease. The most important disease leading to HCC is liver cirrhosis.

Early HCC detection is the key for improving outcome. Currently, we use α-fetoprotein (AFP) and abdominal ultrasound for screening. AFP has been used for HCC diagnosis historically [4]. At levels more than 400 ng/ml, it is considered to be diagnostic [5]. However, many studies have shown unreliable AFP sensitivity and specificity. So HCC diagnosis depends on radiological characteristics and histology [6], which highlights the importance of developing new markers.

The immune system plays an important role in inhibition of cancer proliferation. However, cancer can manipulate the immune system mechanisms and overcome them [7]. The liver microenvironment has

a unique immune response regarding HCC metastasis [8]. Lymphocytes play a very important role by way of inflammation and immunity. HCC develops on top of chronic inflammation where lymphocytes are a major component of this inflammatory microenvironment [9]. They interact with other innate immune cells directly or through chemokines and cytokines, e.g. interferon γ (IFN-γ) affecting tumor growth [10]. Both T and B lymphocytes infiltrate HCC, interfering with its proliferation and interacting with each other again through chemokines and cytokines [11] with better survival [12]. Although there is substantial lymphocytic infiltration, a tumor can progress [13]. This indicates that there is either inactivation of anti-tumor effector T cells or immune tolerance induction.

Soluble CD25 is involved in the immune response to many tumors including HCC. It is a protein that is encoded by the *IL-2RA* gene in humans [14]. It binds competitively to IL-2R, inhibiting lymphocyte proliferation and down-regulating NK activity. This interferes with the immune system function, making the level of sCD25 an indicator of immune system inhibition [15]. Cabrena *et al*. [16] found that HCC patients have significantly higher levels of sCD25 compared to control with a significant positive correlation between its level and tumor stage.

Material and methods

Studied subjects

Eighty-eight subjects were enrolled in our study. They were recruited from Beni-Suef University Hospital, Egypt in the years 2017-2018. This study was approved by the Research Ethical Committee of Beni-Suef University and all individuals provided written informed consent prior to participation in any procedure. They were divided into three groups as follows: group 1, HCC group (n = 44) patients, represented by BCLC stage A (n = 16) patients, stage B (n = 14) patients and stage C (n = 14) patients for each stage. In all HCC patients it was on top of cirrhosis; group 2, cirrhotic group without HCC (n = 32) patients; 50% of them were Child-Turcotte-Pugh class A (n = 16) while class B was represented only by 43.7% (n = 14) patients; group 3, control group (n = 12), healthy subjects.

All subjects were subjected to: 1. History taking and physical examination. 2. Routine laboratory investigations (complete blood count [CBC], liver profile and creatinine), chronic viral hepatitis screening, AFP and sCD25 assay. AFP was measured by ELISA using a kit from R & D Systems Inc., USA, while sCD25 was assayed using an ELISA kit of Boster Biological Technology Co Ltd, Pleasanton, CA. 3. Abdominal imaging: a) abdominal ultrasound; b) triphasic computed tomography (CT): diagnosis of HCC depended on typical criteria of enhancement of the focal lesion(s) in the arterial phase with rapid washout in the portal phase. Cirrhotic patients were diagnosed depended on clinical, laboratory and radiological findings. In group 1 patients (HCC cases), staging was decided based on the Barcelona clinic liver cancer (BCLC) guidelines [17]. Cirrhotic patients with or without HCC are classified according to Child-Turcotte-Pugh classification [18]. Performance status of HCC patients was according to World Health Organization (WHO) performance status [19].

Statistical analysis

We used the ANOVA test to test the mean difference of age and laboratory investigations between different groups. Receiver operator characteristic (ROC) curve analysis was used to generate sensitivity and specificity at different cut-offs. The best cut-off was set at the value of maximal sensitivity and specificity. A statistically significant result was at p value < 0.05. Non-parametric Spearman's rho correlation was also used.

Results

The mean age of the studied individuals was 54.9 ±5.8 years in HCC group while it was 54.5 ±6.9 and 50.4 ±8.8 years in cirrhotic and healthy groups respectively. Males represented 81.8% of patients among the HCC group while females represented 65.6% and 58.3% of subjects among the cirrhotic group and control group respectively. Regarding clinical characteristics splenomegaly was the most prominent feature as 66.66% and 81.81% of both cirrhotic and HCC patients respectively presented with it. Chronic HCV infection was the underlying cause of liver cirrhosis in all patients included in the study. Regarding hematological parameters, patients with liver cirrhosis had more significant anemia and thrombocytopenia than the other two groups, as presented in Table 1.

Regarding Child-Pugh classification, class B represented 47.7% of HCC patients and 43.8% of the cirrhotic group, while class A represented 50% of the cirrhotic group and 40.9% of HCC group. There was no statistically significant difference between the groups (p-value = 0.628).

The serum levels of both sCD25 and AFP were detected at a higher level in the HCC patients than cirrhotic and control groups. There was no a statistically significant difference (p-value > 0.05) between different

Table 1. Comparison between hepatocellular carcinoma, cirrhotic and control groups regarding baseline characteristics

Characteristics	Group	*N*	Mean ±SD	*p*-value	95% CI for mean		Range
					Lower bound	Upper bound	
WBCs (× 10^3/dl)	HCC	44	6.6 ±4.02	0.656	5.4	7.8	2-23
	Cirrhotic	32	6.7 ±3.5		5.4	7.9	2.5-19
	Control	12	5.6 ±1.4		4.7	6.5	3.5-8
HB (g/dl)	HCC	44	11.04 ±1.9	0.001	10.5	11.6	7.57-14.3
	Cirrhotic	32	9.9 ±1.5		9.5	10.5	7-12
	Control	12	11.9 ±1.3		11.2	12.8	9.9-14
PLT (× 10^3/dl)	HCC	44	137.5 ±56.9	< 0.001	120.2	154.8	21-320
	Cirrhotic	12	115.7 ±57.2		95.1	136.3	9.8-325
	Control	12	260.3 ±75.7		212.1	308.3	166-400
Albumin (g/dl)	HCC	44	3.1 ±0.6	< 0.001	2.9	3.2	2-5
	Cirrhotic	32	2.6 ±0.7		2.4	2.9	1.2-3.9
	Control	12	4.1 ±0.4		3.8	4.3	3.5-5
INR	HCC	44	1.4 ±0.3	0.005	1.3	1.5	1-2.2
	Cirrhotic	32	1.6 ±0.7		1.3	1.9	1-4.3
	Control	12	1.1 ±0.1		0.9	1.1	1-1.3
Creatinine (mg/dl)	HCC	44	1.4 ±1.03	0.094	1.1	1.7	0.5-5.9
	Cirrhotic	32	1.1 ±0.5		0.9	1.3	0.5-2.8
	Control	12	0.8 ±0.3		0.7	1	0.5-1.3
BIL (mg/dl)	HCC	44	3.5 ±5.7	0.084	1.7	5.2	0.5-30
	Cirrhotic	32	1.7 ±1.6		1.1	2.4	0.5-10.25
	Control	12	0.9 ±0.3		0.6	1.1	0.3-1.25
AST (U/ml)	HCC	44	83.8 ±64.3	0.001	64.3	103.4	16-346
	Cirrhotic	32	64.2 ±32.9		52.3	76.1	26-169
	Control	12	20.8 ±7.5		16.1	25.6	10-33
ALT (U/ml)	HCC	44	66.9 ±59.1	< 0.001	48.9	84.9	12-264
	Cirrhotic	32	34 ±14.1		28.9	39.1	11-64
	Control	12	20.8 ±7.1		16.3	25.3	10-31

SD – standard deviation, WBCs – white blood cells, HCC – hepatocellular carcinoma, HB – hemoglobin, PLT – platelets, INR – international normalized ratio, BIL – bilirubin, AST – aspartate aminotransferase, ALT – alanine transaminase

groups for both markers. The levels of both markers in different studied groups are summarized in Table 2.

We compared between different tumor size (less than 2 cm, 2-5 cm and more than 5 cm) groups regarding serum levels of sCD25 and AFP. There was no statistically significant difference between mean sCD25 or AFP and different tumor size categories (p-value > 0.05) (Table 3).

This analysis showed that at a cut-off value of 1.1 × 10^3 pg/ml, sCD25 had a sensitivity of 86.4% and a specificity of 29.5% for detecting HCC and the area under the curve (AUC) value was 0.619 (p = 0.054). The positive predictive value (PPV) was 33.2% while the negative predictive value (NPV) was 68.44%. By comparison, AFP had a sensitivity of 65.9% and a specificity of 99.1% at a cut-off value of 30.8 ng/ml (AUC = 0.860, p < 0.001, PPV = 98.7%, NPV = 74.3%) (Fig. 1). We investigated the role of sCD25 in detecting early HCC (stage A). We compared the level of sCD25 in patients with BCLC stage A HCC with the sCD25 responses of cirrhotic patients. In ROC analysis, an optimal cut-off value of 1.575 × 10^3 pg/ml for sCD25 had a sensitivity of 70.5% and a specificity of 30.9% (AUC = 0.577, p = 0.251, PPV = 58.5%, NPV = 43.1%). By comparison, at a cut-off value of 9.5 ng/ml, AFP had a sensitivity of 75% and a specificity of 62.5% (AUC = 0.828, p = 0.000, PPV = 73.4%, NPV = 64.4%) (Fig. 2).

Table 2. Comparison between hepatocellular carcinoma, cirrhotic and control groups regarding sCD25 and AFP tumor markers

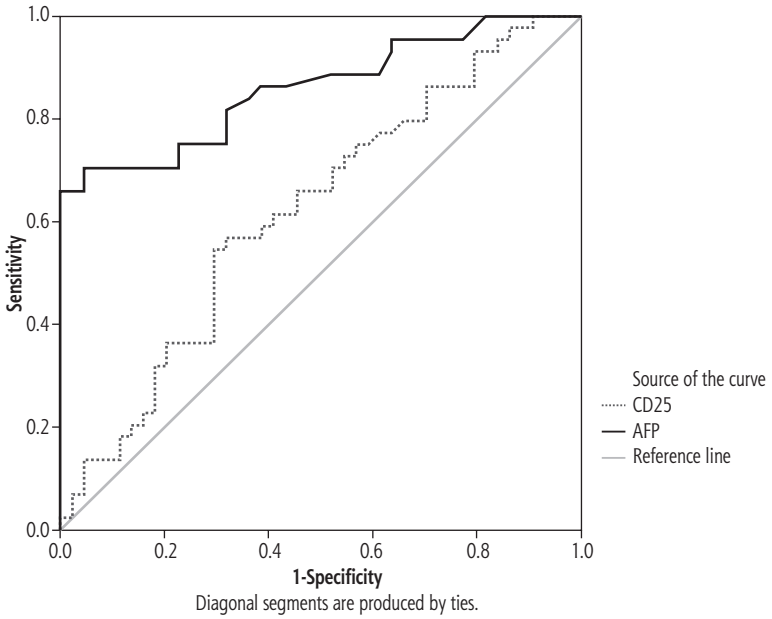
Tumor markers	Group	*N*	Mean ±SD	*p*-value	Range
sCD25 (pg/ml)	HCC	44	2752 ±1684	0.098	525.2-7142
	Cirrhotic	32	2325 ±1542		438.4-7010
	Control	12	1631 ±1595		107.2-6071
AFP (ng/ml)	HCC	44	10814 ±6403	0.574	2.5-447575
	Cirrhotic	32	8.9 ±7.3		1.5-30
	Control	12	3.1 ±1.9		1-7

SD – standard deviation, sCD25 – soluble CD25, HCC – hepatocellular carcinoma, AFP – α-fetoprotein

Table 3. Comparison between different tumor sizes (less than 2 cm, 2-5 cm and more than 5 cm) groups regarding sCD25 and AFP tumor markers

Marker	Tumor size (cm)	*N*	Mean	Standard deviation	*p*-value
sCD25 (pg/ml)	< 2	8	1952	997.2	0.195
	2-5	24	2722	1553	
	> 5	12	3344	2134	
	Total	44	2752	1684	
AFP (ng/ml)	< 2	8	163.3	163	0.284
	2-5	24	1095	2593	
	> 5	12	37354	129186	
	Total	44	10814	67403	

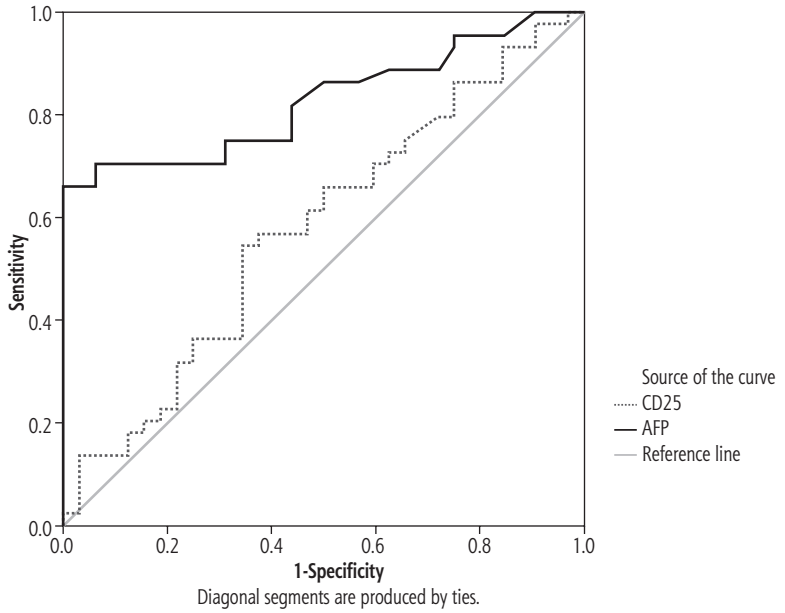
sCD25 – soluble CD25, AFP – α-fetoprotein, N – number



Marker	Cut-off	AUC	Standard error	*p*-value	Asymptotic 95% CI		Sens. %	Spec. %	PPV %	NPV %
					Lower bound	Upper bound				
sCD25 (pg/ml)	1.1×10^3	0.619	0.060	0.054	0.502	0.737	86.4	29.5	33.2	68.44
AFP (ng/ml)	30.8	0.860	0.040	< 0.001*	0.781	0.938	65.9	99.1	98.7	74.3

AUC – area under the curve, Sens. – sensitivity, Spec. – specificity, PPV – positive predictive value, NPV – negative predictive value, sCD25 – soluble CD25, AFP – α-fetoprotein

Fig. 1. Receiver operator characteristic (ROC) curve illustrates the potential of soluble CD25 (sCD25) and α-fetoprotein (AFP) as predictors of hepatocellular carcinoma (HCC)



Marker	Cut-off	AUC	Standard error	*p*-value	Asymptotic 95% CI		Sens. %	Spec. %	PPV %	NPV %
					Lower bound	Upper bound				
sCD25 (pg/ml)	1.575 × 10^3	0.577	0.067	0.251	0.446	0.709	70.5	30.9	58.5	43.1
AFP (ng/ml)	9.5	0.828	0.047	0.000	0.736	0.920	75	62.5	73.4	64.4

AUC – area under the curve, Sens. – sensitivity, Spec. – specificity, PPV – positive predictive value, NPV – negative predictive value, sCD25 – soluble CD25, AFP – α-fetoprotein

Fig. 2. Receiver operator characteristic (ROC) curve illustrates the potential of soluble CD25 (sCD25) and alpha-fetoprotein (AFP) as predictors of the stage (A) of hepatocellular carcinoma (early stage HCC)

Table 4. Correlation between tumor markers (sCD25 and AFP) and tumor stage

Tumor markers		Tumor stage
sCD25	Correlation coefficient	0.260
	Sig. (2-tailed)	0.088
	Number	44
AFP	Correlation coefficient	0.084
	Sig. (2-tailed)	0.588
	Number	44

sCD25 – soluble CD2, AFP – α-fetoprotein

Table 5. Correlation between tumor markers (sCD25 and AFP) and tumor size

Tumor markers		Tumor size
sCD25	Correlation coefficient	0.223
	Sig. (2-tailed)	0.145
	Number	44
AFP	Correlation coefficient	–0.060
	Sig. (2-tailed)	0.700
	Number	44

sCD25 – soluble CD2, AFP – α-fetoprotein

We tried to study the correlation between both markers and tumor stage or size. There was no statistically significant correlation between both markers and tumor stage (Table 4). We also did not find any statistically significant correlation between them and tumor size (Table 5).

Discussion

Hepatocellular carcinoma is a tumor whose early detection has a very good impact on its prognosis and patient survival. So it is important to search for new markers other than AFP with a better sensitivity and specificity for early detection. In our study, the mean age of the studied individuals was 54.9 ±5.8 years in the HCC group. This is in agreement with the study by Mohamed *et al.* [20], who reported that the most frequent age category affected by HCC was between 51 and 60 years (45.7%). Chronic HCV infection was the underlying cause of liver cirrhosis in all patients included in the study. This is due to high prevalence of HCV in Egypt, and this is in agreement with Mohamed *et al.* [20]. The serum levels of sCD25 were detected at a higher level in HCC patients than cirrhotic and con-

trol groups. The mean sCD25 level was 2752 ±1684, 2325 ±1542, 1631 ±1595 pg/ml in HCC, cirrhotic and control respectively (p = 0.098). AFP level also was higher in HCC patients than the other two groups, also without a statistically significant difference (p = 0.574). In comparison with a study conducted by Cabrena *et al.* [16], they found that levels of sCD25 in HCC patients were significantly higher than those in normal and disease control groups (p < 0.0001). Rizk *et al.* [21] also found the same as Cabrena *et al.* [16] as sCD25 levels were significantly higher in HCC versus cirrhotic and control groups. Sameea *et al.* [22] also found in a similar study that serum sCD25 level was significantly higher in HCC patients than cirrhotic patients (p < 0.0001) and healthy controls (p = 0.013).

We found that at a cut-off value of 1.1×10^3 pg/ml, sCD25 had a sensitivity of 86.4% and a specificity of 29.5% for detecting HCC (AUC = 0.619, p = 0.054, PPV = 33.2%, NPV = 68.44%). By comparison, AFP had a lower sensitivity (65.9%) and a higher specificity (99.1%) at a cut-off value of 30.8 ng/ml (AUC = 0.860, p < 0.001, PPV = 98.7%, NPV = 74.3%). Cabrena *et al.* [16] found that sCD25 had a sensitivity of 92.3% and specificity of 37.7% at a cut-off value of 2,180 pg/ml for the presence of HCC (AUC = 0.685), and when they compared sCD25 with AFP, they found that sCD25 had a higher sensitivity (92.3%) than AFP (53.8%) in detecting the presence of HCC. Rizk *et al.* [21] found that by using a cut-off value of 1425 pg/ml, sCD25 had a lower sensitivity (64%) and a higher specificity (96.15%) for the presence of HCC than AFP (AUC = 0.7959), while Sameea *et al.* [22] found a sensitivity of (90%) and a specificity of (84.2%) at a cut-off value of 7 ng/ml for sCD25 (AUC = 0.969, p < 0.0001).

We evaluated the performance of sCD25 in detecting early HCC (stage A). sCD25 had both lower sensitivity and lower specificity than AFP regarding early detection of HCC. By comparing the levels of sCD25 in both cirrhotic patients and BCLC (stage A) HCC patients, an optimal cut-off value of 1.575×10^3 pg/ml for sCD25 had a sensitivity of 70.5% and a specificity of 30.9% (AUC = 0.577, p = 0.251, PPV = 58.5%, NPV = 43.1%). By comparison, at a cut-off value of 9.5 ng/ml, AFP had a sensitivity of 75% and a specificity of 62.5% (AUC = 0.828, p = 0.000, PPV = 73.4%, NPV = 64.4%). Cabrena *et al.* [16] found that sCD25 had a higher sensitivity while AFP had a higher specificity for early HCC detection. A cut-off value of 2,859 pg/ml sCD25 had a sensitivity of 89.6% and a specificity of 39.3% (AUC = 0.630, p < 0.0001), while Sameea *et al.* [22] found that the optimal sCD25 cut-off level was 7.15 ng/ml with sensitivity and specificity of 90% and 60% respectively (AUC = 0.717, p = 0.019).

When we evaluated the correlation between both markers (sCD25 and AFP) and tumor stage, we did not find any statistically significant correlation (r) between both markers and tumor stage (r for sCD25 = 0.260, AFP = 0.084). This result conflicts with that of Cabrena *et al.* [16], who found a significant positive correlation between tumor stage and sCD25 levels (R = 0.213, p < 0.0160). They also found a significant positive correlation between serum AFP levels and tumor stage (R = 0.513, p < 0.0001). We also studied the correlation between both markers and tumor size. Again we found no significant correlation between tumor size and either sCD25 or AFP (r for sCD25 = 0.223, AFP = –0.060).

We could not find an explanation for these conflicting results or for the great variations in cut-off levels. There was a difference between their study and ours in the sample size and the underlying risk factors. There was also dissimilarity in ethnic and racial factors. Other important factors are genetic and environmental background. It is important to note that the underlying etiology of liver disease in our study was only HCV infection. In the study of Cabrena *et al.* [16], the HCC group had 60% HCV, 13% cryptogenic, 9% non-alcoholic fatty liver disease (NAFLD) and 9% alcoholic cirrhosis as the underlying etiology while the cirrhosis group had 72% HCV, 5% alcoholic cirrhosis, and 5% NAFLD, while 3% were cryptogenic. It is also important to highlight that GT-4 (and subtype 4a in particular) dominates the HCV epidemic in Egypt [23]. We admit that our study had some limitations such as being monocentric with a small number of subjects included in the study. We also had heterogeneous groups of patients regarding Child-Pugh classification, tumor size and BCLC stages.

Conclusions

sCD25 seems to offer no better detection rate of HCC compared to AFP, with lower sensitivity and specificity, especially at early stage HCC.

Disclosure

Authors report no conflict of interest.

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