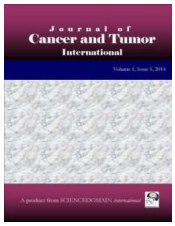

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Serum Soluble CD25 in Hepatocellular Carcinoma, Shall We Able to Change the Natural History?

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Authors' contributions

This work was carried out in collaboration between all authors. Author EAS designed the study, performed the statistical analysis and wrote the protocol. Author TZ was assigned to data analysis and interpretation of results, managed the literature searches, and wrote the first draft as well as the final revised manuscript form. Author KM managed the literature searches, shared in the analyses of the study and was assigned to publication process. Authors AAR, HMK and WMA shared in study design, statistical analysis, writing the protocol, collection and assembly of data and managing the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Although hepatocellular carcinoma (HCC) is one of the most common malignancy related mortality worldwide, it can be curable if detected in early stages. Axiomatically, emergence of a new marker for early prediction of HCC could enable to apply the proper treatment strategy early in the course of the disease and therefore ameliorates the outcome.
Aim: To evaluate the performance of serum soluble CD25 (sCD25) in the prediction of early HCC and compare it to α-fetoprotein (AFP); the classical biomarker of HCC.
Methods: Serum levels of sCD25 and AFP were measured in three groups of population; HCC group (40 patients), cirrhosis without HCC control group (20 patients) and healthy control group (20

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patients). HCC group contained 20 early and 20 late stage patients according to Tumor Lymph Node Metastasis (TNM) staging system (stage I/II and III/IV respectively). Levels of both biomarkers were compared in all groups. Predictive yield of both biomarkers for early HCC was evaluated using ROC curve analysis.

Results: Level of sCD25 was significantly higher in patients with HCC than in both cirrhotic controls and healthy controls (P<0.0001and 0.013 respectively). For the presence of HCC, sensitivity and specificity of sCD25 were 90% and 84.2% respectively at a cut-off value of 7 ng/ml (AUC=0.969; P<0.0001). For prediction of early HCC in patients with cirrhosis, the optimal sCD25 cutoff level was 7.15 ng/ml with sensitivity and specificity of 90% and 60% respectively (AUC=0.717; P=0.019) while sensitivity and specificity of AFP were 70% and 85% respectively at a cut-off value of 9.85 ng/ml (AUC=0.781; P=0.002) in the same settings.

Conclusion: sCD25 seems to be a reliable biomarker for early detection of HCC and therefore could enhance the outcome.

Keywords: Hepatocellular carcinoma; soluble CD25; Alfa fetoprotein; HCC markers.

1. INTRODUCTION

Hepatocellular carcinoma is one of the most serious and life threatening complications of chronic liver disease. It represents the 5th most common malignancy in men, the 7th in women and the 3rd malignancy related mortality worldwide. Curative treatment strategy can be achieved if detected in early stages [1-4]. The role of serum α-fetoprotein (AFP), the classical widely used biomarker for HCC, has been stepped down in the recent European and American surveillance guidelines because of low sensitivity and specificity. This is based on the knowledge that almost 80% of small HCCs do not show increased levels of AFP, and the sensitivity decreases to 25% in tumors smaller than 3 cm [5-8]. Looking for a new marker with a better diagnostic accuracy became an inevitable requirement. This eventually would optimize the HCC surveillance program and improve the outcome through prompt application of the proper treatment strategy early in the course of the disease. Serum soluble CD25 (sCD25) has been recently investigated as a new marker for hepatocellular carcinoma. It quantitatively reflects the immunological activity against the tumor [9-11]. It represents the α-chain of interleukin 2 receptor (IL-2Rα) which is composed of three polypeptide chains: α, β and γ. It is not found on the surface of resting T cells, but rapidly expressed on their surface after being activated. Chronic T-cell stimulation, as in some malignancies, leads to shedding of IL-2Rα (CD25) into plasma with subsequent elevation of its level [11-16]. Cabrena and colleagues reported that serum level of sCD25 was correlating with tumor burden and poor survival in HCC patients and believed that measuring serum level of sCD25 might provide a clue for early diagnosis of HCC [12]. When we designed the current study, we hypothesized that sCD25 could have an impressive diagnostic value and a potential ability for detection of early HCC. We assessed the performance of sCD25 in the prediction of early HCC and its correlation with the tumor stage and compare it with AFP.

2. SUBJECTS AND METHODS

The study was conducted in National liver institute, Menoufiya, Egypt. After obtaining an informed consent, eighty persons in 3 groups were included; HCC on a background of cirrhosis (40 patients), liver cirrhosis with no evidence of HCC (20 patients) and healthy control group (20 patients). HCC group comprised 20 early and 20 late stage HCC patients, according to Tumor Lymph Node Metastasis (TNM) staging system (stage I/II and III/IV respectively) [17]. Cirrhotic and healthy controls had matched age and sex with HCC patients. All included cases of HCC was diagnosed on the basis of the presence of typical vascular enhancement pattern of liver lesion (s) in contrast enhanced dynamic CT scan or MRI [18]. Diagnosis of cirrhosis was based on combined historical, clinical, laboratory and radiological findings. Severity of cirrhosis was assessed by Child Pugh classification [19]. All patients had complete laboratory profile including CBC, liver panel, creatinin as well as serum level of sCD25 and AFP. ELISA kit (R&D systems Inc., USA) was used to quantify blood level of AFP while ELISA kit (Cell Science, Inc, Bldg Canton, MA) was used to measure serum level of sCD25.

2.1 Statistical Methods

SPSS, version 21 for windows (Inc, Chicago, IL, USA) was used for all statistical analyses. Qualitative data were presented as frequency

and percentage. Chi square and Fisher's exact tests were used to compare groups. Quantitative data were presented as mean and standard deviation. For non- parametric data, student t-test and Mann-Whitney U test were used to compare level difference of sCD25 between two groups while ANOVA and Kruskal Wallis were used to compare level difference of sCD25 between more than two groups. Receiver-operator characteristic (ROC) curve analysis was used to generate sensitivity and specificity at different cutoffs. The best cutoff was set at the value where sensitivity and specificity were maximal. Correlation between serum level of sCD25 and laboratory parameters was assessed by Spearman's correlation coefficient. The statistical significance was set at P-value of less than 0.05 for all tests.

3. RESULTS

The studied populations were mostly males representing 77.5, 75 and 60% in HCC, cirrhotic and healthy control groups respectively. The mean age was 56.38±5.934 years in HCC group while was 53.75±7.383 and 54.20±5.863 years in cirrhotic and healthy controls respectively. Hepatitis C virus (HCV) represented the underlying etiology of cirrhosis in 92.5% of HCC group and 90% in cirrhotic control group while 7.5 and 10% were referred to combined hepatitis C and B etiology in HCC and cirrhotic control group respectively. The mean sCD25 level was 13.07±6.645, 13.15±6.967, 8.938±6.487 and 4.97±3.031 ng/ml in early HCC, late HCC, cirrhotic and healthy control groups respectively. Level of sCD25 was significantly higher in patients with HCC than in both cirrhotic and healthy controls (P<0.0001 and 0.013 respectively) and significantly higher in cirrhotic patients than healthy controls (P=0.042). sCD25 level was significantly and positively correlated with the severity of liver disease as assessed by Child-Pugh classification (r=0.56, P<0.001). There was no statistical difference between sCD25 in early and late HCC (P=0.968). The mean AFP level was 17.66±12.092, 244±302.041, 8.01±6.965 and 2.95±2.175 ng/ml in early HCC, late HCC, cirrhotic and healthy control groups respectively with significant statistical difference between HCC versus cirrhotics and early versus late HCC as well (P= 0.010 and 0.003 respectively). The rest of demographic and laboratory data as well as their statistical differences between the studied groups are shown in Table 1. Correlation analyses between sCD25 and laboratory parameters among the studied groups are shown in Table 2. There was no significant correlation with all laboratory parameters a part from a negative correlation with WBCs in early HCC group (r=-0.478, P=0.033) and a positive correlation with AFP in healthy control group (r=0.503, P=0.028). sCD25 performed well in predicting HCC presence among patients with cirrhosis; sensitivity and specificity were 90% and 84.2% respectively at a cut-off value of 7 ng/ml (AUC=0.969; P<0.0001). For prediction of early HCC in patients with cirrhosis, the optimal sCD25 cutoff level was 7.15 ng/ml with sensitivity and specificity of 90% and 60% respectively (AUC=0.717; P=0.019) while, sensitivity and specificity of AFP were 70% and 85% respectively at a cut-off value of 9.85 ng/ml (AUC=0.781; P=0.002) in the same settings (Fig. 1).

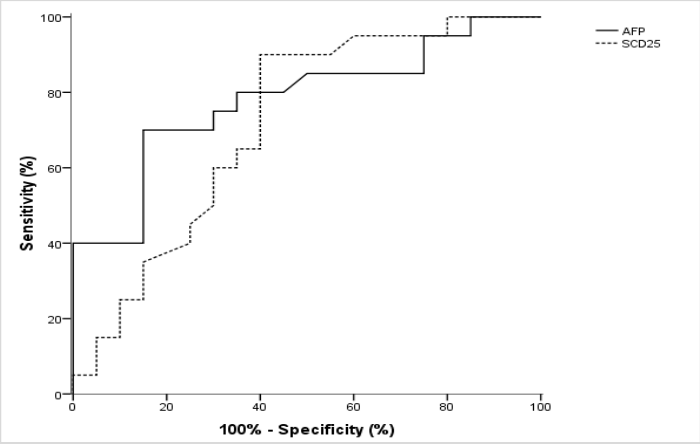

Figure 1. Receiver operator curve (ROC) of sCD25 and AFP levels for the prediction of early HCC among patients with cirrhosis

Table 1. Statistical difference of demographic and laboratory data among the studied groups

		Total HCC (n=40)	**Early HCC (n=20)**	**Late HCC (n=20)**	**LC (n=20)**	**Healthy control (n=20)**	***P***	***P****	***P^***	***P#***
Sex	♂s	31 (77.5)	15 (75)	16 (80)	15 (75)	12 (60)	0.156	0.311	0.829	0.705
n (%)	♀s	9 (22.5)	5 (25)	4 (20)	5 (25)	8 (40)				
		Mean±SD								
Age (years)		56.38±5.934	58.40±5.576	55.35±5.706	53.75±7.383	54.20±5.863	0.212	0.822	0.133	0.539
Hb (g/dl)		11.07±1.097	11.14±1.268	11.01±0.925	10.52±0.928	12.71±1.091	<0.001	<0.001	0.058	0.724
WBCs (x10^3/dl)		4.88±1.717	5.18±2.247	4.59±0.903	4.87±1.242	7.00±1.693	<0.001	<0.001	0.977	0.282
Platelets (x10^3/dl)		119.65±35.246	122.55±34.264	116.75±36.854	169.05±31.749	217.80±47.522	<0.001	<0.001	<0.001	0.609
INR		1.37±0.196	1.43±0.197	1.32±0.185	1.31±0.236	1.07±0.081	<0.001	<0.001	0.225	0.091
Albumin (g/dl)		3.19±0.371	3.334±0.382	3.04±0.299	3.55±0.445	4.34±0.463	<0.001	<0.001	0.002	0.009
Bilirubin (mg/dl)		1.64±0.833	1.19±0.415	2.09±0.907	1.73±0.692	0.84±0.154	<0.001	<0.001	0.626	<0.001
ALT (U/ml)		65.15±15.184	61.75±17.278	68.55±12.262	57.05±10.655	24.45±5.276	<0.001	<0.001	<0.001	0.159
AST (U/ml)		89.48±24.724	76.50±17.021	102.45±24.708	67.85±10.069	27.25±4.962	<0.001	<0.001	0.019	<0.001
Creatinin (mg/dl)		0.93±0.159	0.93±0.180	0.94±0.139	0.95±0.161	1.04±0.193	0.025	0.114	0.665	0.845
sCD25 (ng/ml)		13.11±6.719	13.07±6.645	13.15±6.967	8.938±6.487	4.97±3.031	<0.001	0.042	0.013	0.968
AFP (ng/ml)		130.83±240.106	17.66±12.092	244±302.041	8.01±6.965	2.95±2.175	0.008	0.926	0.010	0.003
Child-Pugh score	A	6 (15)	6 (30)	0 (0)	12 (60)	NA	NA	NA	0.001	0.004
	B	29 (72.5)	14 (70)	15 (75)	8 (40)					
	C	5 (12.5)	0 (0)	5 (25)	0 (0)					

AFP, α-fetoprotein; Hb, hemoglobin; HCC, hepatocellular carcinoma; INR, international normalized ratio; LC, liver cirrhosis; NA, not applicable; P, significance between HCC and healthy controls; P, significance between liver cirrhosis and healthy controls; P^, significance between HCC and liver cirrhosis; P#, significance between early and late HCC; sCD25, soluble CD25; ♂s, males; ♀s, females*

Table 2. Correlation between sCD25 and laboratory parameters among the studied groups

	Total HCC (n=40)		Early HCC (n=20)		Late HCC (n=20)		LC (n=20)		Control (n=20)	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Hb (g/dl)	-0.060	0.714	-0.038	0.875	0.040	0.866	0.304	0.193	-0.371-	0.118
WBCs (x10^3/dl)	-0.228	0.157	-0.478	0.033	-0.063	0.792	-0.081	0.736	0.179	0.462
Platelets (x10^3/dl)	0.128	0.431	0.068	0.777	0.290	0.215	-0.136	0.567	-0.269	0.265
INR	0.151	0.352	0.250	0.287	0.039	0.869	-0.224	0.343	0.035	0.887
Albumin (g/dl)	0.002	0.991	0.205	0.387	-0.220	0.352	0.142	0.550	0.064	0.794
Bilirubin (mg/dl)	-0.038	0.816	-0.102	0.668	-0.021	0.928	-0.442	0.051	0.266	0.270
ALT (U/ml)	0.093	0.570	0.078	0.745	0.049	0.838	-0.014	0.955	0.348	0.144
AST (U/ml)	0.124	0.445	0.179	0.450	0.078	0.744	-0.078	0.744	0.390	0.099
Creatinin (mg / dl)	0.062	0.706	0.136	0.569	-0.043	0.856	-0.217	0.359	-0.249	0.303
AFP (ng/ml)	0.023	0.890	0.196	0.407	-0.093	0.697	-0.254	0.279	0.503	0.028

AFP, α-fetoprotein; Hb, hemoglobin; HCC, hepatocellular carcinoma; INR, international normalized ratio; LC, liver cirrhosis; r, Spearman's correlation coefficient

4. DISCUSSION

HCC represents the most serious and lethal complication of cirrhosis. Fortunately, early stages of HCC could be curative. Axiomatically, detection of HCC in early stages would be helpful in changing the poor outcome of late stages by offering the proper treatment early in the course of the disease with subsequent amelioration of the outcome [20-22]. In the current study, we evaluated the performance of sCD25 in predicting early HCC stages among patients with cirrhosis and compare it to AFP. Serum sCD25 level was significantly higher in HCC patients than cirrhotics (P<0.0001) and healthy controls (P=0.013). In the same stream, it was significantly higher in cirrhosis than healthy controls (P=0.042). Additionally, there was a significant positive correlation between serum sCD25 and severity of cirrhosis (Child-Pugh class) (r= 0.56, P<0.001). The optimal sCD25 cut off level in detecting early HCC among cirrhotic patients was 7.15 ng/ml with sensitivity and specificity of 90% and 60% respectively (AUC=0.717; P=0.019). On the other hand, sensitivity and specificity of AFP were 70% and 85% respectively at a cut-off value of 9.85 ng/ml (AUC=0.781; P=0.002) in the same settings. At this point, we intentionally compare the sensitivity of the standard optimal predictive cut-offs of both biomarkers which offers the maximal sensitivity and specificity (closest point on the ROC curve to left upper corner). For fair comparison between both biomarkers, theoretical choice of a lower AFP cutoff at which specificity of both biomarkers are equal (60%), sensitivity would remain lower than that of sCD25 (80 versus 90%). At the same time, this would in turn increase the false positive rates and subsequently cost. Reciprocally, unification of sensitivity of both biomarkers at 90% would come down with specificity of AFP to 20% versus 60% for sCD25. This can be noted in Fig. 1. This potentially higher sensitivity and acceptable specificity of sCD25 highlights its substantial role as a screening marker for HCC. Similar findings were reported by Cabrena and his group. They reported sCD25 cutoff level of 2899 pg/ml as the best cutoff with a sensitivity of 89.6% and a specificity of 39.3% (AUC=0.630, P<0.0001). By comparison, at a cut-off value of 20 ng/ml, AFP had a sensitivity of 41.7% and a specificity of 82.6% (AUC=0.630, P=0.0257) [12] The difference between the optimal cutoff between the current study (7150 pg/ml) and that of Cabrena et al. (2899 pg/ml) might be referred to the variability in the sample size, underlying etiology as well as dissimilarity in racial, ethnic, genetic and environmental factors. It is noteworthy that, the main underlying etiology of liver disease was HCV representing 92.5 and 90% in HCC and cirrhosis groups respectively while 7.5 and 10% were referred to combined HCV and HBV etiology in the same groups respectively. In the study of Cabrena et al., 60% were HCV, 13% were cryptogenic, 9% were alcoholic cirrhosis and 9% were non-alcoholic fatty liver disease (NAFLD) in HCC group while 72% were HCV, 5% alcoholic cirrhosis and 5% NAFLD and 3% were cryptogenic in cirrhosis group. In spite of the presence of a significant positive correlation between serum levels of sCD25 and severity of liver cirrhosis, there was no significant difference in its level in early and late HCC stages which disclaims findings of Cabrena et al. who reported a significant positive correlation between serum levels of sCD25 and tumor stage [12]. We could not eventually find a reasonable explanation for these conflicting results however difference in underlying etiology, tumor differentiation/biology, inter-racial and

inter-ethnic variations between both studies might be accused. A notable finding that should be considered was absent correlation between sCD25 and AFP in HCC and cirrhosis groups (r= 0.023, P=0.89 and r= -0.254, P=0.279 respectively) denoting that measuring both markers in serum can improve the reciprocally holistic diagnostic value of HCC.

5. CONCLUSION

In conclusion, sCD25 sounds to be a good marker for predicting early HCC. There was some discrepancy between the optimal cutoff in the current and previous studies. This calls for a large scale study for further integration and unification of the current results and previous ones and to standardize the optimal cutoff taking into consideration addressing the relationship between sCD25 level and tumor biology rather than tumor size and number.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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