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S100A14 protein as diagnostic and prognostic marker in hepatocellular carcinoma

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Abstract

Background: Protein S100A14 has recently been implicated in the progress of several types of cancers. This study aimed to investigate the clinical significance of S100A14 in the diagnosis of hepatocellular carcinoma (HCC).

Results: S100A14 was significantly elevated in the HCC group. A cut-off value for serum S100A14 between the HCC group and cirrhosis group is > 0.47 with a sensitivity of 100% and specificity of 88.57%. S100A14 level was a significant diagnostic factor for HCC and a good reference for HCC progression.

Conclusion: These results suggest that S100A14 is a good diagnostic marker for HCC.

Keywords: Hepatocellular carcinoma, Cirrhosis, S100A14

Background

Hepatocellular carcinoma is the fifth most frequently diagnosed cancer in adult men worldwide and is the second leading cause of cancer-related death in the world [1]. The primary etiology of HCC is cirrhosis resulting from chronic infection by the hepatitis B virus and hepatitis C virus as well as alcoholic or non-alcoholic liver injury [2]. More than 80% of HCC cases are from the Asian and African continents, and more than 50% of cases are from mainland China with a majority of viral hepatitis patients [3].

Hepatocellular carcinoma diagnosis has relied on several tools combining imaging techniques and the measurement of serum alfa-fetoprotein (AFP) [4]. Although both ways are relatively efficient for large tumors, the specificity of serum AFP is low, especially against a background of chronic hepatitis [5]. The elevation of AFP occurs in hepatocytes regeneration, hepatocarcinogenesis, and embryonic carcinomas [6, 7]. Alpha-fetoprotein determination lacks adequate sensitivity and specificity for effective surveillance and for diagnosis [8, 9]. Thus, the identification of new markers for HCC with high sensitivity and specificity is essential [10].

The S100 protein family has been reported to contribute to multiple biological processes, such as growth, cell motility, signal transduction, transcription, cell survival, and apoptosis, which are related to normal development and tumorigenesis [11]. S100 proteins, a large subgroup of the EF-hand (helix-loop-helix structural domain) protein family, are small calcium-binding proteins that have a broad range of intracellular and extracellular functions [12]. S100 proteins belong to a large subgroup of 25 small, acidic proteins that are characterized by distinctive homo-or hetero-dimeric architecture and EF-hand Ca2+-binding motifs, and are expressed in a variety of cell types [13].

S100A14 is a member of the S100 family. Loss of expression or overexpression of S100A14 has been reported in tumors, its functional role has been proposed to be organ-specific and involved in tumorigenesis [14]. S100A14 is also a target for p53 and could alter p53 transactivity and stability, and by regulating matrix metalloproteinase (MMP)2 transcription, S100A14 affects cell invasiveness in a p53-dependent manner [15]. It is reported to be upregulated in some cancer types, including ovarian, lung, breast, uterine, and cervical cancer [12].

The aim of the current study was to investigate the clinical usefulness of the S100A14 level as a biomarker

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Table 1 Demographic data of all studied groups

		Control group (no. = 20)		Cirrhosis group (no. = 35)		HCC group (no. = 35)		Chi-squared test	
		No.	%	No.	%	No.	%		*p* value
Sex	Female	10	50.0%	17	48.6%	15	42.9%	0.344	0.842
	Male	10	50.0%	18	51.4%	20	57.1%		
Age	Mean ± SD	29.85 ± 8.57		49.97 ± 8.13		54.91 ± 5.48		77.972	< 0.001
	Range	20–60		25–60		40–60			

for hepatocellular carcinoma (HCC) among high-risk patients compared to alpha-fetoprotein (AFP).

Methods

The study was reviewed and approved by Independent Ethics Committees of National Hepatology and Tropical Medicine Research Institute (NHTMRI) number 15-2015 and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All enrolled patients provided written, informed consent prior to the start of the study.

Our study has been carried out in the National Hepatology and Tropical Medicine Research Institute as a single-center prospective observational study on 90 people divided into three groups of individuals: (I) control group: 20 healthy persons aged 20 to 60 years with mean ± SD of 29.85 ± 8.57 years with no evidence of liver diseases. (II) Hepatocellular carcinoma group: 35 persons of inpatients aged 40 to 60 years with mean ± SD of 54.91 ± 5.48 with HCC with chronic hepatitis C (CHC) diagnosed by ultrasound, CT or MRI examinations and CHC diagnosis were based on anti-HCV positive by ELISA and PCR. (III) Liver cirrhosis (LC) group: 35 persons of inpatients aged 25 to 60 years with a mean ± SD of 49.97 ± 8.13 with HCV-related LCdiagnosed histologically by liver biopsy and non-histologically by fibroscane by specialists.

All the patients are naive and did not receive any treatment. All patients included in the study did not complain of portal vein thrombosis.

Aware acceptance from patients was gained and confirmed by the Ethical Committee of the Research of the NationalHepatology and Tropical Medicine Research Institute.

Venous blood samples were taken and centrifuged and the levels of S100A14 have been detected in serum of samples by ELISA (Glory Science Co., Ltd., USA) [16] and Alpha-fetoprotein have been detected in serum of samples by ELISA (Immunospec Corporation, USA) [17] by electrochemiluminescence immunoassay "ECLIA" Cobas e 602 immunoassay analyzers. Reference standards were used to obtain a standard curve to detect S100A14 and AFP levels in serum samples.

A combination of tests for AFP and S100A14 protein was tried to increase the accuracy and performance of the test.

Data management and statistical analysis

Data were collected, coded, revised, and entered into the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution and median with interquartile range (IQR) for the

Table 2 VaL) in all studied group/L) in all studied groups

S100A14(mg/L)	Groups		
	Control group (no. = 20)	Cirrhosis group (no. = 35)	HCC group (no. = 35)
Mean ± SD	0.27 ± 0.06	0.29 ± 0.08	0.65 ± 0.19
Min—max	0.15—0.38	0.2—0.47	0.26—1.1
One-way ANOVA	*F* 84.897		
	p value < 0.001		
Post hoc test			
Cirrhosis group vs control group	*p* value NS		
HCC group vs control group	*p* value < 0.001		
Cirrhosis group vs HCC group	*p* value < 0.001		

Table 3 Values of AFP in all studied groups

AFP(ng/ml)	Groups		
	Control group (no. = 20)	Cirrhosis group (no. = 35)	HCC group (no. = 35)
Mean ± SD	4.89 ± 2.89	109.91 ± 195.84	276.09 ± 346.93
Min—max	1.0—9.37	6.44—819	13.5—1292.5
One-way ANOVA	*F* 8.333		
	p value < 0.001		
Post hoc test			
Cirrhosis group vs control group	*p* value NS		
HCC group vs control group	*p* value < 0.001		
Cirrhosis group vs HCC group	*p* value 0.006		

Table 4 The sensitivity and specificity for S100A14

Cut-off point	AUC	Sensitivity %	Specificity %	–PV	+PV
>0.47	0.964	100.00%	88.57%	89.7	100.0

quantitative data with the non-parametric distribution. Chi-square test was used in the comparison between two groups with qualitative data. Independent *t* test was used in the comparison between two groups with quantitative data and parametric distribution. The comparison between more than two groups with quantitative data and parametric distribution was done by using one-way analysis of variance (ANOVA) test. Spearman correlation coefficients were used to assess the significant relation between two quantitative parameters in the same group. The receiver operating characteristic curve (ROC) was used to assess the best cut-off point between two groups with its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the level of significance was set according to the following *p* values: $p > 0.05$: non-significant (NS), $p < 0.05$: significant (S), and $p < 0.01$: highly significant (HS).

Results

The demographic data showed that there was a statistically significant increase in the age of HCC patients in comparison to cirrhosis and control groups (Table 1).

Regarding S100A14 and AFP, levels showed (Tables 2 and 3) that there was a statistically highly significant increase in HCC group in comparison to cirrhosis and control groups in both parameters.

From ROC curves of S100A14 and AFP in HCC group and cirrhosis group, the sensitivity and specificity for S100A14 were 100.0% and 88.57% at the cut-off point of > 0.47 ng/ml with an area under the curve (AUC) of 0.964, while AFP yielded a sensitivity of 80% and specificity of 54.29% at the cut-off point of 0.648 mg/dl with an area under the curve (AUC) ≤ 98.15 (Tables 4 and 5) (Figs. 1 and 2).

Table 6 shows that there was a statistically significant increase in HCC in comparison to control and cirrhosis group with SGPT, SGOT, Bilirubin total and direct but there was a statistically significant increase in control in comparison to HCC and cirrhosis group with albumin, HB, RBCs, and PLT.

Table 5 The sensitivity and specificity for AFP

Cut-off point	AUC	Sensitivity %	Specificity %	–PV	+PV
0.648	≤ 98.15	80.00%	54.29%	63.6	73.1

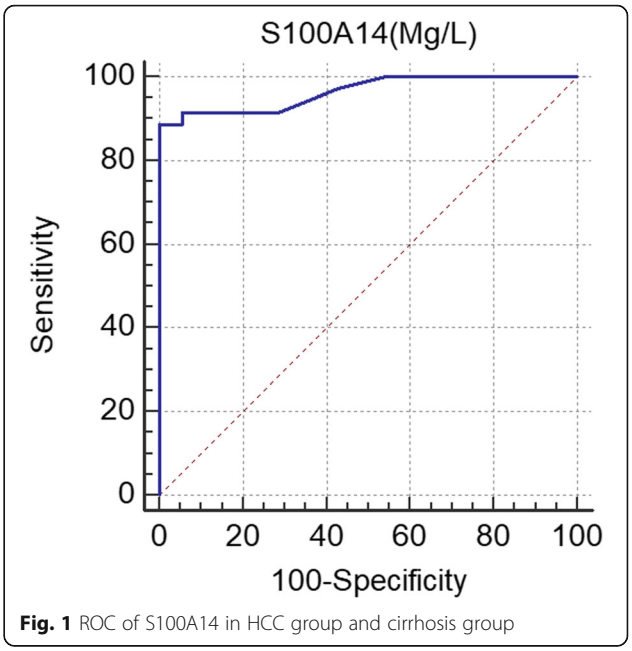

Fig. 1 ROC of S100A14 in HCC group and cirrhosis group

Distribution of stages of tumors in the HCC group (Table 7) according to the AJCC (American Joint Committee on Cancer) TNMn system, stage grouping of tumors which based on three key pieces of information:

- The size and number of tumors (T)
- The spread to nearby lymph nodes (N)
- The metastasis to distant sites (M)

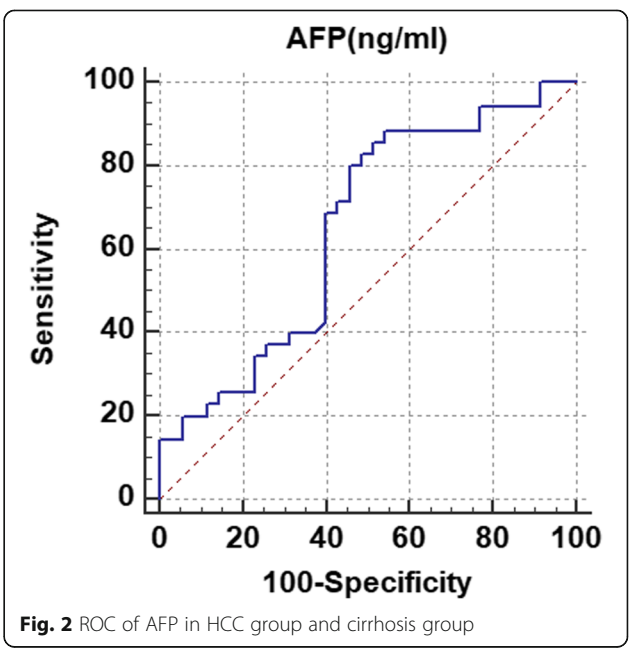

Fig. 2 ROC of AFP in HCC group and cirrhosis group

Table 6 Data of liver function test and CBC in cirrhosis, HCC, control group

	Cirrhosis group		HCC group		Control group		One-way ANOVA	
	Mean ± SD	Min—max	Mean ± SD	Min—max	Mean ± SD	Min—max	*F*	*p* value
S.GPT (U/L)	55.91 ± 33.84	15–138	66.71 ± 43.17	22–201	15.35 ± 5.37	10–26	14.763	0.001
S.GOT (U/L)	84.71 ± 49.10	20–244	145.77 ± 161.89	30–821	18.85 ± 6.54	12–34	9.371	0.001
Albumin (g/dl)	2.40 ± 0.61	1.4–3.8	2.24 ± 0.55	1.3–3.6	4.34 ± 0.31	3.8–4.8	112.256	0.001
Bilirubin Total (mg/dl)	4.25 ± 3.89	0.46–20.7	5.92 ± 6.51	0.6–21.5	0.44 ± 0.17	0.2–0.8	8.561	0.001
Bilirubin Direct (mg/dl)	2.14 ± 2.09	0.1–10.7	3.35 ± 4.04	0.2–12.8	0.15 ± 0.05	0.1–0.2	8.080	0.001
Hemoglobin (g/dl)	10.23 ± 1.99	6–14.8	10.97 ± 1.42	8.3–14.6	12.14 ± 1.58	9.6–14.8	8.046	0.001
RBCs ($\times 10^6$/μL)	3.59 ± 0.79	2.22–5.57	3.86 ± 0.58	3.2–5.79	4.45 ± 0.43	3.71–5.55	11.384	0.001
PLT ($\times 10^3$/μL)	111.71 ± 71.43	24–342	114.31 ± 67.52	18–288	267.75 ± 52.54	174–356	42.545	0.001
WBC ($\times 10^3$/μL)	7.99 ± 3.41	3–15	8.89 ± 5.14	2.5–18.3	6.62 ± 1.29	4.2–9	2.163	0.121

This table shows that there was statistically significant increase in HCC in comparison to control and cirrhosis group with SGPT, SGOT, bilirubin total, and direct but there was statistically significant increase in control in comparison to HCC and cirrhosis group with albumin, HB, RBCs, and PLT

Table 7 shows that 17.1% was IA tumor stage, 8.6% was IB tumor stage, 37.1% was II tumor stage, 20.0% was IIIA tumor stage, and 17.1% was IIIB tumor stage.

Table 8 shows that S100A14 has a positive correlation with stage of tumors in the HCC group.

Discussion

An S100 protein family is a multigenic group of non-ubiquitous cytoplasmic EF-hand Ca2+-binding proteins, sharing significant structural similarities at both genomic and protein levels. They are differentially expressed in a wide variety of cell types [18] and have been reported to be involved in the regulation of inflammatory responses, [19] as well as in the metastasis development of several cancers [20].

S100A14, a member of the S100 family, is involved in several vital functional and pathological processes [21]. S100A14 was reported to be upregulated in several tumor types, including ovarian, lung, breast, and uterine cancer, but downregulated in others, such as kidney, colon, rectal, and esophageal cancer [14]. S100A14 can regulate oral squamous cell carcinoma cell invasion by modulating the expression of matrix metalloproteinase (MMP)-1 and MMP-9 [16].

Regarding the demographic data in the present study, there was statistically significant difference between groups as regards mean of age ($p < 0.001$) with increase in HCC (54.91 ± 5.48) in comparison to cirrhosis (49.97 ± 8.13) and control group (29.85 ± 8.57) but no statistically significant in sex as regards studied groups while male was more than females among groups. This is similar to Choi et al .[22] study in which mean age of cirrhosis group was 54.3 ± 8.6 whereas in the HCC group was 61.2 ± 9.3 with a statistically significant difference while male to female ratio were 34/2 and 86/21.

The effect of S100A14 on tumor metastasis remains controversial. Elevated S100A14 promotes the metastasis of tumor cells and induces worse survival in hepatocellular carcinoma [23]. This is consistent with the results of

Table 7 Distribution of stages of tumors in HCC group according to the AJCC

AJCC stage	Stage grouping	Stage description	No	%
IA	T1a N0 M0	A single tumor 2 cm (4/5 in.) or smaller that has not grown into blood vessels (T1a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).	6	17.1%
IB	T1b N0 M0	A single tumor larger than 2 cm (4/5 in.) that has not grown into blood vessels (T1b). The cancer has not spread to nearby lymph nodes (N0) or to distant sites (M0).	3	8.6%
II	T2 N0 M0	Either a single tumor larger than 2 cm (4/5 in.) that has grown into blood vessels, OR more than one tumor but none larger than 5 cm (about 2 in.) across (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).	13	37.1%
IIIA	T3 N0 M0	More than one tumor, with at least one tumor larger than 5 cm across (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).	7	20.0%
IIIB	T4 N0 M0	At least one tumor (any size) that has grown into a major branch of a large vein of the liver (the portal or hepatic vein) (T4). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).	6	17.1%

This Table 7 shows that 17.1% was IA tumor stage, 8.6% was IB tumor stage, 37.1% was II tumor stage, 20.0% was IIIA tumor stage, and 17.1% was IIIB tumor stage

Table 8 Relation between S100A14 as regards stage of tumors in HCC group

AJCC stage	S100A14 (mg/L)	One-way ANOVA	
	Mean ± SD	*f*	*p* value
IA	0.38 ± 0.12	17.716	<0.001
IB	0.57 ± 0.06		
II	0.64 ± 0.09		
IIIA	0.78 ± 0.05		
IIIB	0.86 ± 0.18		

This table shows that S100A14 has positive correlation with stage of tumors in HCC group

the present study in which there was a statistically significant increase in HCC in comparison to cirrhosis and control group with S100A14 with the highest mean among HCC group (0.65 ± 0.19).

Previous studies found that elevated AFP levels are associated with higher pathological grade [24, 25]. AFP measurements among groups of the current study showed a statistically significant difference between groups regarding AFP which increased in HCC in comparison to cirrhosis and control group with the highest mean among HCC group (276.09 ± 346.93). This is in agreement with Luo et al. [26] study in which the mean among HCC group was 306.6 and in cirrhosis group 238.5. In this study, ROC area under the curve for AFP was ≤ 98.15 at 0.648 points AFP had 80% sensitivity, 54.29% specificity, 73.1% PPV, and 63.6% NPV.

The role of S100A14 in sustaining HCC proliferation, migration, and invasion were confirmed in HCC cell culture and in vivo (mice) analysis, thus supporting the role of S100A14 in sustaining HCC metastasis [23]. In the current study, S100A14 at 0.47 point or less S100A14 had 100% sensitivity, 88.57% specificity, 100% PPV, and 89.7% NPV.

Zhao et al. [23] used an extensive collection of HCC tumors to show that S100A14 was significantly elevated in HCC tissues. The increased S100A14 expression was correlated with multiple tumor nodes, high Edmondson-Steiner grade, and vascular invasion. These observations were reminiscent of previous reports in other malignancies such as esophageal squamous cell carcinoma [27] and colorectal cancer [28].

This study shows that protein S100A14 is a more sensitive and specific biomarker for the diagnosis of HCC disease in comparison to AFP.

Conclusion

Protein S100A14 have been reported to be involved in the regulation of inflammatory responses, as well as in the metastasis development of several cancers. Protein S100A14 is a more sensitive and specific biomarker for the diagnosis of HCC disease in comparison to AFP. It fair to say that S100A14 is a good diagnostic marker for HCC

Abbreviations

HCC: Hepatocellular carcinoma; AFP: Alpha-fetoprotein

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Authors' contributions

BF, the main author, ran the chemical tests over the serum samples to detect levels of AFP and Protein S100A14. She also wrote the manuscript. WS was responsible for analyzing samples with basma and statistical analysis of the results. RA was responsible for analyzing the samples with basma and statistical analysis of the results. HF was responsible for choosing patients with cirrhosis and HCC. She was also responsible for clinical assessment of the patients and extracting the venous samples. All authors have read and approved the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Ethics approval and consent to participate

The study was reviewed and approved by Independent Ethics Committees of national hepatology and tropical medicine research institute (NHTMRI) number 15-2015 and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All enrolled patients provided written, informed consent prior to the start of the study.

Consent for publication

Not applicable

Competing interests

Authors declare no competing interests.

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