RESEARCH ARTICLE

Talin-1 and Non-invasive Fibrosis Models in the Assessment of Patients with Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is a dreadful complication of end stage liver disease with high morbidity and mortality. Aim: The aim was to assess the role of serum talin-1 and non-invasive fibrosis in patients with HCC. Materials and Methods: A total of eighty seven subjects were enrolled, with 22 two healthy individuals as a control group (n=22), 22 patients in the cirrhosis group and finally 43 in the group with HCC diagnosed with positive triphasic CT abdomen criteria. Serum talin-1 and noninvasive fibrosis parameters were assessed in all subjects. Results: Compared to the cirrhosis group, patients with HCC had higher serum talin-1 (32.9±12.6 vs. 11.1±2.79 ng/ml), FIB4 (9.96±15.3 *vs.* 2.90±1.87) and fibro-α (10.9±18.1 vs. 1.55±0.28) but not fibrosis index scores (4.47±0.95 vs. 4.98±0.96; p=0.046). Patients with large focal lesions (≥5cm) had different ALBI scores (-1.02±0.63 vs. -1.72±0.59; p=0.001) serum talin-1 (9.72±13.81 vs. 28.6±38.89 ng/ml; p=0.007) and fibrosis index scores (0.85 ± 0.99 vs. 4.20±4.85; p=0.026). No statistical differences were noted between patients with and without portal vein thrombosis. For detection of HCC, serum talin-1 had 97.7% sensitivity and 100% specificity with a 17.2 ng/ml cutoff. AFP at a 13.7 ng/ml cutoff had 72.1% sensitivity and 6.3.6% specificity. The cutoff for the fibro-α score was 1.61 with 81.4% sensitivity and 77.3% specificity. Serum talin-1 (odds=1.08; C.I=1.016-1.150; p=0.014), fibrosis index score (odds=2.35; C.I=1.055-5.217; p=0.037) and the ALBI score (odds=6.9; C.I=1.924-24.708; p=0.003) were predictors of large focal lesions. Conclusions: Serum talin-1, AST/ ALT ratio, fibro-α score are useful for the assessment of HCC patients.

Keywords: Hepatocellular carcinoma - cirrhosis - serum talin-1 - fibro-α - fibrosis index - scores - lesion size

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Introduction

Hepatocellular carcinoma (HCC) is the most common liver malignancy (Byam et al., 2013). It is the sixth malignancy worldwide and the third one of cancer related mortality (Bravi et al., 2013; Waller et al., 2015).

Various factors are associated with HCC development like HCV, HBV, alcohol, metabolic and cholestatic liver diseases (Kirstein and Vogel, 2014). In the old era the diagnosis of HCC relied mainly on high α-fetoprotein (AFP) and the radiological criteria in triphasic CT; namely arterial enhancement and washout in the portal and delayed phases. Recently, AFP studies showed low sensitivity and inability to differentiate cholangiocarcinoma from HCC related focal lesions. This led to that some guidelines omitted its rule in the diagnosis but it may be useful on post-treatment follow up (European Association for the Study of the et al.).

Despite the advances of imaging technique, there are still equivocal focal lesions that are diagnosed by follow up imaging and/or biopsies. Hence there is still a rule for noninvasive HCC biomarkers (Song et al., 2016).

Talin is a large cytoskeletal dimeric adaptor protein that associates with the integrin family of cell adhesion molecules in cell-ECM junctions. It both activates integrins and couples them to the actin cytoskeleton (Bate et al., 2012). It is accused in the cancer progression and metastasis (Desiniotis and Kyprianou, 2011). Talin-1 was studied in some malignancies like colon (Bostanci et al., 2014), prostate(Sakamoto et al., 2010) and oral squamous cell carcinoma (Lai et al., 2011). In addition, recently talin-1 was studied as biomarker for process of the carcinogenesis, infiltration and metastasis of HCC (Zhang et al., 2011; Fang et al., 2014) and the clinical diagnosis of HCC (Youns et al., 2013).

This study aimed to assess the rule of serum talin-1 and noninvasive fibrosis models in patients with HCC.

Materials and Methods

After institutional review board approval, this study was conducted in National Liver Institute hospitals, Menoufia University, Egypt. An informed consent was obtained from all enrolled subjects.

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Eighty seven subjects were enrolled into the study. Twenty two healthy subjects as a control group (n=22), 22 patients in the cirrhosis group and finally 43 patients in the HCC group. The diagnosis of cirrhosis was based on clinical, laboratory, and ultrasonography findings (Schuppan and Afdhal, 2008). HCC was diagnosed according to the EASL guideline (European Association for the Study of the et al.). Exclusion criteria were sepsis, GIT bleeding, concurrent medical disease such as long standing diabetes mellitus, chest or cardiac disease.

All the patients underwent thorough history taking and physical examination. The following labs were done; liver functions tests, blood urea, serum creatinine, sodium, potassium, CBC, random blood sugar and AFP.

Abdominal ultrasonography with Doppler on the portal vein was done for early detection of thrombosis. Triphasic CT abdomen was done for the diagnosis of HCC. Serum talin-1 was measured in all subjects (Youns et al., 2013).

The following non-invasive models were calculated as following; AST/ALT ratio (AAR). APRI score = [(AST/upper limit normal AST) ×100]/number of platelets (10^9/l) (Shaheen and Myers, 2007). FIB4 score = [age (years)] × AST (U/L)]/[number of platelets (10^9/L)] × ALT (U/L) (½)] (Vallet-Pichard et al., 2007). Goteborg University Cirrhosis Index (GUCI) score = normalized AST × prothrombin-INR × 100/platelet count (× 10^9/l) (Islam et al., 2005). LOK score = log odds = -5.56 - 0.0089 × number of platelets (10^3/mm^3) + 1.26 × (AST/ALT) + 5.27 × INR (Lok et al., 2005). King's score = age × AST (U/l) × INR/platelet count (10^9/l) (Cross et al., 2009). Fibrosis index score = 8 - 0.01 × number of platelets (10^9/L) - albumin (g/dl) (Ohta et al., 2006). Fibro-α score = 1.35 + AFP (U/l) × 0.009584 + AAR × 0.243 –platelet count (10^9/l) × 0.001624 (Omran et al., 2011). ALBI score

Table 1. Comparison of Baseline Parameters among the Three Groups

	Groups			P all	P (B*C)
	Control	Cirrhosis	HCC		
	A	B	C		
	N=22	N=22	N=43		
	M±SD	M±SD	M±SD		
Age (years)	54.50±6.20	53.55±10.29	56.19±5.21	0.676	0.478
	55 (43 - 63)	55 (33 - 71)	56 (46 - 70)		
Bilirubin (mg/dl)	0.56±0.17	2.37±2.07	1.55±0.73	0.001	0.284
	0.525 (0.2 - 0.8)	1.875 (0.3 - 9.7)	1.2 (0.65 - 3.5)		
Albumin (mg/dl)	4.35±0.38	2.43±0.78	2.75±0.76	0.001	0.117‡
	4.3 (3.7 - 5)	2.25 (1.4 - 4.1)	2.9 (1.4 - 4.8)		
AST (u/l)	15.54±3.49	30.41±19.52	100.72±82.72	0.001	0.001
	15 (10 -22)	22.5 (11-85)	82 (20 - 392)		
ALT (u/l)	16.46±4.56	74.18±59.33	85.88±142.54	0.043§	0.714‡
	16.4 (10 - 25.2)	49.5 (18 - 256)	56 (13 - 892)		
INR	1.00±0.01	1.51±0.37	1.41±0.43	0.001	0.381‡
	1 (1 - 1.03)	1.465 (1.01 - 2.23)	1.3 (1 - 3.59)		
Hemoglobin (g/dl)	13.37±1.31	10.02±1.90	10.77±2.37	0.001§	0.207‡
	13.1 (11.1 - 15.3)	10.2 (6 - 13.3)	10.9 (5.5 - 15.5)		
WBCs (×10^3/µl)	6.57±1.50	8.51±7.87	8.60±6.38	0.938	0.965‡
	6.5 (4.3 - 10)	6.4 (1.4 - 39)	6.8 (2.9 - 32)		
Platelets (×10^3/µl)	254.73±53.96	86.68±41.92	105.71±57.08	0.001§	0.172‡
	239.5 (163 - 350)	79.5 (30 - 167)	101 (7.7 - 323)		
AFP (ng/ml)	5.14±2.14	21.97±27.90	966.98±1890.41	0.001	0.001
	5.1 (1.5 - 10.6)	9.15 (2 -98)	50 (2.6 - 7250)		
Talin-1 (ng/ml)	3.25±0.90	11.08±2.79	32.93±12.55	0.001	0.001
	3.045 (1.5 - 5.1)	11.15 (4 - 16.22)	29.25 (4 - 62.4)		
AST/ALT ratio	0.98±0.22	0.53±0.26	1.67±0.89	0.001	0.001
	0.93 (0.63 - 1.54)	0.55 (0.07 - 1)	1.54 (0.34 - 4.82)		
APRI score	0.16±0.05	3.37±10.66	5.90±18.86	0.314§	0.563‡
	0.165 (0.09 - 0.27)	0.95 (0.18 - 51)	1.55 (0.59 - 123.05)		
FIB4 score	0.85±0.21	2.90±1.87	9.96±15.26	0.001	0.001
	0.89 (0.44 - 1.19)	2.52 (0.36 - 7.4)	4.94 (2.05 - 98.88)		
GUCI score	0.16±0.05	1.68±1.41	14.83±67.15	0.395§	0.364‡
	0.165 (0.09 - 0.27)	1.44 (0.21 - 6.67)	2.14 (0.78 - 441.76)		
LOK score	0.22±0.09	0.79±0.24	0.86±0.16	0.001	0.293
	0.22 (0.09 - 0.37)	0.895 (0.22 - 1)	0.94 (0.36 - 1)		
Kings score	3.44±0.93	34.75±26.43	348.09±1609.98	0.406§	0.367‡
	3.47 (1.63 - 5.31)	27.47 (4.85 - 112.13)	46.12 (15.04 - 10602.16)		
Fibrosis index	1.38±0.61	4.98±0.96	4.47±0.95	0.001§	0.046‡
	1.49 (0.27 - 2.45)	5.19 (2.68 - 6.09)	4.43 (1.95 - 6.403)		
Fibro-α score	1.22±0.10	1.55±0.28	10.85±18.12	0.001	0.001
	1.23 (1.02 - 1.39)	1.47 (1.23 - 2.25)	2.21 (1.25 - 71.21)		
ALBI score	-3.07 ± 0.36	-1.10 ± 0.78	-1.43 ± 0.69	0.001§	0.069
	-3.06 (-3.56 - -2.42)	-0.77 (-2.67 - -0.18)	-1.45 (-3.24 - -0.12)		

§ANOVA, ‡MWT

= −0.085 × (albumin g/L) + 0.66 × log(bilirubin μmol/L) (Johnson et al., 2015).

Statistical Analysis

Data was statistically analyzed using IBM® SPSS® Statistics® version 21 for Windows. Data are expressed as mean ±standard deviation or median and range if not parametric. All p-values are 2 tailed, with values <0.05 considered statistically significant. Comparisons between two groups were performed using the Student's t-test for parametric data, and Mann-Whitney test for nonparametric data.

Comparisons between multiple groups were performed by usage of ANOVA test for parametric variables and Kruskal Wallis test for nonparametric variables. Univariate and multivariate binary logistic regression was done for detecting the predictors of the large size focal lesions with total size ≥5cm presence. The receiver operating characteristic (ROC) curve analysis was used for detection of the cutoff values for HCC detection. Sensitivity, specificity, positive predictive value and negative predictive value were used to express the cutoff. A value of 0.5-0.59 is of no useful performance for discrimination of the outcome under assessment.

Results

Firstly as shown in Table 1; there was a statistically significant difference among the 3 groups regarding all the studied variables except for the age, WBCs, APRI score, GUCI score and the King's score (p>0.05).

Patients with HCC had statistically significant (p=0.001) higher serum AST (100.72±82.72 *vs.* 30.41±19.52 u/l), serum AFP (966.98±1890.41 *vs.* 21.97±27.9 ng/ml), serum talin-1 (32.93±12.55 *vs.* 11.08±2.79 ng/ml), AST/ALT ratio (1.67±0.89 *vs.* 0.53±0.26), FIB4 score (9.96±15.26 *vs.* 2.90±1.87), fibro-α score (10.85±18.12 *vs.* 1.55±0.28) unlike the fibrosis index score (4.47±0.95 *vs.* 4.98±0.96; p=0.046).

Patients with large focal lesions with total size ≥5cm as seen in Table 2 had higher ALBI score (-1.02±0.63 *vs.* -1.72±0.59; p=0.001) unlike the serum talin-1 (9.72±13.81 *vs.* 28.63±38.89 ng/ml; p=0.007) and the fibrosis index score (0.85±0.99 *vs.* 4.20±4.85; p=0.026). Unfortunately the following variables were not beneficial statistically (p>0.05) namely; the AST/ALT ratio, APRI score, FIB4 score, GUCI score, LOK score, King's score, AFP and the fibro-α score.

The advent or development of malignant portal vein thrombosis was not predicted by serum AFP, Talin-1, AST/ALT ratio, APRI score, FIB4 score, GUCI score, LOK score, King's score, fibrosis index score, fibro-α score and the ALBI score (p>0.05).

The ROC curve analysis (Table 3) revealed the following for detection of liver cirrhosis. AFP at 6.55 ng/ml cutoff had 81.5% sensitivity and 77.3% specificity. Furthermore serum talin-1 had 96.9% sensitivity and 81.8% specificity with 4.885 ng/ml cutoff. At a 0.37 cutoff APRI score had 95.4% sensitivity and 100% specificity. The cutoff for FIB4 score was 1.175 with 93.8% sensitivity and 95.5% specificity meanwhile with 0.235 cutoff GUCI score had 98.5% sensitivity and 95.5% specificity. LOK score cutoff =0.405 with 95.4% sensitivity and 100% specificity in addition King's score had 100% sensitivity and 95.5% specificity with 4.803 as a cutoff. The cutoff for

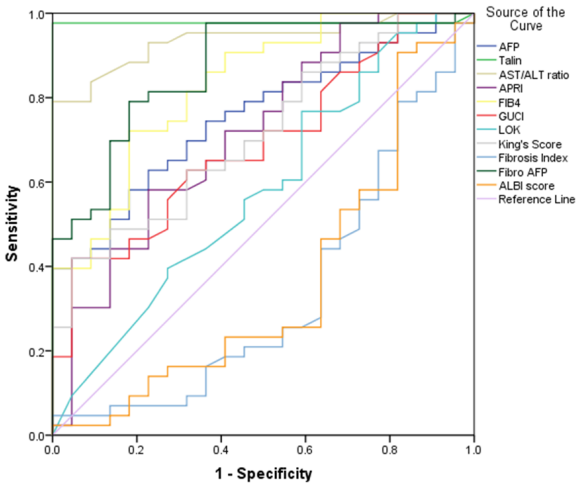

Figure 1. Receiver Operating Characteristic (ROC) Curve Analysis

Table 2. Correlations with Focal Lesion Size

	Focal lesion (FL) size		P
	FL <5cm	FL ≥5cm	
	N=25	N=18	
	M±SD	M±SD	
AFP	878.18 ± 1090.31	1631.21 ± 2246.07	0.721
Talin-1	28.63 ± 38.89	9.72 ± 13.81	0.007
AST/ALT ratio	1.61 ± 1.74	0.93 ± 0.86	0.64
APRI score	3.62 ± 9.06	5.85 ± 28.50	0.357
FIB4 score	8.25 ± 12.34	6.77 ± 22.37	0.393
GUCI score	5.54 ± 27.73	10.39 ± 103.36	0.676‡
	1.72 (0.78 - 52.47)	2.21 (0.78 - 441.76)	
LOK score	0.85 ± 0.88	0.17 ± 0.14	0.506
Kings score	121.41 ± 662.92	216.86 ± 2481.31	0.787‡
	40.85 (18.92 - 1091.44)	68.39 (15.04 - 10602.16)	
Fibrosis index score	4.20 ± 4.85	0.85 ± 0.99	0.026
Fibro-α score	9.99 ± 12.04	15.61 ± 21.56	0.72
ALBI score	-1.72 ± 0.59	-1.02 ± 0.63	0.001

‡MWT

Table 3. Receiver Operating Characteristic Curve Analysis

		AUC	P	Cutoff	Sen	Spec	PPV	NPV
AFP	a§	0.856	0.001	6.55	81.5	77.3	91.4	58.6
	b†	0.755	0.001	13.65	72.1	63.6	79.5	53.8
Talin-1	a§	0.993	0.001	4.885	96.9	81.8	94	90
	b†	0.977	0.001	17.235	97.7	100	100	95.7
AST/ALT ratio	a§	0.555	0.443					
	b†	0.938	0.001	0.855	86	86.4	92.5	76
APRI score	a§	0.995	0.001	0.37	95.4	100	100	88
	b†	0.714	0.005	1.21	62.8	63.6	77.1	46.7
FIB4 score	a§	0.961	0.001	1.175	93.8	95.5	98.4	84
	b†	0.83	0.001	3.465	74.4	68.2	82.1	57.7
GUCI score	a§	0.997	0.001	0.235	98.5	95.5	98.5	95.5
	b†	0.692	0.012	1.51	65.1	59.1	75.7	46.4
LOK score	a§	0.987	0.001	0.405	95.4	100	100	88
	b†	0.58	0.295					
Kings score	a§	0.999	0.001	4.803	100	95.5	98.5	100
	b†	0.716	0.005	34.906	62.8	63.6	77.1	46.7
Fibrosis index score	a§	0.999	0.001	2.565	98.5	100	100	95.7
	b†	0.337	0.032	4.275	65.1	22.7	62.2	25
Fibro-α score	a§	0.973	0.001	1.352	92.3	86.4	95.2	79.2
	b†	0.87	0.001	1.6145	81.4	77.3	87.5	68
ALBI score	a§	0.983	0.001	-2.45	93.8	90.9	96.8	83.3
	b†	0.362	0.069					

a§; control versus both cirrhosis and HCC. b†; cirrhosis versus HCC

fibrosis index score was 2.565 with 98.5% sensitivity and 100% specificity however, the cutoff for fibro-α score was 1.352 with 92.3% sensitivity and 86.4% specificity. ALBI score for detection of cirrhosis had a cutoff equaling -4.45 with 93.8% sensitivity and 90.9% specificity.

The ROC curve analysis (Table 3, Figure 1) revealed the following for detection of hepatocellular carcinoma. AFP at 13.65 ng/ml cutoff had 72.1% sensitivity and 6.3.6% specificity. Furthermore serum talin-1 had 97.7% sensitivity and 100% specificity with 17.235ng/ml cutoff. At a 1.21 cutoff APRI score had 62.8% sensitivity and 63.6% specificity. The cutoff for FIB4 score was 3.465 with 74.4% sensitivity and 68.2% specificity meanwhile with 1.51 cutoff GUCI score had 65.1% sensitivity and 59.1% specificity. AST/ALT ratio cutoff =0.855 with 86% sensitivity and 86.4% specificity in addition King's score had 62.8% sensitivity and 63.6% specificity with 34.906 as a cutoff. The cutoff for fibrosis index score was 4.275 with 65.1% sensitivity and 22.7% specificity however, the cutoff for the fibro-α score was 1.6145 with 81.4% sensitivity and 77.3% specificity.

The large focal lesions with total size ≥5cm presence were studied by the univariate logistic regression analysis test. Only the serum talin-1 (odds=1.08; C.I=1.016-1.150; p=0.014), fibrosis index score (odds=2.35; C.I=1.055-5.217; p=0.037) and the ALBI score (odds=6.9; C.I=1.924-24.708; p=0.003) were the predictors. However by the application of multivariate regression analysis test, both the serum talin-1 (odds=1.07; C.I=1.005-1.149; p=0.036), and the ALBI score (odds=15.63; C.I=1.574-155.182; p=0.019) were the predictors.

Discussion

Hepatocellular carcinoma is a major health problem. More than 700000 cases are diagnosed yearly (Forner et al., 2012). Hepatocellular carcinoma is the sixth most prevalent cancer and the third most frequent cause of cancer-related death (Bruix et al., 2014). There are a lot of risk factors for the development of HCC e.g. viral hepatitis, aflatoxin, etc. (Kirstein and Vogel, 2014). In the previous years, AFP had upper hand in the diagnosis and follow up of patients. Unfortunately recent guidelines had neglected it and depended mainly in the radiological diagnosis (European Association for the Study of the et al.). However there are focal lesions that are equivocal in the diagnosis, hence the need for various biomarkers though the debate on clinical utility (Kim et al., 2015; Song et al., 2016).

Recently there is trend towards noninvasive diagnosis of liver fibrosis and portal hypertension. Various models were postulated. But the question is "are they beneficial in patients with HCC".

Serum talin-1 in a recent study (Youns et al., 2013) was a useful biomarker of HCC. Patients with HCC had higher serum AFP and talin 1 than those with just cirrhosis; (123.3±35.59 *vs.* 80.2±26.6 ng/ml; p=0.006) and (61.63±2.47 *vs.* 17.24±4.78 ng/ml; p=0.001) respectively. The serum talin 1 levels were unaffected by the gender. At a cutoff equals 33.75 ng/ml; the talin 1 had 100% sensitivity, 87% specificity, 88% PPV and 100% NPP. Meanwhile at a cutoff equals 9 ng/ml the AFP had 80% sensitivity, 65% specificity, 69% PPV and 76% NPP. When both are combined, at cutoff equals 33.75 they had 100% sensitivity, 57% specificity, 70% PPV and 100% NPP. APRI score was predictive in HBV patients of hepatocellular carcinoma (Hann et al., 2015) and post-resection recurrence in HBV patients (Shen et al., 2014). High APRI value is associated with HCC recurrence after radiofrequency ablation (Chung et al., 2016). FIB4 score is associated with the development of HCC in longitudinal studies (Park et al., 2011; Ito et al., 2015b; Suh et al., 2015) and is useful in the assessment of the prognosis (Ito et al., 2015a). King's score is effective index for predicting

overall survival in hepatitis B-associated HCC (Pang et al., 2015). It may be useful if integrated to BCLC system (Pinato et al., 2015). Recently ALBI score developed as a better model for assessment of the liver function in patients with HCC and assessment of the prognosis (Hiraoka et al., 2015). It was proposed be to integrated in BCLC system (Chan et al., 2016) and requirement of sorafenib therapy (Ogasawara et al., 2015). LOK score,(Lok et al., 2005), fibrosis index score (Ohta et al., 2006; Bota et al., 2011), GUCI score (Islam et al., 2005) and Fibro-α score (Omran et al., 2011) were not in our knowledge assessed in patients with HCC.

In the current study patients with HCC had higher values of serum AFP, serum talin-1, AST/ALT ratio, FIB4 score and fibro-α score than those with cirrhosis in contrary to the fibrosis index score. The presence of large sized focal lesions with total size ≥5cm was associated with higher ALBI score value than those with less size unlike serum talin-1 and the fibrosis index score. The rest of studied scores were useless. None of the studies variables were more associated with malignant vein thrombosis. The serum talin-1, AST/ALT ratio, fibro-α score had the better sensitivity and specificity than the rest of the studied scores. The cutoff of serum talin-1 was 17.235ng/ml. It was lower than previously studied cutoff (Youns et al., 2013). It is not affected by the gender or the presence of portal vein thrombosis.

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