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THE SIGNIFICANCE OF NEUROPILIN-1 FOR THE DIAGNOSIS OF HEPATOCELLULAR CARCINOMA IN EGYPTIAN PATIENTS

Hoda Aly Abd El Moety [(1)], Dalia Aly Maharem [(2)]
Chemical Pathology, Medical Research Institute, Alexandria University, Egypt [(1)]
Internal Medicine, Medical Research Institute, Alexandria University, Egypt [(2)]

Abstract

Background: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults and is a leading cause of cancer-related death worldwide. Approximately 750,000 new HCC cases are diagnosed annually. Despite advances in prevention techniques, screening, and new technologies in diagnosis and treatment, incidence and mortality continue to rise. Furthermore, biomarkers that are currently used clinically to predict the prognosis of HCC patients after curative surgical resection remain unsatisfactory in terms of both accuracy and reproducibility. Neuropilin-1 (NRP-1) plays an important role in angiogenesis and malignant progression of many human cancers. However, the role of NRP-1 in hepatocellular carcinoma (HCC) is not well understood.

Aim of this work: to determine whether neuropilin-1 is a marker for diagnosis of hepatocellular carcinoma.

Subjects and methods: patients were categorized into two groups: forty five HCV patients with liver cirrhosis and thirty HCV patients with liver cirrhosis and HCC with ten healthy subjects of matched age and sex. All patients were subjected to: detailed history taking, systemic physical examination, measurement of BMI, MBP and abdominal ultrasonography. Laboratory investigations including: serum creatinine, AST, ALT, GGT, ALP, total proteins, albumin, bilirubin (Total and direct), CBP, prothrombin activity, INR, hepatitis B surface antigen, hepatitis C virus antibodies, determination of serum AFP and neuropilin-1. Assessment of Child-Pugh score, MELD score and ALBI score.

Results: The mean value of neuropilin-1 was statistically significantly higher in patients groups than control group and also statistically significantly higher in patients with liver cirrhosis and HCC than in those with liver cirrhosis alone and it showed positive statistical significant correlation with child class score, MELD score and ALBI score in patients with liver cirrhosis and HCC.

Conclusions: Higher neuropilin-1 in patients with hepatocellular carcinoma signifies its importance as a marker for diagnosis of patients with HCC and may play a role in pathogenesis of hepatocellular carcinoma.

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Key words: Neuropilin-1, hepatocellular carcinoma, albumin-bilirubin score.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. [1] It is the second most common cause of cancer-related death in the world and seventh most common cause in the United States (US) and the most common cause of death in people with cirrhosis. [2-4] HCC occurred more often in males than females (2.4:1), with a higher incidence in Eastern and Southern Asia, Middle and Western Africa. [5] HCC represents an important public health problem that facing the health authorities in Egypt. Liver cancer forms 11.75% of the malignancies of all digestive organs and 1.68% of the total malignancies. HCC constitutes 70.48% of all liver tumors among Egyptians. [6, 7]

Hepatitis C virus (HCV) mostly plays an indirect role in tumour development and increase the risk of HCC by promoting fibrosis and cirrhosis. On the other hand, HCV may play a direct role in hepatic carcinogenesis through the involvement of viral gene products in inducing liver cell proliferation. [8, 9]

To obtain the best treatment result for HCC, early diagnosis is the key. Unfortunately, the diagnosis of HCC is too often made with advanced disease when patients have become symptomatic and have some degree of liver impairment. [10] Furthermore, the prognosis of HCC remains poor due to its high intra-hepatic recurrence rate post curative hepatectomy. [11] Therefore, novel biomarkers that improve the diagnosis and treatment of HCC patients are awaiting discovery.

Neuropilin- 1 (NRP-1) is a transmembrane glycoprotein composed of a large N-terminal extracellular region, a short transmembrane domain and a small cytoplasmic tail (44 aa), that acts as a co-receptor for a number of extracellular ligands including class III/IV semaphorins, certain isoforms of vascular endothelial growth factor (VEGF) and transforming growth factor beta. [12, 13] NRP-1 plays versatile roles in angiogenesis, axon guidance, cell survival, migration, and invasion. [14] It is expressed in endothelial cells, where it interacts with several members of the VEGF family of angiogenic factors and some of their tyrosine kinase receptors enhancing the signaling and promoting angiogenesis. [15, 16]

NRP-1 is expressed in a variety of cancers suggesting a role in tumor progression. NRP-1 has been detected in blood vessels in more than 98% of cases. [17, 18] Its expression has been detected in several tumor biopsies, such as brain, prostate, breast, bladder, kidney, colon, pancreas, skin, ovarian, and lung carcinomas. [19- 24] Increased levels of NRP-1 correlate with tumor aggressiveness, advanced disease stage, and poor prognosis. [25, 26] NRP-1 up-regulation appears to be associated with the tumor invasive behavior and metastatic potential. [27] It has been indicated as a promoter of epithelial-mesenchymal transition, a critical step in tumor invasion and disease progression. [28]

Elpek et al reviewed the role of NRPs in liver diseases and concluded that they were involved in liver regeneration, liver fibrosis, and malignant transformation. [29] NRP-1 expression was increased in human HCC, and ~50% of primary HCC samples were positively stained for NRP-1.[30] Angiogenesis was closely associated with liver fibrosis and

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has reported that hepatic stellate cells secreted NRP-1 to induce angiogenesis in liver fibrosis.[31]

Furthermore, NRP-1 expression in HCC has been associated with intrahepatic metastasis, TNM classification and portal vein invasion, shorter recurrence-free survival, and shorter overall survival. [32]

Berge M et al concluded that blocking NRP-1 function with peptide N leads to the inhibition of vascular remodeling and tumor liver growth in HCC mice and highlight the possibility of therapeutically targeting NRP-1 for the treatment of HCC. [30]

Recently, a simple evaluation method for hepatic function, termed albumin-bilirubin (ALBI) grade, which is calculated using only serum albumin and total bilirubin, has been proposed and some have reported its usefulness for HCC treatment planning. [33-35]

Aim of work

The aim of this work was to determine whether neuropilin-1 is a marker for diagnosis of hepatocellular carcinoma.

Subjects and methods

This study included 75 patients with liver cirrhosis. Patients were selected from the Internal Medicine department and Hepatology unit in the Medical Research Institute, Alexandria University. Written consent was obtained from all participants before starting the study.

Patients were categorized into two groups:

Group I: Forty five HCV patients with liver cirrhosis.

Group II: Thirty HCV patients with liver cirrhosis and HCC.

Group III: Ten healthy subjects of matched age and sex as the patients as control group.

Patients with diabetes mellitus, hepatitis B, active infections or other malignancies were excluded from this study.

All patients were subjected to the following:

- Detailed history taking with stress on history of gastrointestinal bleeding and history of hepatic encephalopathy.
- Thorough systemic physical examination including presence of splenomegaly, ascites and oedema of lower limbs.
- Measurement of body mass index [36] and mean blood pressure.[37]
- Abdominal ultrasound evaluation to assess the presence of portal hypertension, splenomegaly, ascites and extend of hepatocellular carcinoma.[38]
- Laboratory investigations including:

a. Serum creatinine. [39]
b. Liver function tests including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total proteins, albumin, bilirubin (Total and direct).[39]

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c. Complete blood picture, prothrombin activity and INR. [40]

d. Hepatitis virus markers: Hepatitis B surface antigen. [41] and Hepatitis C virus antibodies done by the Eliza technique. [42]

e. Determination of serum AFP [43] and neuropilin-1 by the Eliza technique. [44]

f. Assessment of Child-Pugh score.[45]

g. Calculation of Model for End Liver Disease (MELD) score. [46]

h. Calculation of Albumin- Bilirubin score (ALBI) based on serum albumin and total bilirubin using the following formula:
ALBI-score = (log10 bilirubin [μmol/L] × 0.66) + (albumin [g/L] ×0.085). Then ALBI grade was defined by the resulting score: grade 1≤ -2.60; grade 2 > -2.60 to ≤ -1.39; and grade 3 > - 1.39. [47]

Statistical analysis of the data:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). F-test (ANOVA) Post Hoc test) (LSD) was used to compare three groups for normally distributed quantitative variables. Student t-test was used to compare two groups for normally distributed quantitative variables. Kruskal Wallis test**,** for abnormally quantitative variables, to compare between more than two studied groups, and Post Hoc (Dunn's multiple comparisons test) for pair wise comparisons**.** Mann Whitney test was used to compare two groups for abnormally distributed quantitative variables. Significance of the obtained results was judged at the 5% level. Qualitative data were described using number and percent, normally quantitative data was expressed in mean ± SD while abnormally distributed data was expressed in median (Min.- Max.).

Results

In this study, group I included 33 (73.3%) males and 12 (26.7%) females, their mean age was 56.8±8.7 years, while group II included 17 (56.7%) males and 13 (43.3%) females, their mean age was 58.7±9.0 years and the healthy control group included 12 (60%) males and 8(40%) females with mean age 52.5±7.9 years with no statistical significant difference between groups. (Table 1)

BMI in group I was 26.6±4.7 kg/m^2 while it was 28.7±5.8 kg/m^2 in group II and 27.01±2.6 kg/m^2 in group III. MBP in group I was 87.9±11.1mmHg while it was 88.8 ±12.3mmHg in group II and 87.2±3.9mmHg in group III with no statistical significant difference between groups. (P=0.185, 0.863 respectively) (Table 1)

No statistical significant difference between the two patients groups as regard the presenting symptoms and signs. (Table 2)

The mean value of serum creatinine showed no statistical significant difference between both groups (P=0.285). The mean value of AST, ALT, direct bilirubin and ALP were statistically significant higher in group II than group I (P=0.001, 0.002, 0.027 and 0.036 respectively) while the mean value of total proteins and serum albumin were statistically significant lower in group II than group I (P=0.030, 0.037 respectively). Total bilirubin and

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GGT showed no statistical significant difference between both groups. (P=0.067, 0.081respectively) (Table 3)

The mean value of HB, WBCs, platelets, prothrombin activity and INR showed no statistical significance differences between group I and group II. (Table 4)

No statistical significance differences between both groups as regard child class or the mean value of its score or model of end stage liver disease score (P= 0.080, 0.239 respectively) but the mean value of albumin bilirubin score was statistically significantly higher in group II than group I. (P=0.031) (Table 5).

The mean value of Alpha fetoprotein and neuropilin-1 were statistically significantly higher in patients groups than control group and also statistically significantly higher in group II than in group I. (P <0.001, <0.001respectively) (Table 6).

Correlation of some demographic and laboratory variables with neuropilin-1 in group II showed that there was negative statistical significant correlation between neuropilin-1 and platelets, prothrombin activity (P=0.002 and 0.005 respectively). There was positive statistical significant correlation between neuropilin-1 and INR, child class score, MELD and ALBI score. (P=0.014, 0.040, 0.049 and 0.002 respectively) (Table 7). Total patients showed positive statistical significant correlation between neuropilin-1 and AFP (P<0.001). ALBI score showed positive statistical significant correlation with AFP and NRP-1. (P<0.001 and 0.001 respectively) (Table 8).

The area under the receiver operating characteristic curve [AUC- ROC] for serum NRP-1 was 1.000, presenting better diagnostic performance compared to AFP. AUC-ROC for serum NRP-1 was (1.000) which was better than AFP (0.830) for the differentiation of HCC patients from healthy individuals. With a cut off >20 ng/ml, sensitivity was 100% and specificity was 100%. (Table 9), (Figure 1).

Table (1): Comparison between the three studied groups according to clinical data

	Group I (n=45)		**Group II (n=30)**		**Group III (n=20)**		**p**
	No.	**%**	**No.**	**%**	**No.**	**%**	
Sex							
Male Female	33 12	73.3 26.7	17 13	56.7 43.3	12 8	60.0 40.0	P = 0.284
Age (years)							
Min. –Max. Mean ± SD Median	41.0-75.0 56.8±8.7 55.0		40.0-75.0 58.7±9.0 57.0		37.0-66.0 52.2±7.9 52.0		P= 0.051
≤ 40	0 (0%) 9 (20%)		1 (3.3%) 3 (10.1%)		2 (10%) 6 (30%)		P= 0.080

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41 – 50 51 – 60 >60	17 (37.8%) 19 (42.2%)	13 (43.3%) 13 (43.3%)	9 (45%) 3 (15%)	
Weight (Kg) Min.- Max Mean± SD Median	 44.0-111.0 73.7±13.6 72.0	 42.0-115.0 77.2±15.7 76.0	 55.0-90.0 72.9±10.7 73.5	P= 0.465
Height (Cm) Min.- Max Mean± SD Median	 155.0-182.0 166.7±7.1 168.0	 148.0-180.0 166.0±7.0 167.0	 152.0-178.0 164.1±7.5 162.5	P= 0.408
BMI (kg/m^2) Min.- Max Mean± SD Median	 17.7-39.8 26.6±4.7 26.6	 16.2-39.0 28.7±5.8 29.6	 22.5-31.6 27.01±2.6 27.3	P= 0.185
MBP (mmHg) Min.- Max Mean± SD Median	 70.0-120.0 87.9±11.1 83.0	 70.0-120.0 88.8±12.3 83.0	 83.0-93.0 87.2±3.9 86.5	P= 0.863

MBP= Mean blood pressure. BMI= Body mass index.
Group I: liver cirrhosis group, Group II: liver cirrhosis with hepatocellular carcinoma group, Group III: Control group
*: Statistically significant at $p \leq 0.05$

Table (2): Clinical presentations of patients groups

Presenting symptoms and signs	Group I (n=45)	Group II (n=30)	P
Bleeder	28 (62.2%)	15 (50%)	0.294
Ascites	31 (68.9%)	26 (86.7%)	0.077
HE	19 (42.2%)	13 (43.3%)	0.924
Hypertension	11 (24.4%)	9 (30%)	0.594
IHD	5 (11.1%)	6 (20%)	0.330

HE= Hepatic encephalopathy. IHD= Ischemic heart disease.
Group I: liver cirrhosis group, Group II: liver cirrhosis with hepatocellular carcinoma group
*: Statistically significant at $p \leq 0.05$

Table (3): Laboratory investigations in patients groups:

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	Group I (n=45)	Group II (n=30)	P
Serum creatinine (mg/dl)			
Min.-Max	0.6-2.8	0.7-2.2	0.285
Mean ± SD	1.05±0.41	1.11±0.36	
Median	0.9	1.1	
AST (U/L)			
Min.- Max	10.0-188.0	23.0- 309.0	0.001*
Mean± SD	53.96±42.45	88.93±64.90	
Median	35.0	78.5	
ALT (U/L)			
Min.- Max	8.0-98.0	6.0-140.0	0.002*
Mean± SD	27.49±20.33	44.93±31.66	
Median	20.0	33.5	
Total bilirubin (mg/dl)			
Min.- Max	0.5-14.0	0.6-25.0	0.067
Mean± SD	2.60±3.01	4.23±5.15	
Median	1.7	2.0	
Direct bilirubin (mg/dl)			
Min.- Max	0.3-10.5	0.3-16.3	0.027*
Mean± SD	1.45±2.13	2.65±3.53	
Median	0.8	1.1	
Total proteins (mg/dl)			
Min.- Max	5.4-8.8	4.5-8.6	0.030*
Mean± SD	7.3±1.0	6.8±0.9	
Median	7.2	6.9	
Serum albumin (gm/dl)			
Min.- Max	1.7-4.0	1.5-3.2	0.037*
Mean± SD	2.7±0.6	2.4±0.4	
Median	2.6	2.5	
GGT (IU/L)			
Min.- Max	6.5-208.0	14.0-479.0	0.081
Mean± SD	46.71±46.71	76.83±90.79	
Median	40.0	37.0	

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ALP (IU/L)			
Min.- Max	52.0-333.0	47.0-522.0	0.036*
Mean± SD	111.0±81.8	145.6±81.9	
Median	87.0	128.0	

ALT= Alanine aminotransferase AST= Aspartate aminotransferase.
GGT= Gamma glutamyl transpeptidase ALP= Alkaline phosphatase.
Group I: liver cirrhosis group, Group II: liver cirrhosis with hepatocellular carcinoma group
*: Statistically significant at $p \leq 0.05$

Table (4): Haematological investigations in patients groups:

	Group I (n=45)	**Group II (n=30)**	**P**
HB (g/dl)			
Min.-Max	5.8-13.2	6.9-14.5	0.677
Mean ± SD	10.1±1.8	9.9±1.9	
Median	9.8	9.6	
WBCs ($x10^3$)			
Min.- Max	1.1-15.8	1.9-13.3	0.559
Mean± SD	5.4±2.9	5.3±2.9	
Median	4.8	4.1	
Platelets ($x10^3$)			
Min.- Max	35.0-255.0	35.0-209.0	0.087
Mean± SD	129.2±60.8	103.0±49.7	
Median	131.0	92.0	
Prothrombin activity			
Min.-Max	26.1-92.3	23.3-91.3	0.513
Mean± SD	52.2±15.0	54.5±16.7	
Median	49.1	51.2	
INR			
Min.-Max	1.1-2.5	1.1-3.2	0.828
Mean± SD	1.7±0.4	1.6±0.5	
Median	1.6	1.5	

Hb=Haemoglobin. WBCs= White blood cells.
INR=International normalised ratio.
Group I: liver cirrhosis group, Group II: liver cirrhosis with hepatocellular carcinoma group
*: Statistically significant at $p \leq 0.05$

Table (5): Comparison between patients groups according to child class, MELD score and ALBI score

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	Group I (n=45)	Group II (n=30)	P
Child class			
A	8 (17.8%)	1 (3.3%)	0.088
B	23 (51.1%)	14 (46.7%)	
C	14 (31.1%)	15 (50%)	
Child class score			
Min.- Max	6.0-14.0	6.0-14.0	0.080
Mean± SD	1.7±0.4	1.6±0.5	
Median	9.0	9.5	
MELD score			
Min.- Max	7.0-28.0	8.0-28.0	0.239
Mean± SD	15.5±5.0	16.7±4.5	
Median	15.0	16.5	
ALBI score			
Min.- Max	-2.52- -0.14	-1.85-0.28	0.031
Mean± SD	-1.29±0.62	-0.91±0.46	
Median	-1.16	-1.01	

MELD= Model of end stage liver disease. ALBI= Albumin Bilirubin score.
Group I: liver cirrhosis group, Group II: liver cirrhosis with hepatocellular carcinoma group
*: Statistically significant at $p \leq 0.05$

Table (6): comparison between the studied groups according to alpha fetoprotein and neuropilin-1

	Group I (n =45)	Group II (n =30)	Group III (n =20)	P
AFP (ng/ml)				
Min. – Max.	2.3-63.9	22.7-10271	2.0-10.0	<0.001*
Mean ± SD	16.2±17.2	1407.0±2213.0	6.4±2.5	
Median	10.3	462.0	6.3	
NRP-1 (ng/ml)				
Min. – Max.	50.0-350.0	100.0-600.0	0.3-20.0	<0.001*
Mean ± SD	177.2±87.4	316.5±127.5	8.5±7.7	
Median	154.0	302.5	10.8	

AFP= Alpha fetoprotein NRP-1= Neuropilin-1
Group I: liver cirrhosis group, Group II: liver cirrhosis with hepatocellular carcinoma group, Group III: Control group
*: Statistically significant at $p \leq 0.05$

Table (7): Correlation of some demographic and laboratory variables with NRP-1 in group II

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Variable		NRP-1
Age (years)	R	0.002
	P	0.991
BMI (kg/m^2)	R	-0.274
	P	0.143
MBP (mmHg)	R	0.261
	P	0.164
Creatinine (mg/dl)	R	0.010
	P	0.960
AST (U/L)	R	0.112
	P	0.554
ALT (U/L)	R	0.059
	P	0.756
Serum albumin (gm/dl)	R	-0.200
	P	0.290
Platelets (x10^3)	R	-0.549*
	P	0.002
Prothrombin activity (%)	R	-0.498*
	P	0.005
INR	R	0.443*
	P	0.014
AFP (ng/ml)	R	0.009
	P	0.960
Child class score	R	0.378*
	P	0.040
MELD score	R	0.362*
	P	0.049
ALBI score	R	0.533*
	P	0.002

Group II: liver cirrhosis with hepatocellular carcinoma group NRP-1= Neuropilin-1
BMI= Body mass index MBP= Mean blood pressure
AST= Aspartate aminotransferase. ALT= Alanine aminotransferase
INR=International normalised ratio. AFP= Alpha fetoprotein
MELD= Model of end stage liver disease ALBI= Albumin Bilirubin score
*: Statistically significant at $p \leq 0.05$

Table (8): Correlation of ALBI score with AFP and NRP-1 in all patients groups

	ALBI score	
Total patients (n=75)	**r_s**	**P**
AFP	0.529*	<0.001
NRP–1	0.371*	0.001

ALBI score= Albumin- Bilirubin score AFP= Alpha fetoprotein
NRP-1= Neuropilin-1

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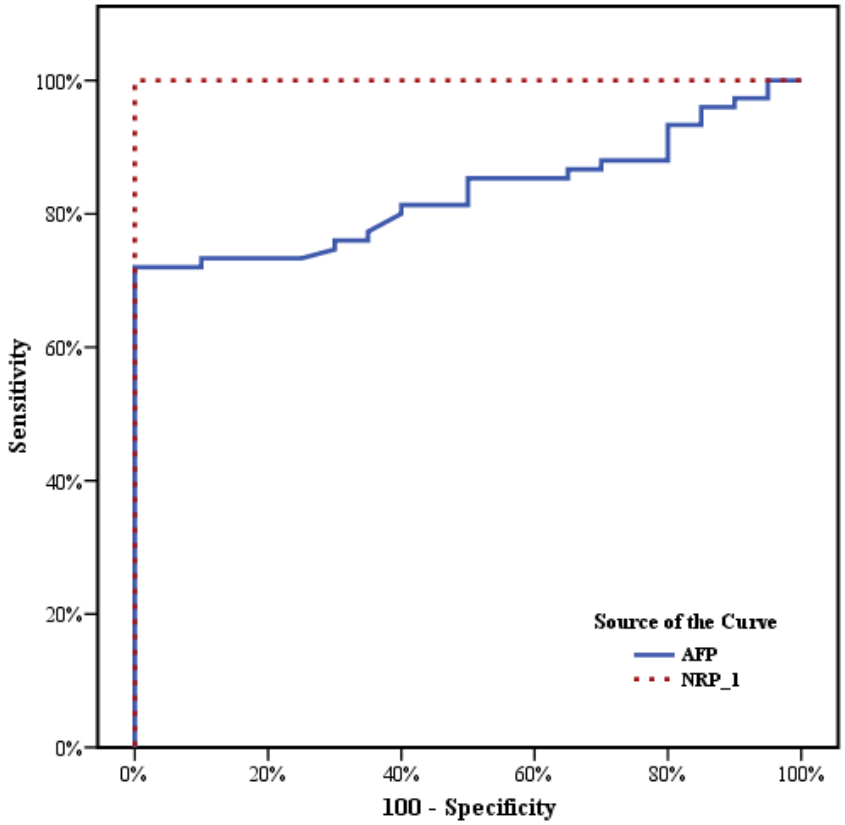

Figure (1): ROC curve for AFP and NRP-1 to predict cases group from control group

Table (9): Agreement (sensitivity, specificity) for AFP and NRP-1to predict cases group from control group

	AUC	P	95% C.I		Cut off	Sensitivity	Specificity	PPV	NPV
			L.L	U.L					
AFP	0.830*	<0.001*	0.751	0.909	>10	72.0	100.0	100.0	48.8
NRP_1	1.000*	<0.001*	1.000	1.000	>20	100.0	100.0	100.0	100.0

AUC: Area under a Curve
CI: Confidence Intervals
P value: Probability value
*: Statistically significant at $p \leq 0.05$

Discussion

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. The development of cirrhosis is associated with high risk for developing HCC. Due to the wide prevalence of HCC, it carries a significant economic burden on society at large, especially in the East Asian countries. HCV is the second most common risk factor for HCC, with an estimated 10%–25% of all cases attributed to it around the world. [48] Early diagnosis is crucial in order to provide effective treatment. Among patients with cirrhosis, current recommendations include aggressive screening. The rate of resectable HCC

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diagnosed in patients who are at high risk reaches 30-50%, which is nearly twice the rate of unscreened populations. Despite the significant risk of recurrence, even in treated patients, the screening protocols appear to be cost effective in this population. (49, 50)

Neuropilin-1 (NRP-1) is a transmembrane glycoprotein that acts as a co-receptor for various members of the vascular endothelial growth factor (VEGF) family. Its ability to bind or modulate the activity of a number of other extracellular ligands, has suggested the involvement of NRP-1 in a variety of physiological and pathological processes. (18)

Zhang Y et al concluded that NRP-1 expression may play an important role in the progression of HCC, and that high NRP-1 expression suggests unfavorable clinic-pathological characteristics and survival in HCC patients. (32)

This study included 75 patients with liver cirrhosis. They were categorized into two groups; Group I: Forty five HCV patients with liver cirrhosis. Group II: Thirty HCV patients with liver cirrhosis and HCC and Group III: Ten healthy subjects of matched age and sex as the patients as control group. In this study, group I included 33 (73.3%) males and 12 (26.7%) females, while group II included 17 (56.7%) males and 13 (43.3%) females with no statistical significant differences between groups as regard age and sex.

No statistical significant difference between groups as regard BMI and MBP also no statistical significant difference between the two patients groups as regard the presenting symptoms and signs. The mean value of serum creatinine showed no statistical significant difference between both groups. The mean value of AST, ALT, direct bilirubin and ALP were statistically significant higher in group II than group I while the mean value of total proteins and serum albumin were statistically significant lower in group II than group I. Total bilirubin and GGT showed no statistical significant difference between both groups. The mean value of HB, WBCs, platelets, prothrombin activity and INR showed no statistical significance differences between group I and group II.

No statistical significance differences between both groups as regard child class or the mean value of its score or model of end stage liver disease score but the mean value of albumin bilirubin (ALBI) score was statistically significantly higher in group II than group I.

Child-Pugh classification is used worldwide for evaluation of hepatic function in patients with liver cirrhosis but the highly subjective evaluation of ascites and encephalopathy might reduce the accuracy of assessment. (51)

The albumin-bilirubin (ALBI) score is a new model for assessing the severity of liver dysfunction. Johnson and colleagues reported that the ALBI score more accurately predicts patients' mortality without requiring subjective determinants of liver failure, including ascites and encephalopathy, in patients with HCC. (52) A retrospective study also investigated the prognostic significance of the ALBI score among patients with primary biliary cirrhosis and they found that the ALBI score seems to be superior to other scores (such Child–Pugh and MELD score) for predicting the occurrence of hepatic events in such

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patients.[53] Furthermore, Chen et al demonstrated that ALBI score had a significantly better performance for long-term survival prediction in patients with HBV-related cirrhosis than the Child–Pugh or MELD scores. [54] It was concluded also that ALBI score showed an assessment ability similar to that of liver damage (LD) grade and there was a small improvement in prognosis following radiofrequancy ablation (RFA) in patients with an ALBI score of 3, furthermore the assessment with ALBI score may be more useful than with LD-grade for avoiding a non-beneficial RFA procedure. [55]

The mean value of Alpha fetoprotein and neuropilin-1 were statistically significantly higher in patients groups than control group and also statistically significantly higher in group II than in group I. The area under the receiver operating characteristic curve [AUC-ROC] for serum NRP-1 was 1.000, presenting better diagnostic performance compared to AFP. AUC-ROC for serum NRP-1 was (1.000) which was better than AFP (0.830) for the differentiation of HCC patients from healthy individuals. With a cut off >20 ng/ml, sensitivity was 100% and specificity was 100%.

Lin J et al concluded that serum concentration of neuropilin-1 was significantly higher in patients with HCC than in healthy individuals or those with HBV, HCV, breast, colon, gastric or lung cancer. The area under ROC curve for serum neuropilin-1 was 0.971 presenting better diagnostic performance compared to AFP. They concluded also that higher NRP-1 was significantly associated with higher HCC tumor stages. [56]

Berge M et al indicated a specific role of NRP-1 in HCC growth and vascular remodelling and highlight the possibility of therapeutically targeting NRP-1 for the treatment of HCC. [30]

Correlation of some demographic and laboratory variables with neuropilin-1 in group II showed that there was negative statistical significant correlation between neuropilin-1 and platelets, prothrombin activity. There was positive statistical significant correlation between neuropilin-1 and INR, child class score, MELD and ALBI score. Total patients showed positive statistical significant correlation between neuropilin-1 and AFP. ALBI score showed positive statistical significant correlation with AFP and NRP-1. These correlations signify the role of neuropilin-1 in the diagnosis of HCC and it may play a role in the progress of the tumor in these patients with HCC.

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