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Original article

Neuropilin1 as a Diagnostic Marker for Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is a global health problem. It is the second most common cause of cancer-related mortality and the sixth most common cause of cancer worldwide, related cirrhosis include chronic viral hepatitis, alcoholic and non-alcoholic fatty liver disorders and other forms of chronic hepatitis inflammatory illnesses ,**The aim**: to study the clinical usefulness of serum Neuropilin 1(NRP 1) as a diagnostic marker for HCC. **Methods**: This cross-sectional study was conducted on 90 individuals divided into three groups: Group I: Thirty patients with HCC, Group II: Thirty patients with liver cirrhosis (LC), Group III: Thirty apparently healthy subjects. All patients were subjected to full medical history taking, thorough clinical examination and determination of the serum level of NRP 1. ROC curve was done to detect validity of NRP1 to predict HCC and LC. **Results;** NRP1 level was significantly higher in HCC when compared to LC group. Also, NRP 1 level was significantly higher in HCC and LC groups when compared to control group. ROC curve of serum NRP1 showed sensitivity was 93.3%, specificity 80%, PPV of 82.4% and NPV of 92.3% with AUC of 0.842 at cutoff value of 4030 pg/ml. **Conclusion:** NRP-1 may represent a potential diagnostic marker for HCC.

Keywords: Neuropilin1; Hepatocellular; Carcinoma; HCC

Introduction

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and mainly occurs in patients having chronic liver disease and cirrhosis. (1) Alpha-fetoprotein (AFP) is the most acknowledged biomarker for early detection and the follow-up of HCC patients during treatment.

The clinical diagnostic accuracy of AFP is unsatisfactory due to low sensitivity and specificity (2).

Neuropilin 1(NRP1) is a type I transmembrane glycoprotein that was originally found to play a role in neuronal axon guidance and embryonic angiogenesis (3).

Neuropilin 1 (NRP-1) which was first described as a receptor important for the guidance of developing neurons , is expressed on endothelial cells and acts as a co-receptor for vascular endothelial growth factor receptor 2 (VEGFR-2)/VEGF-A, thereby being implicated in VEGF-A mediated angiogenesis and vasculo-genesis (4).

Vascular endothelial growth factor (VEGF) is a master regulator of angiogenesis in normal and malignant tissues. There are various family members of VEGF and each of them exerts biological functions by binding to different receptors. VEGF plays important roles in prompting proliferation of endothelial cells**.** Overexpression of VEGF is observed in HCC (5).

Aim

To study the clinical usefulness of serum NRP 1 as a diagnostic marker for HCC.

Patients and methods

This cross-sectional study was conducted on 90 individuals admitted Department of Hepatology, Gastroenterology and Infectious Diseases in Sheikh Zayed Al-Nahian Hospital, Cairo, Egypt, during the period from February 2020 to February 2021.

The study protocol was approved by the ethical committee of Benha faculty of Medicine, Benha University. An informed written consent was obtained from all patients participating in this study after explaining the study measures in details.

Subjects included in this study were classified into the following groups:

- **Group I:** included 30 patients with HCC diagnosed by ultrasonography (U/S) and confirmed by Triphasic Computed Tomography (CT).
- **Group II:** included 30 patients with liver cirrhosis (LC) diagnosed by clinical, laboratory and U/S assessment.
- **Group III:** included 30 apparently healthy persons served as a control group.

Inclusion criteria

- Patients aging ≥ 18 years old.
- Patients with untreated HCC.

Exclusion criteria

- Patients with cardiovascular, chest or renal diseases.
- Alcoholic patients.
- Patients suffering from fever or autoimmune disease.
- Patients on warfarin therapy.
- Patients receiving chemotherapy, radiotherapy or local injection for the tumor.

All patients were subjected to full medical history taking, thorough clinical examination, U/S scanning of the abdomen, abdominal triphasic CT (to patients with HCC) and Laboratory research including:

Pelvi - abdominal ultrasonography:

i. Liver: size, texture, border, reflectivity, homogeneity, periportal thickening, hepatic veins and pattern.
ii. Portal vein: diameter, patency, direction of flow, respiratory variation and velocity by color Doppler assessment.
iii. Spleen: size, splenic vein diameter, collaterals.
iv. Presence of ascites and internal echoes.
v. Lymph nodes and extrahepatic spread.
vi. Portal hypertension and superior mesenteric vein patency.

CT or MRI

CT or MRI examination was done for diagnosis of HCC by characteristic vascular enhancement pattern (6).

Laboratory investigations as;

• Complete Blood Count (CBC).

• Liver biochemical testes: alanine transaminase (ALT) (U/L) and aspartate transaminase (AST) (U/L), seem bilirubin total and direct (mg/dl), serum albumin (gm/dl), Prothrombin Time (PT) in seconds, prothrombin concentration (PC) and international normalization ratio (INR).

• Kidney function testes: Serum creatinine (mg/dl) and blood urea (mg/dl). .

• Viral Markers: HBsAg and anti-HCV antibody using 3rd generation ELISA test.

• Serum AFP measurement:

The severity of disease was assessed by Child Pugh classification (7)**.**

Determination of the serum level of NRP 1 using enzyme linked immunosorbent assay (ELISA) methods. Human NRP1 ELISA Kit (Sunred Biological Co., Ltd).

The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human NRP1 in samples. NRP1 in the sample was added to monoclonal antibody Enzyme well which is pre-coated with Human NRP1 monoclonal antibody, incubation; then, NRP1 antibodies labeled with biotin were added, and combined with Streptavidin-HRP to form immune complex; then incubated and washed again to remove the uncombined enzyme. Then Chromogen Solution A, B added, the color of the liquid changed into the blue, and at the effect of acid, the color finally becomes yellow. The chroma of color and the concentration of the Human Substance NRP1 of sample were positively correlated

Statistical analysis

The clinical data were recorded on a report form. These data were tabulated and analysed using the computer program SPSS (Statistical package for social science) version 20 to obtain: Descriptive data: Descriptive statistics were calculated for the data in the form of: Mean, standard deviation, median and inter-quartile range (IQR) for quantitative data. Frequency and distribution for qualitative data were used. Analytical statistics: In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests after establishing their normality by K-S test (One-Sample Kolmogorov-Smirnov Test) of normality. ANOVA test (F value):-Used to compare mean of more than two groups of quantitative data. Inter-group comparison of categorical data was performed by using chi square test (X2-value) and fisher exact test (FET). Correlation analysis was used to assess the strength of association between two quantitative variables. The correlation coefficient defines the strength and direction of the linear relationship between two variables. ROC curve was used to detect validity of NRP1 to predict HCC and LC. A P value <0.05 was considered statistically significant (*) while >0.05 statistically insignificant P value <0.01 was considered highly significant (**) in all analyses.

Results

The current study was conducted on 30 cases suffered from HCC. Their mean age was 62.1±6.07 years. They included 23 males (76.7%) and 7 females (23.3%). In addition to 30 cases of LC, their mean age was 57.23±7.6 years. They included 20 males (66.7%) and 10 females (33.3%). A third group of 20 apparently healthy subjects were included as a healthy control. The HCC patients had a significantly higher age when compared to

cirrhotic group. No other significant differences were found between HCC and LC groups regarding other sociodemographic data (table 1).

The weight loss and abdominal pain were significantly more frequent in HCC group. Bleeding was significantly more frequent in LC group while the presence of pallor, jaundice, flapping tremors and lower limb edema did not differ significantly between both groups.

Regarding the laboratory investigations HCC patients showed significantly higher AFP concentration when compared to LC group. HB concentration was significantly higher in HCC group, while INR level show significantly higher level at LC group when compared to HCC group. Otherwise , no significant differences were found in FBG , creatinine and liver function tests among studied cases .

Ultrasonographic examination showed no significant differences between HCC and LC groups according to liver size, texture, spleen size, ascites and portal vein diameter. Radiological examination of HCC group showed that there were 16 single (53.3%) and 14 multiple (46.7%) hepatic focal lesions. The majority of focal lesions were located in right lobe (60%), left lobe in 6.7% and both lobes in 33.3%, there were 28 HCC patient (93.3%) positive for rapid wash out and all had arterial phase enhancement.

Most patients in HCC group were child class C (50%) followed by child class A (26.7%) , while in LC group most patients were child class C (60 %) followed by child class B (26.7%) . MELD score did not differ significantly between both groups. The grading of HCC patients according to OKUDA staging system showed that 46.7% of patients were stage III, 33.3% were stage II (33.3%) followed by stage I (20 %).

Neuropilin 1 (NRP1) level was significantly higher in HCC when compared to LC group. Also, NRP 1 level was significantly higher in HCC and LC groups when compared to control group (table: 2, figure:1).

Residents at rural areas had significantly higher NRP 1 level than others at urban areas, while no significant difference were found in NRP 1 level according to gender (table: 3).

There were no significant correlation between NRP 1 level with smoking, blood transfusion, bilharziasis, DM and HTN in LC and HCC groups (table: 4).

There were no significant correlation between NRP 1 level and Child classes in LC and HCC groups (table: 5).

There were no significant correlation between NRP 1 level and HFL features in HCC group (table: 6).

Neuropilin 1 (NRP 1) level showed significant direct correlation with TLC , AST, serum bilirubin and AFP level in LC group. Otherwise, no significant correlations were found in NRP 1 level with other studied data in LC (table: 7).

NRP 1 level showed significant inverse correlations with male sex and AFP level. Otherwise, no significant correlations were found in NRP 1 level with other studied data in HCC group (table: 8).

NRP 1 level showed significant direct correlation with TLC and serum bilirubin. Otherwise, NRP 1 level showed no significant correlation with other studied data in HCC and LC groups (table: 9).

The ROC curve for the diagnostic performance of serum alfa fetoprotein showed that at a cutoff value 388 ng/ml, sensitivity was 86.7%, specificity 73.3%, PPV 76.5 % and NPV 84.6%, AUC of 0.836, while for serum NRP1, ROC curve showed that at a cutoff value 4030 pg/ml, sensitivity was 93.3%, specificity 80%, PPV 82.4% and NPV 92.3%, AUC of 0.842. Comparing AUCs, revealed that combined AFP+NRP1 showed that sensitivity was 96.7%, specificity 70% , PPV 76.3% and NPV 95.5% ,AUC of 0.833, it was non significantly better than each marker alone (figure: 2).

Table 1: Comparison between the studied groups according to socio demographic data.

Personal data	HCC (30) No	%	LC (30) No	%	Statistical test(x2)	P value
Gender					0.74	0.39
Male	23	76.7	20	66.7		
Female	7	23.3	10	33.3		
Age (yrs) mean ±SD	62.1±6.07		57.23±7.6		St t= 2.74	0.008**
Occupation					0	1
Farmer	8	26.7	8	26.7		
Non farmer	22	73.3	22	73.3		
Residence					0.27	0.6
Rural	14	46.7	12	40		
Urban	16	53.3	18	60		
Special habits					0.098	0.75
Non smoker	23	76.7	24	80		
Smoker	7	23.3	6	20		

HCC: Hepatocellular carcinoma, LC: liver cirrhosis

Table (2): Comparison of Serum NRP1/pg/ml concentration among studied groups

NRP 1/pg/ml	HCC (30)	LC (30)	Control (30)	P^1	P^2	P^3	P^4
Mean ±SD	12715.67± 8309.34	5598.67± 7393.25	1698.2± 509.26				
Minimum	2360.0	1300.0	567.0	<0.001**	<0.001**	0.006**	0.001**
Maximum	27900.0	25900.0	2670.0				

NRP1: Neuropilin 1, HCC: hepatocellular carcinoma, LC: liver cirrhosis
P1: significance () HCC, LC and Control
P2: significance () HCC and control
P3: significance () LC and control
P4: significance () HCC and LC

Table (3). Comparison of NRP 1/pg/ml level according to gender and residence among all studied groups:

NRP 1/pg/ml	All studied groups (n=90)			
	Mean ±SD	**Minimum**	**Maximum**	**p**
Males(67)	6288.75± **7401.63**	567.0	27900.0	0.433
Females(23)	7783.91± **9079.05**	1300.0	27900.0	
Rural (38)	8878.68± **9802.04**	690.0	27900.0	0.021*
Urban (52)	5057.42± **5586.95**	567.0	24500.0	

NRP1: Neuropilin 1

Table (4): Comparison of NRP 1/pg/ml level according to history in LC and HCC groups **:**

NRP 1/pg/ml	LC and HCC N=60			
	Mean ±SD	**Minimum**	**Maximum**	**p**
No Smoker	8586.38± **8349.99**	1300.0	27900.0	0.33
Smoker	11220.77± **9439.85**	1590.0	27900.0	
No Blood Transfusion	9760.47± **9130.59**	1300.0	27900.0	0.39
Blood Transfusion	7631.18±**7029.19**	1680.0	21800.0	
No Bilharziasis	9382.98±**8697.39**	1300.0	27900.0	0.38
Bilharziasis	4866.67±**5147.76**	1590.0	10800.0	
No DM	9832.5±**8528.58**	1300.0	25900.0	0.32
DM	7300.0±**8734.21**	1890.0	27900.0	
No HTN	9317.2±**8682.29**	1300.0	27900.0	0.75
HTN	8357.0±**8470.99**	1890.0	27900.0	

NRP1: Neuropilin 1, DM: diabetes mellitus, HTN: hypertension, HCC: hepatocellular carcinoma, LC: liver cirrhosis

Table (5): Comparison of NRP 1/pg/ml level according to Child-Pugh classes in LC and HCC groups :

NRP 1/pg/ml		**LC and HCC N=60**			
		Mean ±SD	**Minimum**	**Maximum**	***p***
Child-Pugh	**A**	6623.33±**6099.61**	1300.0	24500.0	
	B	9295.33±**8636.38**	1680.0	24900.0	**0.51**
	C	10015.76±**9340.93**	1590.0	27900.0	

NRP1: Neuropilin 1, HCC: hepatocellular carcinoma, LC: liver cirrhosis

Table (6). Comparison of NRP 1/pg/ml level according to HFL features in HCC group:

NRP 1/pg/ml		**HCC N=35**			***p***
		Mean ±SD	**Minimum**	**Maximum**	
Multiplicity	**Single**	14906.25±**8590.0**	4090.0	27900.0	0.13
	multiple	10212.14±**7498.53**	2360.0	27900.0	
Site	**Right lobe**	14050.56±**8486.16**	3420.0	27900.0	0.32
	Left lobe	4930.0±**1187.94**	4090.0	5770.0	
	Both lobes	11870.0±**8274.38**	2360.0	27900.0	
Size (cm)	**<2**	-	-	-	0.77
	2-5	12538.46±**8284.72**	2360.0	27900.0	
	>5	13867.5±**9665.62**	5770.0	27900.0	
Echogenicity	**Hyperechoic**	10800.0±-	10800.0	10800.0	0.39
	Hypoechoic	4965.0±**799.03**	4400.0	5530.0	
	Isoechoic	13360.74±**8473.08**	2360.0	27900.0	
PV patency	**Patent**	11880.0±**8276.41**	3420.0	27900.0	0.51
	Thrombosed	13969.17±**8562.09**	2360.0	24500.0	
Homogenecity	**Non homogenous**	12825.0±**8625.13**	2360.0	27900.0	0.86
	Homogenous	12005.0±**6835.11**	3420.0	19700.0	

HCC: hepatocellular carcinoma, PV: portal vein

Table (7): Correlations of NRP 1/pg/ml level with other studied data in LC group :

	LC group NRP 1/pg/ml	
	r	***p***
Age (Yrs)	-.122-	.521
Sex	.315	.090
Residence	-.272-	.146
Smoking	.212	.261
History of blood transfusion	-.231-	.220
FBG (mg/dl)	-.136-	.475
Haemoglobin (g/dl)	-.266-	.156
TLC ($X10^6$/L)	.499**	.005
Platelets (($X10^6$/L)	.240	.201
Creatinine (mg/dl)	.242	.198
ALT (U/L)	.310	.096
AST (U/L)	.576**	.001
Bilirubin (mg/dl)	.651**	.000
Albumin (g/dl)	.081	.670
INR	-.234-	.213
PV diameter	.337	.068
AFP (ng/ml)	.488	.006**

LC: liver cirrhosis, NRP1: Neuropilin 1, FBS: fasting blood sugar, TLC: total leucocyte count, ALT: alanine aminotransferase, AST: aspartate aminotransferase, INR: international normalized ratio, PV: portal vein, AFP: Alpha-fetoprotein

Table (8): Correlations of NRP 1/pg level with other studied data in HCC group:

	HCC group NRP 1/pg	
	r	***p***
Age (yrs)	.227	.228
Sex	-.531-**	.003
Residence	-.352-	.056
Smoking	.046	.808
History of blood transfusion	-.065-	.734
FBG (mg/dl)	.333	.072
Haemoglobin (g/dl)	-.242-	.198
TLC ($X10^6$/L)	.076	.691
Platelets ($X10^6$/L)	-.340-	.066
Creatinine (mg/dL)	-.086-	.653
ALT (U/L)	-.267-	.154
AST (U/L)	-.058-	.762
Bilirubin (mg/dl)	.088	.643
Albumin (g/dl)	-.223-	.236
INR	.313	.092
PV diameter	.223	.237
AFP (ng/dl)	-.176	.353

HCC: hepatocellular carcinoma, NRP1: Neuropilin 1, FBS: fasting blood sugar, TLC: total leucocyte count, ALT: alanine aminotransferase, AST: aspartate aminotransferase, INR: international normalized ratio, PV: portal vein, AFP: Alpha-fetoprotein

Table (9): Correlations of NRP 1/pg level with other studied data in HCC and LC groups:

	HCC and LC NRP 1/pg	
	r	***p***
Age (yrs)	.178	.174
Sex	-.052-	.692
Residence	-.313-*	.015
Smoking	.128	.332
History of blood transfusion	-.113-	.391
FBG (mg/dl)	-.007-	.955
Haemoglobin (g/dl)	-.066-	.616
TLC ($X10^6$/L)	.280*	.030
Platelets ($X10^6$/L)	-.046-	.724
Creatinine (mg/dl)	.030	.817
ALT (U/L)	.088	.506
AST (U/L)	.228	.079
Bilirubin (mg/dl)	.296*	.021
Albumin (g/dl)	-.026-	.842
INR	-.040-	.762
PV diameter	.176	.178
AFP (ng/dl)	.006	.965

HCC: hepatocellular carcinoma, LC: liver cirrhosis, NRP1: Neuropilin 1, FBS: fasting blood sugar, TLC: total leucocyte count, ALT: alanine aminotransferase, AST: aspartate aminotransferase, INR: international normalized ratio, PV: portal vein, AFP: Alpha-fetoprotein

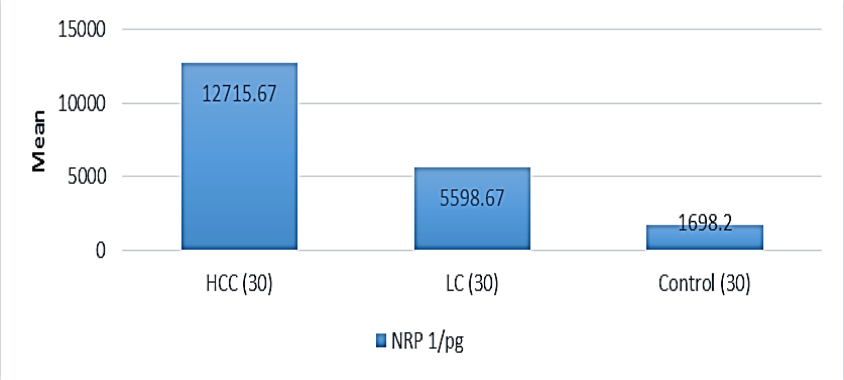

Fig (1): Comparison of Serum NRP 1/pg /ml concentration among studied groups

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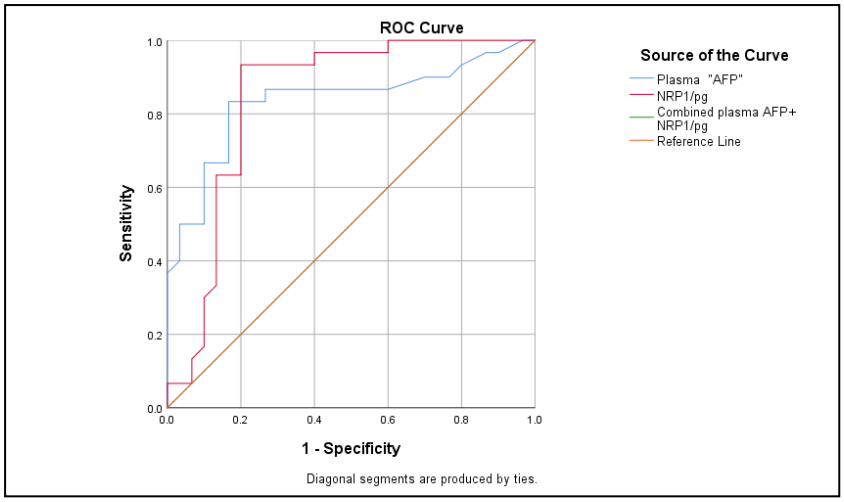

Figure (2) ROC curve of serum AFP, NRP 1 and combined markers for discrimination between HCC and LC cases.

Discussion

Neuropilin 1($NRP_{1)}$ has been found in several tumour, including melanoma, astrocytoma and neuroblastoma. It has been suggested that NRP_1 is more prevalently expressed in carcinomas (mainly of epithelial origin).

This study aimed to study the clinical usefulness of serum Neuropilin 1 as a diagnostic marker for hepatocellular carcinoma.

In the current study, NRP1 level was significantly higher in HCC when compared to LC group. Also, NRP 1 level was significantly higher in HCC and LC groups when compared to control group. In a report by another study (8), a high NRP-1 expression was detected in HCC endothelial cells lining the higher order vessels, whereas no or low expression was found in normal sinusoidal endothelial cells. They interpreted this finding by that NRP-1 was identified as a specific marker in determining the arterial or venous identity of blood vessels. The upregulation of NRP-1 in HCC is, therefore, consistent with the enhancement of arterial blood supply in HCC and supports a phenotypic switch of hepatic vasculature towards the arterial phenotype.

Another study (9) described that the upregulation of NRP-1 may be involved in the induction of local invasiveness of neoplasia and angiogenesis and have direct relevance to the progression of osteosarcoma. another study (10) suggested that the enhanced expression of NRP-1 may be not only associated with oncogenesis, but also with nasopharyngeal

cancer malignancy, and this molecule may be a targeting candidate for the treatment of nasopharyngeal malignancies. They suggested that the possibility that upregulated expression of NRP-1 may provide a selective advantage in the HCC tumorigenic processes.

In the current study, ROC curve of serum AFP showed AUC of 0.836, at cutoff value 388 ng/ml, sensitivity was 86.7% , specificity 73.3%, PPV 76.5% and NPV 84.6%, while for serum NRP1, ROC curve showed AUC of 0.842, at cutoff value of 4030 pg/ml, sensitivity was 93.3%, specificity 80%, PPV 82.4% and NPV 92.3%. Comparing AUCs revealed that combined AFP+NRP1 were non-significantly better than each marker alone.

A study**,** (11) demonstrated that serum NRP1 is a better diagnostic marker than AFP, with an area under the receiver operating characteristic curve of 0.971, compared with 0.862 for AFP. At an NRP1 cutoff of 68 pg/mL, NRP1 had a sensitivity of 93.7%, and a specificity of 98.7%. Combining NRP1 with AFP only slightly improved the diagnostic accuracy. The single use of NRP1 is a promising choice for the diagnosis of HCC. They noted that the most of the study subjects were of Han Chinese origin, and that the results need to be validated in people of other ethnicities.

The unfavorable prognostic role of NRP-1 in HCC was similar to its prognostic effect on nasopharyngeal carcinoma (12), bladder cancer (13), and osteosarcoma (9). However, another study (14) found that peri tumoral NRP-1 expression was significantly higher than that of the tumoral tissue, and high peri tumoral expression of NRP-1 prolonged time to recurrence (TTR) and extended OS of HCC patients. Moreover, peri tumoral NRP-1 expression was negatively correlated with peri tumoral hypoxia, tumoral and peri tumoral MVD (microvessel density), primary tumor size, and satellite lesions. These results indicated that abundant peri tumoral NRP-1 expression may play a positive role by providing an infertile soil for endothelial cells and primary tumor and subclinical metastatic tumor cells.

Furthermore, in colon cancer another study (15) reported that the gene expression levels of NRP-1 in the tumor were significantly decreased compared to those in the extra neoplastic tissues, and the preserved NRP-1 expression provides colon cancer patients with a better prognosis. These results suggested that the effect of NRP-1 may be cancer type specific and the abnormal expression of

NRP-1 may play key roles in tumor progression and tumor prognosis.

Kaplan-Meier survival curves was used to evaluate the effects of NRP-1 protein level on the prognosis of HCC patients (14). It was shown that overall survival (OS) and recurrence-free survival (RFS) were significantly lower in patients with high NRP-1 expression than in those with low NRP-1 expression. They indicated that NRP-1 expression was significantly correlated with HCC death and recurrence.

Despite the results of the study, there were some drawbacks as the study conducted on only 60 patients also all 60 patients were HCV infected and other causes of liver cirrhosis and HCC not included at the study, also comparison between NRP 1 level at HCC and other tumours as colon cancer, breast cancer and lung cancer not included.

The current study suggested that NRP-1 expression was significantly high in HCC. We suggested also that NRP-1 could be recognized as a novel biomarker for HCC. The role of Neuropilin1 in predicting the prognosis and treatment optimization is recommended to be evaluated through further clinical trials.

Conclusion

Serum NRP-1 was significantly high in HCC. It could be suggested as a potential diagnostic biomarker for HCC.

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