

Diagnostic Value of Basic Fibroblast Growth Factor and Platelet-Derived Growth Factor-AB Circulating Levels in Hepatitis C Virus-Associated Hepatocellular Carcinoma

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Abstract

Background: As a hypervascular tumor, Hepatocellular Carcinoma (HCC) is characterized by neovascularization which plays an important role in its growth and progression. Basic Fibroblast Growth Factor (bFGF) is a potent endothelial cell mitogen and angiogenic factor that was found to be elevated in different cancers. Platelet-Derived Growth Factor-AB (PDGF-AB) is another factor implicated in enhanced proliferation and migration of pericytes and is a potent stimulator of angiogenesis in many tumors.

Aim of Study: This study aimed to evaluate the circulating levels of bFGF and PDGF-AB and to examine their diagnostic significance in Hepatitis C Virus (HCV)-associated HCC.

Methods: This study included one hundred subjects divided into healthy controls (n=25), HCV patients (n=25), and HCV-associated HCC patients (n=50). The levels of bFGF, PDGF-AB, and Alpha-Fetoprotein (AFP) in addition to the activities of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase as well as total bilirubin and albumin concentrations were determined in sera of the enrolled subjects.

Results: Levels of bFGF and PDGF-AB were higher in HCC patients compared to controls and HCV patients and were found to be associated with increased susceptibility to HCV-associated HCC. Additionally, the diagnostic values of bFGF and PDGF-AB to distinguish HCC patients from non-cancerous patients were good, although they are still inferior to that of AFP. However, the combination of bFGF and PDGF-AB with AFP enhanced the efficacy of the latter.

Conclusion: Serum bFGF and PDGF-AB may contribute to the pathogenesis of HCV-associated HCC, and they seem to be good diagnostic biomarkers of HCC along with AFP.

Key Words: *Basic fibroblast growth factor (bFGF) – Platelet-derived growth factor-AB (PDGF-AB) – Alpha-fetoprotein (AFP) – Hepatocellular carcinoma (HCC) – Hepatitis C Virus (HCV).*

Introduction

HEPATOCELLULAR Carcinoma (HCC) is one of the commonest malignancies worldwide and a major cause of cancer-related mortality with an increased incidence rate at a great scale over the last few decades [1]. The major risk factors for HCC include chronic inflammatory diseases such as hepatitis B and C virus infection, exposure to carcinogens such as aflatoxins, and some genetic disorders such as hemochromatosis [2-4]. In Egypt, HCV infection is considered as the leading etiology for developing HCC [5].

In clinical practice, the most widely used non-invasive biomarkers for HCC screening and diagnosis is Alpha-Fetoprotein (AFP) [6]. However, this use is limited because of its elevation in some patients with other liver diseases while being normal in 15-30% of patients with advanced-stage HCC which decreases its specificity and sensitivity, respectively [7,8]. Therefore, there is an urgent demand to identify new markers that complement the limitations of AFP for more accuracy and feasibility of HCC screening and diagnosis.

Basic Fibroblast Growth Factor (bFGF), also known as FGF-2, is a member of FGFs family, the members of this family are polypeptides that function as mitogens and play important roles in embryonic development, tissue regeneration, wound repair, and hematopoiesis [9]. In HCC, bFGF was found to act as a mitogen for cell proliferation [10]. Moreover, bFGF is an extremely potent pro-angiogenic growth factor that exerts its activity by interacting with various endothelial cell surface receptors leading to cascade reaction that results in endothelial cell proliferation, migration, protease

production, and angiogenesis [11]. The latter plays a crucial role in HCC development and progression [12]. The importance of bFGF in HCC progression and metastasis have been highlighted by several studies; Tsunematsu et al., [13] found that bFGF was over-expressed in liver tissues of patients with chronic HCV and HCC compared to normal, this was reflected on its circulating level which was higher in patients than controls. Another study showed that plasma bFGF levels were increased in liver cirrhosis and raised with HCC development [14].

Another family that has a significant pro-angiogenic effect is Platelet-Derived Growth Factors (PDGFs). Of the five dimeric members constituting this family, PDGF-AB is the only heterodimer molecule [15]. Previous reports showed that PDGF-AB alone is not sufficient for targeting vascular pericytes for vascular stability. On the other hand, the combination of bFGF and PDGF-AB in an animal model for in vivo angiogenesis was able to stabilize the newly formed vasculature by recruiting pericytes [16-18].

Therefore, this study was conducted to assess the circulating levels of bFGF and PDGF-AB in HCV-associated HCC, to evaluate their diagnostic efficacy to detect the disease, and to explore the impact of combining AFP and these parameters for better screening and diagnosis of HCC.

Subjects and Methods

Study population:

Fifty patients with newly diagnosed HCV-associated HCC in addition to 25 HCV infected patients were recruited from early detection and cancer prevention unit, National Cancer Institute (NCI), Cairo University during the period from June 2017 to March 2019. HCC was diagnosed by histopathological evidence or with typical radiological findings in Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). Twenty-five apparently healthy subjects were included as a control group. HCC patients who received any line of treatment, patients with HBV infection, or those who received HCV antiviral therapy were excluded.

Informed written consent was obtained from all participants included in the study. This work was carried out in accordance with the Declaration of Helsinki for experiments involving humans, and the study protocol was approved by the Local Ethical Committee of NCI.

Five ml of overnight fasting venous blood samples were collected from all subjects; one part of the sample (1.5ml) was collected on potassium-EDTA containing tubes and was used to determine the complete blood picture by KX-21N hematology analyzer (Sysmex, Hyogo, Japan). The other part (3.5ml) was collected on plain vacutainer tubes, left to clot and centrifuged at 3000xg for 10min to obtain sera used for biochemical analyses.

Biochemical analyses:

Serum activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) alongside the total bilirubin and albumin concentrations were determined using available commercial kits provided by Biodiagnostics (Giza, Egypt).

AFP, bFGF, and PDGF-AB levels:

Serum levels of AFP (Cat# CSB-E04770h), bFGF (Cat# CSB-E08000h), and PDGF-AB (CSB-E04701h) were determined by commercial sandwich Enzyme-Linked Immunosorbent Assay (ELISA) kits according to the manufacturer's instruction (Cusabio, TX, USA). The sensitivity of the assays was 1.332ng/ml for AFP, 0.39pg/ml for bFGF, and 7.8pg/ml for PDGF-AB with an intra-, and inter-assay coefficients of variation (CV) of <8% and <10%, respectively for the assays. The test was performed on ChroMate® microplate reader (Awareness Technology Inc., FL, USA).

Statistical analysis:

Data analysis was implemented by using IBM SPSS advanced statistics version 25 (IBM Corp, NY, US). For categorical data, the descriptive measures were presented in frequencies and percentages. For quantitative data, Shapiro-Wilk test was performed to determine the type of data distribution, normally distributed data were expressed as mean \pm SD and non-normally distributed data were expressed as median and interquartile range (25th and 75th percentile). Continuous variables were compared between groups using independent Student's *t*-test, ANOVA followed by Tukey's post hoc for multiple comparisons or Kruskal-Wallis test followed by Dunn test as a post hoc for multiple comparisons as appropriate. Logistic regression analysis was used to assess the strength of the association between circulating levels of AFP, bFGF and PDGF-AB, and the susceptibility to HCV-associated HCC. To determine the diagnostic value of serum bFGF, and PDGF-AB levels, Receiver Operating Characteristic (ROC) curve analysis was performed. All *p*-values were 2-sided and a *p*-value ≤ 0.05 was considered significant.

Results

General characteristics of study population:

Table (1) shows the basic characteristic of the studied groups. There was no statistically significant difference between all subjects in age, sex distribution, and hemoglobin concentration.

Compared to the control group, HCV patients had considerably elevated total leukocyte count ($p=0.036$) and higher serum activities of ALT ($p=0.002$), and AST ($p=0.001$). In the same context, HCC patients showed significant elevation in serum activities of ALT ($p=0.001$), AST ($p<0.001$), and ALP ($p=0.001$) in addition to total bilirubin ($p<0.001$), and AFP levels ($p=0.009$). In contrast, HCV and HCC patients showed a significant decrease in albumin concentration ($p<0.001$). Further, HCC group had significantly lower counts of RBCs and platelet ($p<0.001$ and $p=0.016$, respectively) compared to the control group.

In comparison with HCV patients, HCC patients had significant increase in serum activity of ALP ($p<0.001$), total bilirubin concentration ($p=0.007$), and AFP level ($p<0.001$), whereas they showed significant decrease in total leukocyte count ($p=0.034$), RBCs count ($p=0.002$), and platelet count ($p=0.007$).

Additionally, more than 75% of HCC patients had Child-Pugh class C while 44% of HCV infected patients were Child-Pugh class B. Moreover, about two-thirds of HCC patients had a tumor >5 cm in size.

Circulating levels of bFGF and PDGF-AB among different groups:

Fig. (1) shows that HCV patients had higher serum PDGF-AB level compared to the control

group (1413 1. 1 0pg/ml vs. 3 699.40pg/ml, $p=0.034$) while HCC patients showed significant elevation in serum levels of both bFGF and PDGF-AB (16.54 pg/ml vs. 1.45pg/ml and 24432.67pg/ml vs. 3699.40 pg/ml; respectively, $p<0.001$). Similarly, HCC patients had a significant increase in serum bFGF level (16.54pg/ml vs. 8.33pg/ml, $p=0.001$) and PDGF-AB level (24432.67pg/ml vs. 14131.10 pg/ml, $p<0.001$) in comparison with HCV patients.

bFGF and PDGF-AB as risk factors for HCV-associated HCC:

The results of the binary logistic regression analyses performed to test the associations of AFP and bFGF circulating levels with the risk to develop HCV-associated HCC are shown in (Table 2). It was found that serum levels of the three parameters were associated with an increased risk of HCC and the results remained significant after adjusting for age, sex, HCV viral load, and Child-Pugh score as potential confounders.

Efficacy of bFGF and PDGF-AB as potential diagnostic biomarkers for HCC:

Fig. (2) illustrates the ROC curves of AFP, bFGF, and PDGF-AB serum levels. Although AFP showed the highest diagnostic ability to discriminate HCC patients with an Area Under Curve (AUC) of 0.982 ($p<0.001$) and an optimal cut-off point of 79ng/ml that could yield sensitivity and specificity of 72% and 100%, respectively, both bFGF and PDGF-AB showed good diagnostic efficacy. The AUC of PDGF-AB was 0.881 ($p<0.001$) and a cut-off point of 16554pg/ml that is associated with 80% sensitivity and 78% specificity. On the other hand, the AUC of bFGF was 0.812 ($p<0.001$) and an optimal cut-off point that associated with sensitivity and specificity of 76% and 78%, respectively.

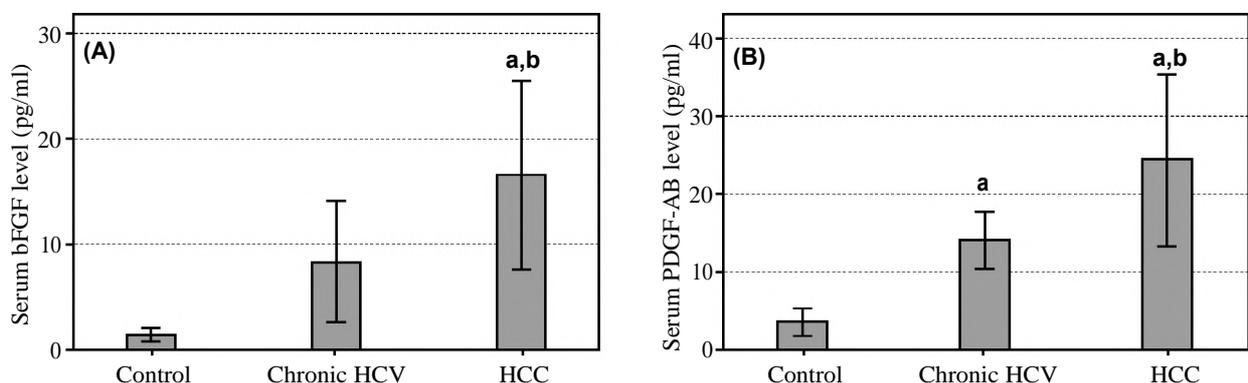
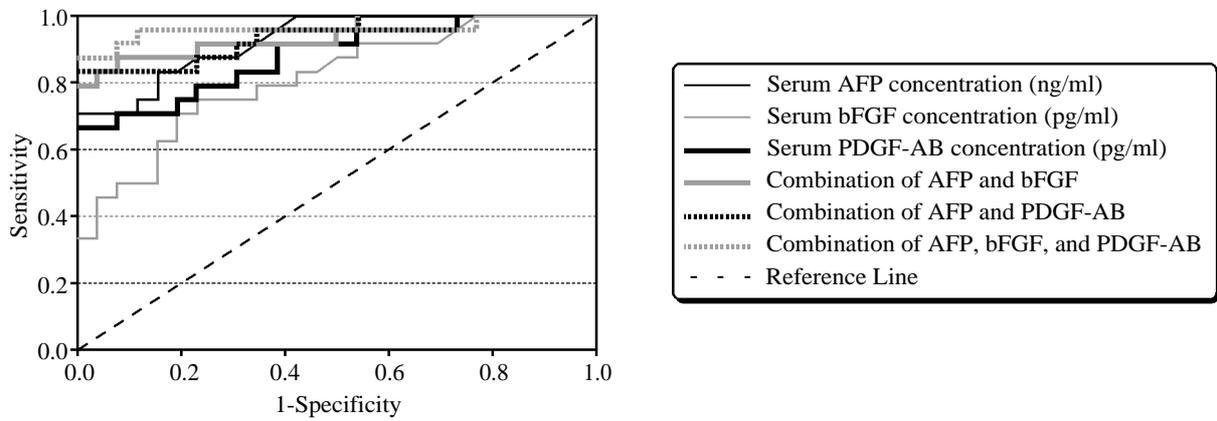


Fig. (1): Serum levels of (A) Basic fibroblast growth factor (bFGF) and (B) Platelet-derived growth factor-AB (PDGF-AB) in different studied groups. In multiple comparisons, a: $p<0.05$ vs. control, and b: $p<0.05$ vs. chronic HCV. Bar length represents mean value for each group, with error bars depicting standard deviation.



Maker	AUC	95% CI		p-value	Cut-off	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Accuracy (%)
		Lower Bound	Upper Bound							
AFP (ng/ml)	0.928	0.862	0.994	<0.001	79	72	100	100	78.12	86
bFGF (pg/ml)	0.812	0.694	0.930	<0.001	11.71	76	78	77.55	76.47	77
PDGF-AB (pg/ml)	0.881	0.788	0.975	<0.001	16554	80	78	78.43	79.59	79
Combination of AFP and bFGF	0.942	0.877	1.000	<0.001	-	88	92	91.67	88.46	90
Combination of AFP and PDGF-AB	0.933	0.859	1.000	<0.001	-	84	100	100	86.21	92
Combination of AFP, bFGF, and PDGF-AB	0.960	0.896	1.000	<0.001	-	96	88	88.90	95.65	92

Fig. (2): Receiver Operating Characteristic (ROC) curves of A) AFP, bFGF, PDGF-AB and their combinations to discriminate HCC patients from healthy controls and chronic HCV patients.

AFP : α -fetoprotein.
 bFGF : Basic Fibroblast Growth Factor.
 PDGF-AB : Platelet-Derived Growth Factor-AB.
 AUC : Area Under Curve.
 95% CI : 95% Confidence Interval.
 Sens. : Sensitivity.
 Spec : Specificity.
 PPV : Positive Predictive Value.
 NPV : Negative Predictive Value.

Table (1): General characteristics of study population.

	Control (n=25)	Chronic HCV (n=25)	HCC (n=50)	p-value
Age (years)	55.20±2.59	54.67±1.91	59.00 (54.00-60.75)	0.051
Gender (F/M)	15 (60)/10 (40)	12 (48)/13 (52)	21 (42)/29 (58)	0.742
Total leukocyte count (cell/ μ l)	6578.60±1292.97	8761.81±2010.64 ^a	7437.00±1482.24 ^b	0.011
RBCs count (million/ μ l)	4.84±0.30	4.00 (3.00-5.00)	3.00 (3.00-4.00) ^{a}	<0.001
Platelets count/ μ l (\times 1000)	205.40±37.17	183.05±23.52	147.00 (90.75-172.25) ^{a}	0.002
Hb concentration (g/dl)	14.52±1.41	13.00 (13.00-14.00)	13.00 (12.00-14.00)	0.257
ALT (U/L)	27.80±2.17	98.24±29.61 ^a	101.17±48.63 ^a	0.001
AST (U/L)	28.20±5.93	87.00 (62.50-169.00) ^a	114.17±26.91 ^a	<0.001
ALP (U/L)	42.60±14.88	73.10±14.34	175.50 (142.50-284.50) ^{a}	<0.001
Albumin (g/dl)	4.40±0.49	3.88±0.46	2.72±0.40 ^{a}	<0.001
Total bilirubin (mg/dl)	0.86±0.23	2.00 (1.00-2.50)	3.00 (2.00-7.25) ^{a}	<0.001
HCV viral load (U/L) X 1000	-	761.73 (460.96-1020.90)	688.24±374.62	0.233
Child-Pugh score:				
A	-	5 (20)	4 (8)	0.044
B	-	11 (44)	8 (16)	
C	-	9 (36)	38 (76)	
Tumor size:				
<5cm	-	-	19 (38)	
≥5cm	-	-	31 (62)	
AFP (ng/ml)	7.20±3.11	31.67±20.03	163.50 (49.75-304.50) ^{a}	<0.001

Data are expressed as mean \pm SD for Gaussian data, median (interquartile range) for non-Gaussian data, and frequency (percentage) for categorical data.
 HCV : Hepatitis C Virus.
 HCC : Hepatocellular Carcinoma.
 RBCs : Red Blood Corpuscles.
 Hb : Hemoglobin.
 ALT : Alanine aminotransferase.
 AST : Aspartate aminotransferase.
 ALP : Alkaline Phosphatase.
 AFP : α -fetoprotein.
 In multiple comparisons, ^a: $p < 0.05$ vs. control, and ^b: $p < 0.05$ vs. chronic HCV.

Table (2): Binary logistic regression analysis of AFP, and b-FGF as risk factors of HCV associated HCC.

Variable	Crude OR (95% CI)	<i>p</i> -value	†Adjusted OR (95% CI)	<i>p</i> -value
AFP (ng/ml)	1.052 (1.012-1.095)	0.011	1.091 (1.018-1.169)	0.014
bFGF (pg/ml)	1.156 (1.048-1.275)	0.004	1.389 (1.046-1.844)	0.023
PDGF-AB (pg/ml)	1.000 (1.000-1.001)	0.003	1.000 (1.000-1.001)	0.003

AFP : a-fetoprotein.

b-FGF : Basic Fibroblast Growth Factor.

† : Adjusted for age, sex, HCV viral load, and Child-Pugh score as potential confounders.

OR : Odd Ratio.

95% CI : 95% Confidence Interval.

Combinational ROC analysis indicated that the combination of the AFP with bFGF and/or PDGF-AB increased the values of sensitivity, and Negative Predictive Value (NPV). The highest increase resulted from the combination of the three parameters which yielded 96% sensitivity and 95.65% NPV followed by the combination of AFP and bFGF that resulted in sensitivity and NPV of 88% and 88.46%, respectively while the combination of AFP and PDGF-AB came last with 84% sensitivity and 86.21% NPV.

Discussion

Early and accurate diagnosis of HCC is necessary to improve the clinical outcome because of the high mortality and morbidity rates of the disease [19]. Despite the use of AFP as a biomarker for HCC, its sensitivity and specificity are far from satisfactory. Thus and because of the lack of diagnostic biomarkers, only 30%-40% of HCC patients are diagnosed in time, possibly receiving a curative intervention [20]. Accordingly, this study was designed to explore the circulating levels of bFGF and PDGF-AB in HCV-associated HCC, to assess their utility as potential diagnostic markers of HCC, and to determine the possibility of combining AFP and growth factors as an effective approach to improve the diagnosis of the disease.

In this study, serum activities of ALT, AST, and ALP as well as the total bilirubin concentration were elevated with the decrease of albumin level in HCV and HCC groups, as expected, which is in line with the results of previous studies [21,22]. In HCC, this may reflect the damage of the adjacent hepatocytes as a direct result of tumor growth or the damage of the more remote liver cells caused by the interference with their blood supply or venous drainage. It may also be due to continuing liver cell necrosis in those with concomitant active cirrhosis or chronic active hepatitis [22].

In the current work, AFP was significantly elevated in sera of HCC patients, as expected, compared to HCV patients and normal controls. This is consistent with previous studies that reported

the significant increase of AFP in HCC patients compared to cirrhosis, hepatitis and healthy controls [23-25]. AFP is a glycoprotein derived from embryonic endoderm tissue cells. Serum AFP level in the fetus is high and decreases gradually after birth to the level of adults mainly due to the loss of the ability of mature hepatocytes to synthesize AFP, however, liver cancer cells can regain the ability to synthesize AFP and this can explain the elevation of its level in sera of HCC patients [26,27].

Regarding bFGF, there was a dramatic rise in its level in HCC compared to HCV and control groups which concurs with the results reported by Joo et al., [28] who found that bFGF levels were higher in HCC patients than patients with other liver diseases (chronic hepatitis, and liver cirrhosis). Further, Hsu et al., [29] reported that bFGF was markedly increased in sera of cirrhotic and HCC patients as compared to those with chronic hepatitis or healthy individuals, however, the authors did not find a significant difference in bFGF levels between cirrhotic and HCC groups.

Additionally, a significant increase in serum level of PDGF-AB was observed in HCC group compared to HCV and control groups which echo the results of previous studies carried out on different cancer types such as pleural mesothelioma, colorectal cancer, in addition to head and neck cancer [30-32] and seems to confirm the hypothesis that cancer tissue is a PDGF-AB source.

Further, this study showed that the elevated levels of bFGF and PDGF-AB were associated with increased the risk to develop HCV-associated HCC. This can be explained in light of being HCC one of the most vascular solid tumors in which angiogenesis plays an important role in its development, progression, and metastasis [33]. Because HCC cells display rapid growth, they are consequently in need for high oxygen and nutrient supply and to fulfill this aspiration they induce the formation of new blood vessels [34]. To do so, tumors secrete a number of angiogenic growth factors, such as Vascular Endothelial Growth Factor (VEGF), PDGF, and bFGF alongside down-

regulation of the expression of angiogenesis inhibitors. This activates extracellular cells and basement membranes to remodel existing vessels and stimulates the release of endothelial progenitor stem cells from the bone marrow to form new vessels [35].

Moreover, both bFGF and PDGF-AB exert their biologic actions via activation of specific tyrosine kinases receptors. There are five known FGF Receptors (FGFR) named FGFR1-5; bFGF binds only to FGFR1, 2 and 4 [9]. To initiate signaling, bFGF interacts with cell surface Heparan Sulfate Proteoglycans (HSPGs) and FGFR in a ternary complex resulting in activation of downstream signaling pathways, including Ras-Mitogen Activated Protein Kinase (MAPK) and Phosphoinositide 3-Kinase (PI3K)-protein kinase Akt/Protein Kinase B (PKB) pathways [36]. Similarly, the biological activity of PDGFs is linked to two receptors, PDGFR- α and - β [37]. The binding of PDGF-AB causes dimerization and autophosphorylation of the receptors [38]. The phosphorylated residues in the receptors bind signaling molecules such as tyrosine kinases of the Src family, GTPase Activating Protein (GAP), and PI3K resulting finally in activating Ras and the Erk MAPK pathway [39]. Taken together, the activation of these signaling pathways enhances cell proliferation and survival, as well as cell migration.

Herein, the diagnostic value of bFGF and PDGF-AB was examined to discriminate HCV-associated HCC patients from non-cancerous patients. The results showed that both parameters were good diagnostic markers which seem to be in line with previous studies that reported the value of bFGF and PDGF-AB in the detection of different types of cancer [40-43]. However, AFP in this study was found to have a superior diagnostic impact to detect HCC over bFGF and PDGF-AB although the combinational analysis enhanced the efficacy of the former.

In conclusion, this works pointed out that the high levels of bFGF and PDGF-AB are associated with higher risk to develop HCV-associated HCC and establishing their serum levels might be of diagnostic importance together with AFP although the latter still has a superior value.

Conflict of interest:

No conflict is assumed by all authors.

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القيمة التشخيصية لمستويات عامل نمو الخلايا الليفية القاعدي وعامل النمو المستمد من الصفائح الدموية-AB في سرطان الكبد الخلوي المصاحب لإلتهاب الكبد الفيروسي (سى)

الخلفية: كونه ورم مفرط التشعب الدموي، يتميز سرطان الكبد الخلوي بنمو خبيث للأوعية الدموية والتي تلعب دوراً مهماً في نموه وتقدمه. إن عامل نمو الخلايا الليفية القاعدي (bFGF) هو عامل فعال في تحفيز إنقسام الخلايا البطانية كما أنه محفز لتكوين الأوعية الدموية والذي وجد أنه يزداد في العديد من السرطانات. عامل النمو المشتق من الصفائح-AB (PDGF-AB) هو عامل آخر متورط في تعزيز إنتشار وهجرة البيرسيات وهو أيضاً محفز قوى لتولد الأوعية في العديد من الأورام.

الهدف: هدفت هذه الدراسة إلى تقييم مستويات bFGF و PDGF-AB ودراسة أهميتها التشخيصية في سرطان الكبد الخلوي المصاحب للإصابة بإلتهاب الكبد الفيروسي (سى).

المنهجية: إشمطت هذه الدراسة على مائة مشارك قسموا إلى مجموعة ضابطة، ومرضى مصابون بإلتهاب الكبد الفيروسي (سى)، ومرضى مصابون بسرطان الكبد الخلوي. تم تحديد مستويات bFGF و PDGF-AB والألfa فيتوبروتين (AFP) بالإضافة إلى فعالية إنزيمات الكبد (ناقل أمين الألانين، ناقل أمين الأسبرتات والفوسفاتيز القلوي) وكذلك تركيز البيليروبين الكلي والألبومين في أمصال دم الأشخاص المشاركين.

النتائج: كانت مستويات bFGF و PDGF-AB أعلى في مرضى سرطان الكبد الخلوي مقارنةً مع المجموعة الضابطة ومرضى إلتهاب الكبد الفيروسي (سى)، كما وجد أن إرتفاع bFGF و PDGF-AB قد إرتبط بزيادة القابلية للإصابة بسرطان الكبد الخلوي المصاحب للإلتهاب الكبدي الفيروسي (سى). بالإضافة إلى ذلك، كانت القيمة التشخيصية ل bFGF و PDGF-AB لتمييز مرضى سرطان الكبد الخلوي عن الأشخاص غير المصابين بالسرطان جيدة، على الرغم من أنها لا تزال أدنى من تلك لدى AFP. ومع ذلك، فإن الجمع بين bFGF و PDGF-AB مع AFP يعزز من فعالية هذا الأخير.

الخلاصة: قد يساهم مستوى مصل الدم ل bFGF و PDGF-AB في التسبب في حدوث سرطان الكبد الخلوي المصاحب لإلتهاب الكبد الفيروسي (سى)، ويبدو أنهما مؤشران بيولوجيان تشخيصيان جيدان لسرطان الكبد الخلوي إلى جانب AFP.