Evaluation of the Effectiveness of Serum Golgi Protein 73 as Tumor Marker for Diagnosis of Hepatocellular Carcinoma

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Abstract: Introduction: Hepatocellular carcinoma (HCC) is common throughout the world. Most HCCs are diagnosed at an advanced stage so that there is an urgent need to find new methods for screening and surveillance of individuals at risk. Serum Golgi protein 73 (GP73) is a novel and promising biomarker for detection of HCC. The aim of this study was evaluation of the effectiveness of serum Golgi protein 73 as tumor marker for diagnosis of HCC. **Material and methods:** This study was performed on 125 subjects; they were divided into 3 groups. 50 patients with HCC, 50 patients with liver cirrhosis and 25 healthy subjects as a control. All subjects were subjected to full history taking and complete clinical examination, laboratory investigations, serum alpha-fetoprotein **(**AFP) and GP73 (by ELISA), abdominal ultrasonography and triphasic CT or magnetic resonance imaging for patients with hepatic focal lesion(HFL). Patients who had a prior locoregional therapy, systemic therapy, any surgical intervention and patients with any other hepatic or non hepatic malignancy were excluded from the study. **Results:** The serum levels of AFP and GP73 were significantly elevated in patients with HCC compared to cirrhotic patients and controls (P<0.001). A significant correlation was found between serum GP73 level and prognostic markers of liver cirrhosis i.e. (Bilirubin, creatinine, INR and AFP and child pugh score) and more aggressive tumor characters (Tumor size, number and vascular invasion) (P<0.001). On the other hand there was no significant correlation between AFP and number and overall size of focal lesions (P>0.05).The sensitivity and specificity of GP73 for HCC were superior to those of AFP.GP73 had a sensitivity of 88% and a specificity of 84% at the optimal cut-off value of 5.7ng/ml with accuracy of 84.3%. While, AFP had a sensitivity of 76.3% and a specificity of 76.2% at the optimal cut-off value of 23.12 ng /ml with accuracy of 81.7% for detection of HCC. On combining both AFP and GP73 values for selective detection of HCC, they had a sensitivity of 88%, specificity of 96 %. with accuracy of 92 % which is better than each of them alone. **Conclusions**: serum GP 73 can be used as useful biomarkers to confirm the diagnosis of HCC especially if combined with AFP and correlated with the aggressiveness of the tumor.
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1. Introduction

Hepatocellular carcinoma is a global health problem. The incidence of HCC has continued to rise in recent years and considered the fifth most common cancer and the third leading cause of cancer death worldwide [1-2]. This increase has been attributed to the rising number of hepatitis B and C viral infections, alcohol-induced liver diseases and metabolic syndrome [3].Since HCC is among the cancers with the worst prognosis, early diagnosis is the key for effective treatment. The use of serological markers in patients at the highest risk for developing HCC may thus decrease HCC mortality and reduce medical costs. [4-5]

Alpha-fetoprotein has been used as a serum marker for HCC for many years, but the clinical value of AFP is challenged in recent years due to low sensitivity and specificity [6-7]**.**In the search for serum markers for HCC, several investigators have recently focused on GP73 (also known as Golgi membrane protein 1) which is a 400-amino acid, 73-kDa transmembrane glycoprotein that normally resides within the *cis*-Golgi complex.[8-10]. GP73 is a novel and promising biomarker for HCC. However, there are few reports on the pattern of GP73 expression in HCC and the relationship of this expression to clinicopathologic features of patients.[11]Although the GP73 functions and the mechanisms of regulation in normal and neoplastic tissues are still not completely understood; many studies have identified it as a potential biomarker for HCC.[12] Subsequent studies showed that the GP73 serum level is elevated in diverse viral and non-viral liver diseases, including hepatitis, cirrhosis and HCC, and also in non-liver malignances.[13] in a recent study by **Jia *et al*.** [14] Serum GP73 is dramatically elevated in patients with HCC, and the sensitivity and specificity of GP73 for HCC might be superior to those of AFP.

Aim of the Work

To evaluate the effectiveness of serum GP 73 as a tumor marker for diagnosis of HCC.

2. Patients and Methods

This study was performed on 125 subjects from the outpatient clinic and inpatient of Gastroenterology and Hepatology department at Ain Shams University Hospital during the period from January 2013 to January 2014.

The subjects were classified to three groups:

Group I: 50 patients with HCC.

Group II: 50 patients with liver cirrhosis without HCC.

Group III: 25 normal individuals as a control group.

Inclusion criteria:

1. Age >18 years old.
2. Liver cirrhosis was diagnosed based on physical examination, laboratory tests, abdominal ultrasonography or computed tomography (CT) scan, and liver biopsy or fibroscan when possible.
3. Hepatocelluler carcinoma was diagnosed based on at least one of the following criteria in the guidelines of clinical diagnosis and staging for hepatocellular carcinoma.[15]

- Hepatic space-occupying lesion with a serum AFP level ≥ 400 ng/ml.
- Hepatic space occupying lesions with arterial phase enhancement and rapid washout in portovenous phase in triphasic CT or magnetic resonance imaging.
- Liver biopsy in some patients.

Exclusion criteria: all patients who had a prior locoregional therapy, systemic therapy and/or any surgical intervention (liver resection or transplantation) were excluded from the analysis. Also Patients with any other hepatic or non hepatic malignancy.

An informed consent was obtained from all subjects involved in the study.

All subjects were subjected to the following:

1. Full history taking and complete clinical examination.
2. Routine laboratory investigations including: complete blood count, kidney function tests (serum creatinine and blood urea nitrogen), liver function tests (serum alanine aminotransferase, serum aspartate aminotransferase, serum alkaline phophatase, total and direct bilirubin, serum albumin and prothrombin time), viral markers (HCV Ab and HBsAg).
3. Serum AFP: determined using a commercially available ELISA kit (Cobus Core; Roche Diagnostics,Basel, Switzerland).
4. Serum Golgi protein 73 (GP73): determined by ELISA Kit for GP73 provided by Glory Science Co., Ltd, USA. The kit is a sandwich enzyme immunoassay for the in vitro quantitative measurement of GP73 in human serum, plasma, tissue homogenate and cell culture medium.[16]
5. Radiological investigations include abdominal ultrasonography and triphasic CT or magnetic resonance imaging for patients with HFLs.
6. Liver biopsy when possible.

Statistical methods

The SPSS 10.0 for windows was used for data management and analysis and the Microsoft power point for charts. Quantitative data were presented as mean ±SD. For comparison of the two groups' mean, the Student's t-test was used, while for the comparison of the three groups' mean, one way analysis of variance (ANOVA) was used followed by Post Hoc test. Non parametric quantitative data were expressed as median (range), Kruskall -wallis and Mann- whitney tests were used for comparison of means. Qualitative data was expressed as frequency and percentage. Association between qualitative data was done using Chi- square test. Risk estimate was done by odds ratio. Receiver operating curve (ROC curve) was used to detect the best cut off value. *P* value was considered significant at 0.05.

3. Results

The ages of the studied subjects ranged between 30-74 years with mean of 49.5 ± 14.21. As regards the sex of the study population 112 subjects (74.67 %) were males, while 38 subjects (25.33%) were females. The patients in the HCC group were 38 males and 12 females, their ages ranged from 38-74 with a mean of 59.7±8.14 years, the patient in the cirrhotic group were 38 males and 12 females, their ages ranged from 45-65 with a mean of 54.64±5.55 years. On the other hand the subjects in the control group were 18 males and 7 females, their age ranged from 30-67 with a mean of 53.24±12.12 years. There was no statistical significant difference between the three groups as regards age and sex (*P*>0.05).

Comparing the three groups regarding the laboratory data revealed a significant difference between them as regards all laboratory data (<0.001). **(Table 1)**

Comparing the three groups regarding GP73 and AFP revealed a statistically significant difference between them where the highest values in HCC group and lowest values in control group (<0.001). **(Tables 2, 3)**

As regards the modified Child-Pugh score, comparison between group I and II revealed

statistically no significant difference (p>0.05).**(Table 4)**

Comparing the number of HFLs in group I, 18 patients had one focal lesion, 18 had two focal lesions, 12 had three focal lesions and two patients had four focal lesions. **(Table 5)**

A significant correlation was found between GP73 and T.bilirubin, creatinine, INR and AFP and child pugh score **(**<0.001**). (Table 6)**

As regards vascular invasion, there was a positive significant correlation between both AFP and GP73 and portal vein thrombosis (PVT) (P<0.001). **(Table 7 and 8)**

A significant correlation was found between GP73 and number and overall size of HFLs (P<0.001). **(Table 9).** On the other hand there was no significant correlation between AFP and number and overall size of HFLs (P>0.05)**. (Table 10)**

At the best cut off value 5.7 ng/ml, GP73 had a sensitivity of 88%, a specificity of 84%, positive predictive value (PPV) of 84.6% and negative predictive value (NPV) of 87.5%. The accuracy of the test was 84.3% for detection of HCC. (**Table 11 & Figure 1)**

At the best cut off value 23.12 ng/ml, AFP had a sensitivity of 76.3%, specificity of 76.2%. The PPV was 76% and the NPV was 76%. The accuracy of the test was 81.7% for detection of HCC. (**Table 12**& **Figure 2)**

On combining both AFP and GP 73 values for selective detection of HCC, they had a sensitivity of 88%, specificity of 96 %. The PPV was 95.7%, the NPV was 88.8% and the accuracy of 92 % which is better than each of them alone. (**Table 13)**

Table (1): Comparison between the three groups regarding the laboratory data

	Group I (n=50)	Group II (n=50)	Group III (n=25)	ANOVA	
	Mean ± SD	Mean ± SD	Mean ± SD	F	P value
AST (U/L)	77.64 ± 49.32	58.48 ± 19.49	17.72 ± 5.47	24.72	<0.001
ALT (U/L)	57.08 ± 26.96	46.12 ± 27.51	28.92 ± 9.11	9.65	<0.001
T.bili (mg/dl)	4.79 ± 4.25	3.66 ± 3.60	0.74 ± 0.23	10.51	<0.001
Albumin (gm/dl)	2.42 ± 0.63	2.62 ± 0.49	4.60 ± 0.56	115.2	<0.001
Alk.P (U/L)	252.08 ± 171.49	200.76 ± 124.96	68.88 ± 14.30	14.81	<0.001
BUN (mg/dl)	19.64 ± 16.41	26.84 ± 16.51	13.68 ± 4.20	5.82	<0.01
Creat. (mg/dl)	0.98 ± 0.49	1.42 ± 0.95	0.85 ± 0.21	5.46	<0.01
INR	1.74 ± 0.47	1.59 ± 0.31	0.84 ± 0.19	49.71	<0.001
Hb (g/dl)	10.71 ± 1.53	10.19 ± 1.81	13.04 ± 0.79	27.86	<0.001
TLC (cell/mm^3)	4.98 ± 4.63	3.12 ± 0.96	6.97 ± 1.42	11.38	<0.001
Platelet(/mm)	97.72 ± 25.99	100.72 ± 39.07	260.28 ± 67.80	95.41	<0.001

Table (2): comparison between the three groups as regards GP73

Groups	GP 73(ng/ml)		ANOVA	
	Range	Mean ± SD	F	*P*-value
Group I	1.2 - 34	11.25 ± 9.50	20.71	<0.001
Group II	1.3 - 11.3	3.78 ± 2.07		
Group III	0.1 - 7.8	1.33 ± 1.46		
TUKEY'S Test				
I&II	I&III	II&III		
<0.001	<0.001	>0.05		

Table (3): Comparison between the three groups as regards AFP

Groups	AFP(ng/ml)			Kruskal-Wallis Test	
	Range	Median	Interquartile Range	X^2	*P*-value
Group I	1.8-200000	63	981.46	26.40	<0.001
Group II	1.9-63	3.77	5.91		
Group III	1.6-5	3.5	1.10		

Table (4): Comparison between group I and II as regards modified Child-Pugh score

Child	Groups						Chi-Square	
	Group I		Group II		Total			
	N	%	N	%	N	%	X^2	*P*-value
A	4	8.00	2	4.00	6	6.00	2.078	>0.05
B	20	40.00	30	60.00	50	50.00		
C	26	52.00	18	36.00	44	44.00		
Total	50	100.00	50	100.00	100	100.00		

Table (5): Number of focal lesions in patients with HCC

Number of HFL	No of patients	%
1	18	36.00
2	18	36.00
3	12	24.00
4	2	4.00

Table (6): Correlation between GP73 and all other parameters in the three groups

	GP 73(ng/ml)	
	r	*P*-value
AST(U/L)	0.156	>0.05
ALT(U/L)	0.274	>0.05
T.bilirubin(mg/dl)	0.381	<0.001
Albumin(gm/dl)	0.122	>0.05
ALK.P(IU/L)	0.042	>0.05
BUN(mg/dl)	-0.142	>0.05
Creat. (mg/dl)	0.335	<0.001
INR	0.078	<0.001
Hb(gm/dl)	0.172	>0.05
TLC(cell/mm^3)	0.264	>0.05
Plt/mcl	0.097	>0.05
AFP(ng/ml)	0.346	<0.001
Child pugh score	0.082	<0.001
Esophageal Varices	0.063	>0.05

Table (7): Relation between AFP and vascular invasion

PVT	AFP(ng/ml)			Mann-Whitney Test		
	Range	Interquartile Range	Mean Rank	Z	*P*-value	
Negative	1.8 - 821	6.3	12.4	22.15	4.03	<0.001
Positive	63 - 200000	3900	30045	46.07		

Table (8): Relation between GP73 and vascular invasion

PVT	GP 73(ng/ml)			T-Test	
	Mean	±	SD	t	*P*-value
Negative	6.486	±	6.143	2.429	<0.001
Positive	13.829	±	13.264		

Table (9): Correlation between GP73 and number and overall size of HFLs

	GP73(ng/ml)	
	R	*P*-value
Number of HFL	0.421	<0.001
Overall size of HFL	0.395	<0.001

Table (10): Correlation between AFP and number and overall size of HFLs

	AFP(ng/ml)	
	R	***P*-value**
Number of HFL	0.316	>0.05
Overall size of HFL	0.202	>0.05

Table (11): Diagnostic sensitivity and specificity of GP73 for prediction of HCC

Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
>5.7*	88%	84%	84.6%	87.5%	84.3%

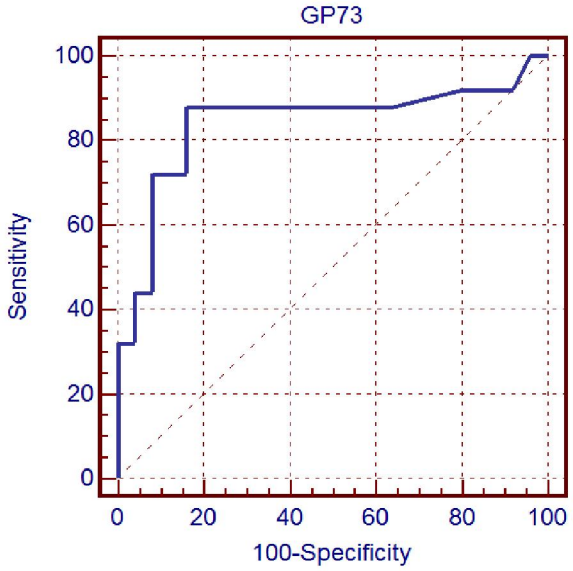

Figure (1): Receiver operating curve (ROC) curve analysis of GP73

Table (12): Diagnostic sensitivity and specificity of AFP for prediction of HCC

Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
> 23.12 *	76.3%	76.2%	76%	76%	81.7%

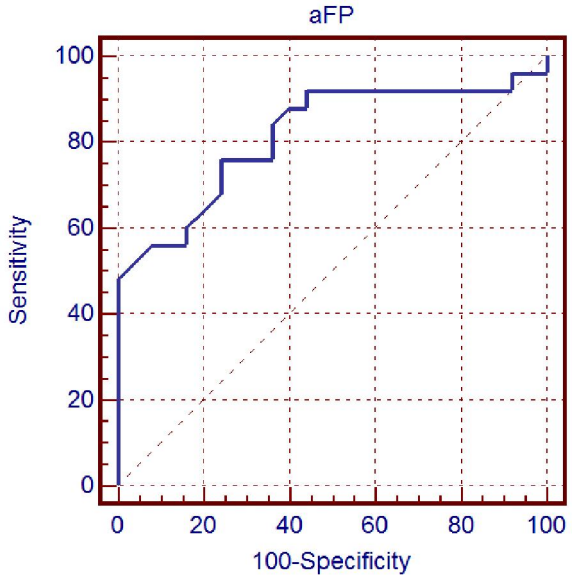

Figure (2): Receiver operating curve (ROC) curve analysis of AFP

Table (13): Diagnostic sensitivity and specificity of combined GP73 and AFP For prediction of HCC

Sensitivity	Specificity	PPV	NPV	Accuracy
88%	96%	95.7%	88.8%	92%

4. Discussion

Hepatocellular carcinoma closely associated with liver cirrhosis and, in fact, the main cause of death in patients with such disease. [17] Since HCC is among the cancers with the worst prognosis, early diagnosis and treatment are the keys for effective treatment of patients with HCC. The use of serological markers in patients at the highest risk for developing HCC may thus decrease HCC mortality and reduce medical costs [18].There are four categories of tumor markers that are currently being used or studied for the detection of HCC. These include oncofetal antigens and glycoprotein antigens; enzymes and isoenzymes; genes; and cytokines. [19] But none of these markers has been validated enough for clinical use. AFP has been used as a serum marker for HCC for many years. Measurements of AFP detect HCC with low levels of sensitivity and specificity, and therefore are not recommended for use in liver cancer surveillance. [20]Although some studies have identified serum GP73 as a potential biomarker for HCC, the GP73 functions and the mechanisms of regulation in normal and neoplastic tissues are still unclear.[5,12]

In the current study we determine the serum levels of AFP, there was a significant difference between patients with HCC and those with liver cirrhosis and control where the median was 63ng/ml in patients with HCC, 3.77ng/ml in patients with liver cirrhosis and 3.5ng/ml in the control group with a p value <0.001, this was in agreement with **Özkan *et al***. [21] who stated that median AFP levels significantly differed in patients with HCC compared with patients with liver cirrhosis (50.65 and 2.32ng/ml respectively) with p value <0.001.These results weren't consistent with **Zhou *et al***. [22] who didn't find a significant difference between patients with HCC and patients with liver cirrhosis with a mean values of 295.89 ± 440.54 and 227.06 ± 413.76ng/ml respectively which may be due to fewer number of patients with cirrhosis compared to those with HCC (47 versus 118).

Exploring the diagnostic value of AFP in diagnosis of HCC, the sensitivity and specificity varied with different cut off values. In our study, at a cut off value 23.12 ng/ml, the sensitivity of the test was 76.3% while the specificity was 76.2%. The PPV was 76% and the NPV was 76% with an accuracy of 81.7%.those results were close to those of **Mao *et al***. [5]who mentioned a sensitivity of 58.2%and a specificity of 85.3 % at a cut off value 35ng/ml. **Özkan *et al***. [21]got at a cut off value of 13ng/ml a sensitivity of 82.67% and a specificity of 94.55%.A lower diagnostic accuracy of AFP was proved by **Zhou *et al***. [22] where he found a specificity of 90%, sensitivity 28.8% and an overall accuracy of 59.8%.

In the present study there was a statistically significant difference between the mean value of GP3 in patients with HCC compared to patients with liver cirrhosis and control with a mean value of 11.25 ± 9.5 & 3.78± 2.07and 1.33 ± 1.46 ng/mL respectively with a p value <0.001.This came into agreement with **Elshafie *et al***.[23]who found the highest values in HCC with a mean value of 10.32 ± 2.46ng/ml compared to 3.79± 2.18ng/ml in cirrhotics and 1.65±0.79ng/ml in controls and also with **Mao *et al***.[5] who estimated a median value of 14.7ng/ml in HCC patients, 4.7ng/ml in cirrhotic patients and 1.2ng/ml in healthy controls with a *p* value < 0.001 Moreover, they found that both liver benign tumours and non-HCC liver malignant lesions had elevated serum GP73, although the magnitude is much smaller than that in HCC and conclude that serum GP73 can therefore be a useful tool in determining the nature of hepatic tumors (benign vs. HCC). Additionally, **Mao *et al***. [5] in their study demonstrated that surgical resection of the tumor results in reduction in GP73 and recurrence of the tumor associated with elevation in GP73. **Gu *et al***. [16] reported that serum level of GP73 in patients with liver disease was significantly higher than in healthy individuals and in patients with other diseases. In a subsequent study by **Marrero *et al***. [12] GP73 levels were significantly increased in patients with HCV–related HCC.

These results didn't come in agreement with **Özkan *et al***. [21] whose found that levels of GP73 weren't significantly higher in HCC and cirrhotic patients compared to controls where the median of GP73 was 0.27ng/ml in controls, 0.32ng/ml in cirrhotic patients and 0.21ng/ml in those with HCC with a *p* value >0.05 which could support the presence of GP 73 specific auto antibodies interfering with ELISA analysis. On the other hand **Tian *et al***. [24]. reported that, serum GP73 in cirrhotic group was higher than in HCC group and in both groups were higher than those in control group. Another study by **Gu *et al.* [**[16] GP73 was found to be elevated in patients with liver disease but did not distinguish between HCC, cirrhosis, and chronic hepatitis.

Regarding the diagnostic value of GP73, the sensitivity and specificity varied with different cut off points. In this study, at the best cut off value 5.7ng/ml, on comparing the sensitivity and specificity of GP73

in selective diagnosis of HCC over liver cirrhosis, the sensitivity of the test was 88% while the specificity was 84%. The PPV was 84.6% and the NPV was 87.5%. The accuracy of the test was 84.3% compared to 81.7% for the AFP. Those results were comparable to **Elshafie *et al***. [23] who mentioned a higher sensitivity and specificity of GP73 87% and 95% respectively at a cut off point 7.62ng/ml compared to AFP with a sensitivity of 77.4%, a specificity of 60% at a cut off point 28.5ng/ml. The results were also consistent with **Mao *et al***.[5] who mentioned that GP73 had a higher sensitivity and specificity than AFP in the diagnosis of HCC, where GP73 had a sensitivity of 74.6% and specificity of 97.4%, at cut-off value of 8.5ng/ml, compared to AFP with a sensitivity of 58.2% and specificity of 85.3%, at cut-off value of 35ng/ml and with **Zhou *et al***.[22] who estimated an accuracy of 82.6% for GP73 and 59.8% for AFP, also with **Zhao *et al***.[25] who found a better sensitivity for GP73 over AFP (76.7% and 32% respectively). These results was not in agreement with **Özkan *et al***. [21] where the diagnostic accuracy of GP73 was worse than AFP, since with an optimal cutoff point of 0.078ng/ml GP73 had a sensitivity of 82.67%, a specificity of 90% and an accuracy 51.54% versus AFP which at a cutoff of 13ng/ml had a sensitivity of 68.57%, a specificity of 94.55% and an accuracy of 79.23%.

In this study when AFP and GP 73 values were combined for selective detection of HCC, they had a sensitivity of 88%, specificity of 96 % and an accuracy of 92 % which is better than each of them alone this came into agreement with **Elshafie *et al***. [23] who mentioned a sensitivity of 90.3%, specificity of 90% and an overall accuracy of 83% on combining both markers. In another study by **Tian *et al***. [24] on combining AFP and GP73 the sensitivity was 75.8% and specificity was 79.7% with accuracy of 84% versus 81% for AFP alone in detecting early HCC. Also, in other studies by **Wang *et al***. [26], **jia *et al*** [14] and **Mao *et al***.[5] The combined measurement of GP73 and AFP can further increase the sensitivity for the detection of HCC. In a recent study by **Wang *et al***. [8] Serum GP73 levels were significantly increased in HCC patients. No significant differences were observed between GP73 and AFP as markers for HCC diagnosis. However, GP73 was more sensitive than AFP in the diagnosis of small HCC. A combination of GP73 and AFP tests increased the sensitivity and specificity for HCC diagnosis. The area under the ROC curve (AUC) of combined test was 0.93 compared with 0.88 for GP73 and 0.90 for AFP alone.

The correlation study, revealed that, a significant correlation was found between serum GP73 level and prognostic markers of liver cirrhosis (Bilirubin, INR, S. Creatinine, AFP and child Pugh score). This in agreement with the finding of **Tian *et al***. [24] and **Elshafie *et al***. [23]who reported that, serum GP73 in cirrhotic patients with Child-Pugh class A was lower than in class B and C.

In our study, there was a significant positive correlation between GP73 values and tumor number, size and vascular invasion with p value <0.01, on the contrary AFP levels didn't correlate with the tumor number and size with p value >0.05 and correlated with vascular invasion with a p value <0.001. These results were in agreement with **Elshafie *et al***. [23] regarding correlation between GP73 and tumor size ($p < 0.05$) and vascular invasion ($p < 0.01$) while it didn't vary with tumor number ($p > 0.05$). These are similar to **Sun *et al***. [27] who reported that, a significant overexpression of GP73 at both protein and mRNA levels along with overexpression of GP73 protein is associated with aggressive behavior of HCC. **Fimmel and Wright** [28] recorded that, the degree of GP73 expression correlated with the tumor grade.

This wasn't in agreement with **Mao *et al.*** [5] who mentioned that there was no correlation between GP73 values and tumor size while the values of AFP significantly varied with the size of HCC where the AFP value of patients with small HCCs (≤3 cm) was significantly less than that of other HCCs (≥5 cm, >3 and<5 cm, and diffuse HCC) (p<0.001) neither with **Özkan *et al.*** [21] who mentioned that there was no correlation between neither GP73 nor AFP regarding the tumor size or vascular invasion.

In conclusion GP73 levels were significantly high in patients with HCC and it had a high sensitivity and specificity for detection of HCC especially if combined with AFP and can be used as useful biomarkers to confirm the diagnosis of HCC. and correlated with the aggressiveness of the tumor regarding the number, overall size of the tumor and vascular invasion and we recommend future evaluation on a greater number of patients and pre and post intervention for HCC and to determine the potential of GP73 as a therapeutic target.

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