A COMPARATIVE STUDY OF THE DIAGNOSTIC AND PROGNOSTIC VALUE OF GOLGI PROTEIN 73 AND ALFA-FETO PROTEIN IN HEPATOCELLULAR CARCINOMA BEFORE AND AFTER THERAPEUTIC INTERVENTION

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ABSTRACT:

Background: *Hepatocellular carcinoma (HCC) is the seventh most common malignancy and the second leading cause of cancer-related deaths worldwide. Globally, there are approximately 750000 new cases and 700000 deaths of HCC reported per annum.*

Aim of the Study: *To evaluate the diagnostic value of serum level of golgi protein 73 (GP73) as a tumor marker for HCC and its prognostic value after trans arterial chemo embolization (TACE) or radiofrequency ablation (RFA), in comparison to alpha-feto protein (AFP).*

Patients and Methods: *This study will be performed on* ***60 subjects*** *from the outpatient Hepatology clinic and inpatient Gastroenterology and Hepatology Department at Ain Shams University Hospital. They will be classified into three groups:* ***Group I:*** *Fourty (40) patients with hepatocellular carcinoma who will undergo either RFA or TACE,* ***Group II:*** *Ten (10) patients with liver cirrhosis without hepatocellular carcinoma,* ***Group III:*** *The control group composed of Ten (10) age and sex matched healthy subjects.*

Results: *In our study, there was a significant positive correlation between GP73 and AFP values with tumor number and size with p values of 0.001, GP73 levels decreased significantly in patients with HCC after intervention either by RFA or TACE with a p value 0.001*

Conclusion: *Plasma GP73 is a sensitive and specific serum marker for the diagnosis of HCC and we recommend combination of AFP and GP73 in screening and diagnosis of HCC. Also the marked significant reduction of serum GP73 levels in HCC patients subjected to either RF ablation and TACE proved that GP73 may play a prognostic marker in HCC management.*

Keywords: *Golgi Protein 73, Alfa-feto Protein, Hepatocellular Carcinoma, Therapeutic Intervention*

INTRODUCTION:

Hepatocellular carcinoma (HCC) is the seventh most common malignancy and the second leading cause of cancer-related deaths worldwide. Globally, there are approximately 750000 new cases and 700000 deaths of HCC reported per annum[(1)].

Current methods for HCC diagnosis are classified into the following main categories: imaging [abdominal ultrasonography, contrast-enhanced computed tomography

(CT) and magnetic resonance imaging (MRI)] and laboratory biomarker analysis [serum alpha-fetoprotein (AFP) levels [(2)], However, the diagnostic performance of imaging technologies is unsatisfactory, particularly for the diagnosis of small lesions and early-stage HCC [(3)].

AFP is the most commonly used tumor marker for HCC diagnosis and prognosis prediction, but the false negative rate using AFP level alone is as high as 40% for patients with early-stage HCC. AFP levels remain normal in 15%-30% of all the patients, even patients with advanced HCC[(4)].

Studies have identified Golgi protein 73 (GP73; also named Golgi phosphoprotein 2(GOLPH2)), as a potential novel HCC serum marker. GP73 is a 400 amino acid, 73 kDa trans membrane glycoprotein that normally resides within the cis-Golgi complex [(5)].

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. Of significance is that 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 [(6)].

Trans arterial chemo embolization (TACE) and radio frequency ablation (RFA) are widely employed in patients with HCC, and has been recommended as the first choice for the middle to advanced stage HCC patients who cannot accept surgery[(7)]. However, there is still lack of an effective way to evaluate the efficacy of TACE and RFA, whereas the changes of tumor size may not be reliable enough, and AFP is not sensitive[(8)].

AIM OF THE WORK:

The aim of this work is to evaluate the diagnostic value of serum level of golgi protein 73 (GP73) as a tumor marker for HCC and its prognostic value after trans arterial chemo embolization (TACE) or radiofrequency ablation (RFA), in comparison to alpha-feto protein (AFP).

PATIENTS AND METHODS:

A- Patients:

This study will be performed on ***60 subjects*** from the outpatient Hepatology clinic and inpatient Gastroenterology and Hepatology Department at Ain Shams University Hospital.

They will be classified into three groups:

Group I: Fourty (40) patients with hepatocellular carcinoma who will undergo either RFA or TACE

Group II: Ten (10) patients with liver cirrhosis without hepatocellular carcinoma.

Group III: The control group composed of Ten (10) age and sex matched healthy subjects

An informed consent will be obtained from each patient before involvement in the study

The inclusion criteria for RFA:

- Age of 18–70 years.
- Patients diagnosed with HCC based on the American Association for the Study of Liver Diseases (AASLD) guidelines in 2011 with an acceptable safe path between the tumor and the skin as shown on US.
- Patients with Child-Pugh A-B
- A solitary HCC tumor ≤ 5 cm in diameter, or multiple HCC lesions (≤3), each ≤ 3 cm in diameter.
- HCC that was visible on US, with an acceptable safe path between the tumor and the skin as shown on US.

The Inclusion criteria for TACE:

- Age of 18-70

- Patients diagnosed with HCC based on the American Association for the Study of Liver Diseases (AASLD) guidelines in 2011.
- Patients with Child-Pugh A-B
- Large or multifocal HCC which were not suitable for surgical resection or radiofrequency ablation

Exclusion criteria for RF:

- Radiological evidence of invasion into the major portal or hepatic vein branches.
- Patients with extrahepatic metastases.
- Severe liver dysfunction Child-Pugh class C
- Active gastrointestinal bleeding
- Pregnant ladies

Exclusion criteria for TACE:

- Radiological evidence of invasion into the major portal or hepatic vein branches
- Patients with any other malignancies
- Severe liver dysfunction Child-Pugh class C
- Active gastrointestinal bleeding
- Pregnant ladies
- Impaired coagulation functions (platelet count below 50×109/L or prothrombin activity below 50%)

B- Methods:

All subjects will be subjected to the following:

1. Full history taking.
2. Full clinical examination with special emphasis on the presence of signs of chronic liver disease (spider naevi, palmar erythema, level of consciousness, flapping tremors, ascites, splenomegaly, jaundice) or signs of hepatocellular carcinoma (cachexia, loss of weight, refractrory ascites)
3. Routine laboratory investigations including: complete blood count, serum creatinine and blood urea nitrogen, serum alanine aminotransferase, serum aspartate aminotransferase, serum alkaline phophatase, total and direct bilirubin, serum albumin and total proteins, prothrombin time for assessment of the child score.
4. Viral markers: Hepatitis C virus antibody, Hepatitis B virus surface antigen (HBsAg)
5. Serum Alpha fetoprotein
6. Radiological study:
   - Abdominal ultrasonography to assess the presence of liver cirrhosis, ascites and hepatic focal lesions
   - Tri phasic spiral CT abdomen: CT is done in different phases of contrast enhancement (early and late arterial and portal venous phases) it will be done for any patient showing a suspected focal lesion in the abdominal ultrasound.
   - Dynamic MRI; if spiral CT is non conclusive.
7. Measurment of serum golgi protein 73 (GP73) for all patients
8. Follow up of the patients who had HCC and undergone either RFA or TACE will be done after 1 month by measuring serum level of alfa feto protein, golgi protein 73 and tri phasic spiral CT abdomen.

<u>Golgi protein 73</u>:

Serum Golgi Protein 73 (GP 73) was measured by Enzyme Linked Immunosorbent assay (ELISA) using Human Golgi protein -73(GP-73) ELISA Kit by Glory Science Co., Ltd 2400 Veterans Blvd. Suite 16 - 101, Del Rio, TX 78840, USA.

Sample collection:

Blood samples were collected using serum separator tubes (SST) and allowed to clot for two hours at room temperature before centrifugation for 15 minutes at 1000 ×g, then serum was removed and stored at -20°C. Repeated freeze-thaw cycles were avoided.

Sample preparation:

Serum samples required about a 100 fold dilution. A suggested 100-fold dilution is 10µL Sample + 990µL PBS. Sample should be diluted by 0.01mol/L PBS (PH =7.0-7.2).

Reagent preparation:

- Biotin-antibody.
- HRP-avidin.
- Wash Buffer.
- Standard.

Statistical methods:

The SPSS 10.0 for windows was used for data management and analysis and the Microsoft power point for charts. P value was considered significant at 0.05.

RESULTS

Table 1: Comparison between the three groups regarding the median of AFP (n=60):

AFP (mg/dL)	Group I (N=40)	Group II (N=10)	Group III (N=10)	Kruskal-Wallis Test		Mann-Whitney Test		
				X^2	P-value	I&II	I&III	II&III
Range	1.8-200000	1.9-20	2-4.6	22.010	<0.001*	0.002*	<0.001*	0.272
Median (IQR)	144.50 (1148.10)	5.95 (11.05)	3.30(1.13)					

On comparing the three groups regarding the median of AFP, it was found that the median value was higher in patients with HCC than those with liver cirrhosis and healthy subjects (144.5, 5.95 and 3.30 respectively), on doing Mann Whitney Test it was found that there was a statistically significant difference between group I and group II, group I and group III with p value 0.002, <0.001 respectively and there was no significant difference between group II and group III.

Table 2: Comparison between the three groups regarding the mean value of GP73 (n=60):

GP 73	Group I (N=40)			Group II (N=10)			Group III (N=10)			ANOVA		TUKEY'S Test		
										F	P-value	I&II	I&III	II&III
Range	2	-	340	12.5	-	50	2.5	-	18	10.614	<0.001*	0.007*	0.001*	0.829
Mean ±SD	122.200	±	98.619	30.600	±	11.065	9.250	±	4.786					

Comparison between the three groups regarding the range of GP73 showed that there was a significant range difference between the three groups such that it was higher in HCC group than the liver cirrhosis and healthy group (2-340, 12.5-50 and 2.5-18 respectively). on comparing the mean of the golgi protein 73 there was a statistical significant difference between them with a p value < 0.001, it was higher among HCC than that of liver cirrhosis only and healthy subjects (122.200 ± 98.619, 30.600 ± 11.065 and 9.250 ± 4.786 respectively), on doing tukey test there was a significant difference between group I and group II, group I and group III, with p value 0.007 and 0.001 respectively but there was no significant difference between group II and group III.

Table 3: Change in the mean of GP73 pre and post intervention

Time	GP 73						Paired Differences		Paired Samples Test	
	Range			Mean	±	SD	Mean	SD	t	P-value
Pre	2	-	340	122.200	±	98.619	84.618	76.707	6.977	<0.001*
Post	0.5	-	200	37.583	±	57.730				

The range of GP73 pre intervention was 2-340, this range decreased significantly post intervention to 0.5-200 with a mean value 122.200 ± 98.619 and 37.583 ± 57.730 respectively and p value <0.001.

Table 4: Change in the mean of GP73 before and after each intervention modality

GP 73	TACE			RF			T-Test	
	Mean	±	SD	Mean	±	SD	t	P-value
Pre	153.440	±	111.347	70.133	±	34.519	2.805	0.008*
Post	51.820	±	66.368	13.854	±	27.709	2.100	0.042*
Differences	101.620	±	90.087	56.279	±	33.191		
Paired Test	<0.001*			<0.001*				

The paired test for the difference in the value of GP73 pre and post intervention by TACE or RF was 101.620 ± 90.087 and 56.279 ± 33.191 respectively and this was statistically significant with p value less than 0.001.

Table 5: Show the relation between the size of HFL and mean of GP73 pre and post intervention

GP 73	<3 cm			3-5 cm			>5 cm			ANOVA	
	Mean	±	SD	Mean	±	SD	Mean	±	SD	F	P-value
Pre	81.500	±	54.060	106.455	±	76.973	152.737	±	119.429	2.000	0.150
Post	24.288	±	33.837	38.836	±	79.691	43.854	±	54.586	0.368	0.695
Differences	57.212	±	43.378	67.618	±	30.318	108.883	±	100.407		
Paired Test	0.002*			<0.001*			<0.001*				

The paired T –TEST showed that the differences in the mean values of GP73 pre and post intervention was statistically significant whatever the size of the HFL with p value 0.002 if HFL size was less than 3 cm and less than 0.001 if HFL size was 3-5 cm or more than 5 cm.

Table 6: Change in the median of AFP pre and post intervention

Time	AFP (mg/dL)					Wilcoxon Signed Ranks Test	
	Range			Median	IQR	Z	P-value
Pre	1.8	-	200000	144.50	1148.10	5.514	<0.001*
Post	1	-	100000	100.00	995.00		

On doing the Wilcoxon signed rank test for the median of AFP pre and post intervention there was a statistically significant change between them with a p value less than 0.001.

Table 7: Change in the median of AFP pre and post each intervention modality

AFP (mg/dL)	Intervention				Mann-Whitney Test	
	TACE		RF			
	Median	IQR	Median	IQR	Z	P-value
Pre	777.90	1347.50	10.00	59.00	3.732	<0.001*
Post	700.00	1145.00	8.00	58.00	3.525	<0.001*

The median value of AFP pre and post TACE is 777.9 and 700 respectively while the median value of AFP pre and post RF is 10 and 8 respectively. on doing the Mann Whitney test there was a statistically significant change in AFP pre and post TACE and RF with a p value of less than 0.001.

Table 8: Show the relation between the size of HFL and median of AFP pre and post intervention

AFP (mg/dL)	Triphasic Ct Overall size						Kruskal-Wallis Test	
	<3 cm		3-5 cm		>5 cm			
	Median	IQR	Median	IQR	Median	IQR	X^2	P-value
Pre	6.25	14.40	158.00	767.90	1156.00	1576.00	13.241	0.001*
Post	5.00	10.20	100.00	692.00	1000.00	1190.00	12.077	0.002*
Wilcoxon Test	0.005*		0.003*		<0.001*			

The Wilcoxon test showed that the difference in the median of AFP pre and post intervention in patients who had HFL size less than 3cm, from 3-5 cm and more than 5 cm is statistically significant with a p value of 0.005, 0.003 and less than 0.001 respectively.

Table (9): Diagnostic accuracy of combined GP73 and AFP in discriminating HCC from liver cirrhosis

Combined	Groups						Chi-Square	
	Group I		Group II		Total			
	N	%	N	%	N	%	X^2	P-value
Negative	3	7.50	9	90.00	12	24.00	29.852	<0.001*
Positive	37	92.50	1	10.00	38	76.00		
Total	40	100.00	10	100.00	50	100.00		
Roc								
Sens.	Spec.		PPV		NPV		Accuracy	
92.50	90.00		97.37		75.0		92%	

On using combined AFP and GP73 for discriminating HCC from liver cirrhosis, 37 cases were positive from the 40 patients who had HCC (GROUP I) and 3 were false negative, while in GROUP II 9 patients were negative for HCC and 1 patient was false positive for HCC, this was statistically significant with p value less than 0.001, with sensitivity of 92.5%, specificity of 90%, positive predictive value of 97.37%, negative predictive value of 75% and accuracy of 92%.

DISCUSSION

Liver cancer in men is the fifth most frequently diagnosed cancer worldwide and is the second leading cause of cancer-related death in the world[9].

The incidence of HCC has increased sharply in the last five to ten years, with an especially high incidence in Egypt. This rising incidence of HCC in Egypt may be explained by the increasing prevalence of risk factors such as the emergence of hepatitis C virus (HCV) over the same period of time, the contribution of HBV infection, the improvements in screening programs and diagnostic tools, as well as the increased survival rate among patients with cirrhosis allowing time for some of them to develop HCC[10].

The majority of HCCs occur in patients with chronic liver disease or cirrhosis which is commonly prevelant in Egypt after the emergence of HCV infection associated with the mass treatment injection campaigns for Schistosomiasis during the years 1950–1980 [11].

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[12].

AFP 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[13].

In the search for serum markers of hepatocellular cancer, 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[14].

GP73 was originally described as a resident Golgi type II transmembrane protein expressed primarily in epithelial cells of many human tissues. GP73 antigen expression is barely detectable in healthy subjects, but it is elevated modestly in virus carriers, moderately in patients with cirrhosis, and dramatically in patients with HCC[15].

Early detection of patients with HCC is attractive because it gives better prognosis as HCC tends to grow slowly and stay confined to the liver. Early detection is possible with ultrasound scanning and AFP monitoring, although the use of AFP as a screening test is complicated by frequent false positive and false negative results, so early diagnosis of HCC would not be difficult if tumor markers and medical imaging were combined [16].

The aim of this study to assess the serum level of golgi protein 73 and alpha fetoprotien in patients with liver cirrhosis and those with hepatocellular carcinoma and to compare them with normal subjects to detect their sensitivity and specificity as a diagnostic marker. Also to study the clinical significance of serum GP73 in patients with HCC as a prognostic marker before and after intervention to improve the outcome of HCC diagnosis and treatment. This study was carried on 60 subjects classified into 3 groups: Group I was 40 patients with hepatocellular carcinoma and liver cirrhosis, Group II was 10 patients with liver cirrhosis only without HCC, Group III was 10 healthy subjects served as control group.

In the present study the ages of patients with HCC ranged between 38-70 years with a mean 59.26 ± 7.48 years which is consistent with *Elshafie et al.*[17] who found that the mean age of patients with HCC was 59.27 ± 9.14 years. Also these results were close to those of *Özkan et al.* [18] who stated that the mean age of patients with HCC was 63±9.9 years which approves the prevalence of HCC in the fifth and sixth decades of life.

In this study HCC was found to be more prevalent in men 25 (83.3%) than in women 5 (16.6%). This was in conformity with that found by *El-Zayadi et al.*[19] in their study. This may at least be explained in part by the differences in exposure to risk factors, sex hormones and other X-linked genetic factors. It has been speculated that estrogens and androgens could modulate hepatocarcino-genesis and explain the higher incidence of HCC in men[20].

Concerning the biochemical profile and synthetic functions of the liver, in the current study there was a significant difference between the study groups where patients with HCC had the worse serum levels of AST, ALT, bilirubin, albumin, INR, Platelet counts in comparison to patients with liver cirrhosis. These results were in agreement with those of *Elshafie et al.*[17], who mentioned an overall deterioration of the biochemical profile and liver functions in patients with HCC where compared to patients with liver cirrhosis. This proves that functions deteriorate with advancement of liver condition.

Nan-Ya Wang et al.[21] mentioned that there is association between liver functions and serum GP73, this coincides with our study where there was correlation between INR, total bilirubin and albumin with GP73 level pre intervention being higher in HCC patients than cirrhotic patients

In our study, there was a significant positive correlation between GP73 and AFP values and tumor number and size with p values of 0.001. These results were in agreement with *Elshafie et al.*[17] regarding correlation between GP73 and tumor size ($p< 0.05$) and vascular invasion ($p< 0.01$) while it didn't vary with tumor number ($p> 0.05$). Which proves the theory of overexpression of GP73 during cellular stress to maintain the integrity of golgi complex.

In the present study the level of GP 73 was higher in HCC patients especially those with hepatic focal lesions more than 3cm, also there was a positive correlation between

the number of HFL and GP73 pre and post intervention with a p value of 0.001 and 0.003 respectively. These results were in agreement with *Elshafie et al.*[17] who mentioned a correlation between GP73 with tumor size and number which proves the theory of overexpression of GP73 during cellular stress to maintain the integrity of golgi complex. This agrees with *Özkan* ***et al.***[18] mentioned that GP73 levels were significantly higher in patients with hepatitis C-derived HCC and a high tumor grade, also these results were in agreement with ***Nan-Ya Wang et al.***[21] who found that there is an association between tumor size and tumor number with GP73 pre and post intervention with radiofrquency, being less after intervention with radiofrequency. This proves that GP73 promotes invasion of hepatocellular carcinoma.

However, this wasn't in agreement with *Mao et al.* [12] 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.* [18] who mentioned that there was no correlation between neither GP73 nor AFP regarding the tumor size

This study showed significant elevation of plasma GP73 levels in HCC patients with a range of 2-340 ng/ml and mean level (122.200 ± 98.619 ng/ml) than cirrhotic patients levels which showed a range of 12.5-50ng/ml and mean value (30.600 ± 11.065 ng/ml) and lower levels in normal control group with range of 2.5-18 ng/ml and a mean level (9.250 ± 4.786 ng/ml).

This came into agreement with *Elshafie et al.*[17] who found the highest values in HCC with a mean 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 *Randa et al.*[22] who estimated a median value of 125ng/ml in HCC patients, 62 ng/ml in cirrhotic patients and 0.89 ng/ml in healthy controls with a p value < 0.001. This proves that More advanced stages of HCC or liver cirrhosis reflect more injured hepatocytes, resulting in higher sGP73 levels in HCC than cirrhosis

These results didn't come in agreement with *Özkan et al.* [18] whose levels of GP73 weren't significantly higher in HCC and cirrhotic patients compared to controls without liver disease 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 =0.373 which could support the presence of GP73 specific autoantibodies interfering with ELISA analysis.

GP73 levels decreased significantly in patients with HCC after intervention either by RFA or TACE, such that the mean value of GP 73 pre TACE or RF was 153.440 ± 111.347, 70.133 ± 34.519 respectively and this was statistically significant with p value of 0.008, while the mean value of GP 73 post TACE or RF was 51.820 ± 66.368, 13.854 ± 27.709 respectively.

In our study GP73 levels decreased significantly in patients with HCC after intervention by RFA, such that the mean value of GP73 pre RF was 70.133 ± 34.519, while the mean value of GP73 post RF was 13.854 ± 27.709. This agreed with *Nan-Ya Wang et al.* [21] who proved that GP73 levels sharply decreased after RFA, this indicates that gp73 has diagnostic value for detection of HCC and can be used for follow up the success of treatment of HCC

In our study GP73 levels decreased significantly in patients with HCC after intervention by TACE, such that the mean value of GP73 pre TACE was 153.440 ± 111.347, while the mean value of GP73 post TACE was 51.820 ± 66.368. this agreed with *Kirchhoff et al.* [23] who mentioned that GP 73 decreased significantly after doing TACE, this proves that GP 73 is a promising tumor marker for diagnosis and follow up of HCC before and after intervention however this was against *Jie Pan et al.* [24] who found a progressive increase in the level of GP73

after intervention with TACE, this may be due to small sample size and he used western blotting unlike our study where we used ELISA method.

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 20ng/ml, the sensitivity of the test was 60% while the specificity was 100%. The positive predictive value was 100% and the negative predictive value was 38.5% with an accuracy of 81.5%. Those results were close to those of *Mao et al.* [12] who mentioned a sensitivity of 58.2%and a specificity of 85.3 % at a cut off value 35ng/ml, which implies AFP as a tumor marker for HCC. However, A lower diagnostic accuracy of AFP was proved by *Zhiling and colleagues* [25] who reported sensitivity 68.2%, and specificity75%, when the cutoff value 19.8ng/ml, accuracy 70.3%.

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 41ng/ml, on comparing the sensitivity and specificity of GP73 in selective diagnosis of HCC over liver cirrhosis, the sensitivity of the test was 86.67% while the specificity was 93.3%. The positive predictive value was 97.2% and the negative predictive value was 64.3%. The accuracy of the test was 89.3%. Those results were close to *Elshafie et al.* [17] who mentioned a higher sensitivity and specificity of GP73 87% and 95% respectively at a cut off point 7.62ng/ml. this proves that GP73 can be used as a potential reliable tumor marker for detection of HCC.

These results didn't agree with *Zhiling Jia et al.*[25] who recommended a cut-off point of GP73 = 150 ng/ml, the sensitivity of GP73 for HCC was 71% and the specificity was 63%

In our study the GP73 had a higher sensitivity than AFP (87.5% and 60% respectively) and a higher accuracy than AFP (89.3% and 81.5%respectively).

The results were also consistent with *Mao et al.*[12] 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%, and an optimal cut-off value of 8.5ng/ml,compared to AFP with a sensitivity of 58.2% and specificity of 85.3%, and a cut-off of 35ng/ml and with *Zhou et al.*[26] who estimated an accuracy of 82.6% for GP73 and 59.8% for AFP, also with *Zhao et al.*[27] who found a better sensitivity for GP73 over AFP (76.7% and 32% respectively). This proves that GP has a better diagnostic value than AFP

This conclusion was not in agreement with *Özkan et al.* [18] 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 9% 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%.

Zhiling Jia et al. [25] compared both AFP and GP73 in 102 patients with HCC such that AFP was positive in 53 patients while GP73 was positive in79 patients, this agrees with our study in which we compared AFP and GP73 in 50 patients with HCC such that AFP was positive in 24 patients while GP73 was positive in 35 patients. This indicates that GP73 has more diagnostic accuracy in comparison to AFP for detection of HCC

In our study we proved that on using combined AFP and GP73 for discriminating HCC from liver cirrhosis, 37 cases were positive from the 40 patients who had HCC with sensitivity of 92.5%, specificity of 90%, positive predictive value of 97..37%, negative predictive value of 75% and accuracy of 92%. This agrees with *Congcong Jiao et al.* [28] who stated that the accuracy of GP73 and AFP for detection of HCC IS 84% and 71.8% respectively and that the combined usage of both AFP and GP73 increased the accuracy for HCC detection to 90.3%, also *Wang et al.* [29]

mentioned that combining AFP and GP73 would improve the sensitivity and specificity for HCC detection. This proves that the diagnostic value for HCC of both AFP and GP73 combined together is better than the single diagnosis of GP73 or AFP alone

Conclusion:

In conclusion GP73 levels correlated with the liver functions especially the total bilirubin, albumin and INR. This denotes that GP73 can predict the severity of the hepatic affection

Serum GP73 levels were significantly higher in patients with hepatocellular carcinoma than cirrhotic patients with a better diagnostic accuracy than AFP and it correlated with the aggressiveness of the tumor regarding the number and overall size of the tumor. Thus these results may be valuable in the future in implementing GP73 as a biomarker for diagnosing HCC.

Also the marked significant reduction of serum GP73 levels in HCC patients subjected to either RF ablation and TACE proved that GP73 may play a prognostic marker in HCC management.

The combination of AFP and GP73 would improve the sensitivity and specificity for HCC detection.

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دراسة مقارنة للقيمة التشخيصية والتنبؤية لبروتين جولجى ٧٣ والفا فيتو بروتين فى سرطان الكبد قبل و بعد التدخل العلاجى

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الملخص العربي

المقدمة: سرطان الخلايا الكبدية هو سابع ورم خبيث شائع والسبب الرئيسي الثاني للوفيات المرتبطة بالسرطان في جميع أنحاء العالم. على الصعيد العالمي، هناك ما يقرب من ٧٥٠٠٠٠ حالة جديدة و ٧٠٠٠٠٠ حالة وفاة لسرطان الكبد المبلغ عنها سنويًا.

الأهداف: هو تقييم الفائدة التشخيصية لبروتين جولجى ٧٣ فى المصل كدلالة لسرطان الكبد و القيمة التنبؤية له بعد اجراء الحقن الكيميائى بواسطة القسطره او التردد الحرارى و مقارنتهما بالفا فيتو بروتين

المرضى والطرق: هذه الدراسة ستقوم على **٦٠ شخصا** مترددين على عيادة الكبد و محجوزين في قسم الجهاز الهضمى و الكبد فى مستشفى عين شمس الجامعى وسيتم تصنيفها إلى ثلاث مجموعات: المجموعة الأولى: أربعون (٤٠) مريضًا يعانون من سرطان الكبد و سوف يقوموا باجراء الحقن الكيميائى بواسطة القسطره او التردد الحرارى الكبد الذين المجموعة الثانية: عشرة (١٠) مرضى يعانون من التليف الكبدى دون وجود سرطان فى الكبد، المجموعة الثالثة: مجموعة التحكم و تضم ١٠اشخاص لا يعانون من اى امراض.

النتائج: في دراستنا ، كان هناك ارتباط إيجابي كبير بين قيم بروتين جولجي ٧٣ و ألفا فيتو بروتين مع عدد البؤر السرطانية فى الكبد وحجم الورم ، انخفضت مستويات بروتين جولجي ٧٣ بشكل كبير في المرضى الذين يعانون من سرطان الكبد بعد تدخل إما عن طريق الحقن الكيميائى بواسطة القسطره او التردد الحرارى

الخلاصة: بروتين جولجي ٧٣ هو علامة مصلية حساسة ومحددة لتشخيص سرطان الكبد وننصح باستخدام مزيج من بروتين جولجي ٧٣ و ألفا فيتو بروتين في فحص وتشخيص سرطان الكبد. كما أثبت ان الانخفاض الملحوظ لمستويات المصل بروتين جولجي ٧٣ في مرضى سرطان الكبد الذين يتعرضون لأي من الحقن الكيميائى بواسطة القسطره او التردد الحرارى يؤكد القيمة التنبؤية لبروتين جولجي ٧٣ فى تشخيص و متابعة علاج سرطان الكبد.

الكلمات المفتاحية: بروتين جولجي ٧٣ ، بروتين ألفا فيتو ، سرطان خلايا الكبد ، التدخل العلاجي.