



Evaluation of the Role of Alpha-Fetoprotein (AFP) Levels in Chronic Viral Hepatitis C Patients, Without Hepatocellular Carcinoma (HCC)

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Abstract

Background: *elevated serum AFP is not uncommonly seen in patients with CHC, but not HCC.*

Aim of the Study; *is to evaluate the clinical significance of Alpha- Fetoprotein (AFP) levels in chronic hepatitis C patients without hepatocellular carcinoma (HCC).*

Patients And Methods: *We operated our study on selected 70 patients of chronic hepatitis C virus infection diagnosed by history taking, clinical manifestations and positive laboratory investigations for chronic HCV infection. The following investigations were done for all cases; liver function tests, complete blood picture and viral markers (HCV-Ab, HBs-Ag and quantitative PCR for HCV-RNA). Abdominal ultrasound and histopathological examination of ultrasound guided liver biopsy were done for all cases.*

Results: *The study reveals that AFP levels were very much higher in HCV cases compared to controls. There was a positive highly significant correlation. It was found that higher serum AFP levels were associated with more advanced stage of fibrosis especially F3 & F4. Regarding the mean AFP levels in different grades of liver pathology, there was no statistical significant relation. Also, there was no statistical significant relation between the mean AFP levels and the presence of Steatosis. By using a ROC curve, the level of AFP can be used as a screening for chronic HCV infection (sensitivity=75.4%, specificity=85.7%), as well as for advanced fibrosis in chronic HCV infection (sensitivity=69.7%, specificity=83.8%).*

Conclusion: *Serum AFP levels increase with advanced stages of liver fibrosis in chronic hepatitis C infection, even without hepatocellular carcinoma. Serum AFP levels may be used as a marker for prediction of chronic liver affection and staging of fibrosis.*

Key words: *Hepatitis C virus: HCV; Alphafetoprotein: AFP.*

Introduction

Hepatitis C virus (HCV) infection is the second viral cause for chronic liver disease (CLD) in the world¹. Egypt has the highest prevalence of hepatitis C virus (HCV) in the world, estimated nationally at 14.7%².

Alpha-fetoprotein (AFP) is a foetal glycoprotein which has been widely used as a serum marker for diagnosing hepatocellular carcinoma (HCC); however, elevated serum AFP levels have also been documented in non-HCC patients with chronic liver disease³.

Elevated serum AFP is not uncommonly seen in patients with CHC, but not HCC, and the incidence has ranged from 10% to 43%³.

Elevated levels have been shown to be more commonly associated with chronic liver disease and fibrosis and the value of measuring AFP in HCV has been called into question⁴.

Patients and methods

This prospective controlled study was performed in cooperation between Tropical and Internal Medicine Clinics of Ain-Shams University Hospital "EL-Demerdash" and from the Interferon Unit - before treatment - of Sohag Cardiology and Hepato-Gastroenterology Center, Ministry of Health, in the period from January 2010 to January 2013. Sample size was calculated to include 70 patients with post hepatitis C virus compensated liver disease at 95% confidence interval and a power of 0.80 and an expected effect size of 50%. This study included two groups:- Study Group: included (70) patients with chronic hepatitis C (CHC) without evidence of

hepatocellular carcinoma (HCC). And, Control Group: included (20) aged & sex-matched apparently healthy individuals.

Inclusion Criteria: HCV related chronic liver disease patients were recruited according to the protocol of the National Committee for Control of Viral Hepatitis in Egypt and fulfilling the following criteria: Patients aged between 20 and 60 years were included in the study. Patients with proven compensated chronic hepatitis C infection (detectable anti-HCV antibody assessed by third-generation enzyme-linked immunosorbent assay, detectable HCV RNA by polymerase chain reaction (Cobas Amplicor HCV Monitor version 1.0; Roche Diagnostics; lower limit of quantitation [10 IU/mL], and histologic evidence of chronic hepatitis C in a liver biopsy specimen obtained within the preceding year.

Exclusion criteria: Other aetiological causes of chronic liver disease, Child Class B or C, co-infection with HBV, hepatocellular carcinoma. Elevated AFP level \geq 200 ng/ml by ELISA. Patients with positive Anti Schistosoma Ab or with high risk of bleeding during liver biopsy or any other comorbid conditions.

The objective of the study and the possible complications were explained to all patients who met the eligibility criteria and they were asked to sign a written consent form. Approval of the local ethical Committee of the hospital was also obtained.

All the studied cases were subjected to the following:

Complete history taking and thorough clinical evaluation

Laboratory investigations: Including complete blood count (CBC), liver function tests (ALT, AST, albumin, bilirubin, INR), renal function tests (serum creatinine, urea) and hepatitis markers (HCV Ab, HBsAg, HBcore Ab, quantitative determination of HCV RNA was performed). Serum alpha-fetoprotein (was done for both groups) by ELISA. The upper limit of normal value is 10 ng/ml⁵. Diagnostic Level for HCC \geq 200 ng/ml^{6,7}.

Abdominal ultrasonography; was done for all cases.

Liver biopsy and histopathological examination; was performed in order to assess histologic scoring for fibrosis and necro-inflammatory activity according to Metavir score⁸. The enrolled Patients were Child A according to Child-Turcotte Pugh scoring system (A, B, C)⁹.

Statistical Analysis:

Analysis of data was performed using SPSS 17 (Statistical Package for Scientific Studies) for Windows. The level $P < 0.05$ was considered the cut-off value for significance. Description of quantitative variables was in the form of mean, standard deviation (SD). Description of qualitative variables was in the form of numbers (No.) and percents (%).

Data were explored for normality using Kolmogorov-Smirnov test of normality. The results of Kolmogorov-Smirnov test indicated that most of data were normally distributed (parametric data) so parametric tests were used for most of the comparisons; Comparison between quantitative variables was carried out by student

T-test of two independent samples. Repeated measures Analysis of Variance (ANOVA) test was used instead of T- test when comparing between more than two groups of independent variables. Results were expressed in the form of P-values. Comparison between qualitative variables was carried out by Chi-Square test (X²). Fisher exact test was used instead of Chi-square test when one expected cell or more were ≤ 5 .

Binary correlation was carried out by Pearson correlation test in most of cases or Spearman correlation test in case of categorical ordinal variables "fibrosis stages". Results were expressed in the form of correlation coefficient (R) and P-values.

Both univariate and multivariate analysis were used to determine risk factors for elevated AFP level. Factors with a univariable $P < 0.05$ were entered into the multivariate model. Odds ratio was calculated by using logistic regression model. A Receiver operating characteristic (ROC) curve was graphed to determine an appropriate level of AFP in predicting advanced stages of liver fibrosis (F3 & F4) that gives optimal sensitivity and specificity.

Results:

The current study showed that the age of the studied patients was (42.03 \pm 11.03) ranged between (31-53) years old, 58 cases (82.9%) were males while 12 cases (17.1%) were females. The BMI of the studied cases was (26.96 \pm 4.93)

The liver pathology findings among the study group revealed that slightly less than half of cases (around 47%) had advanced fibrosis (F3 or F4),

and the other half (53%) had lower stages of fibrosis (F0-2). Regarding grades, about 35% of cases had grades 2 or 3, with the resting 65% had grades of zero or 1. Steatosis was seen only in slightly higher than one quarter of cases (27%) (Figure 1).

Regarding the laboratory parameters of the two groups, there was a highly statistically significant increase in AST, ALT and AFP ($P < 0.001$) between the study and control group while no change in other parameters as had shown in Table 1.

Correlation between AFP level and patients characteristics in different stages of liver fibrosis: As shown in table (2), Total and direct bilirubin showed positive correlations with all stages above F0, but this result was statistically significant with total bilirubin only in advanced stages of fibrosis (F3 and F4). The Platelets count among F4 patients showed negative and significant correlation with AFP levels.

Concerning correlation between AFP level and PCR in different stages of liver fibrosis among the study group, PCR has none significant correlation with AFP among all HCV patients. This means that the level of AFP is not related to the viral load of HCV (Figure 2). While the **correlation between AFP level and different stages of liver fibrosis in the study group revealed that** AFP has a highly significant correlation with the stage of fibrosis. This means that the AFP level is highly dependent on the stage of liver fibrosis, increasing with increasing the stage of fibrosis.

Table (3) assessed the **mean AFP at different liver pathology findings among the study group;** There was an increase in the mean level of serum alpha-fetoprotein between different liver fibrosis stages as the lowest serum AFP was noticed among cases with stage 0 fibrosis (2.90 ng/mL); with steadily increase in AFP level, and so the highest serum AFP level was noticed among cases with stage 4 fibrosis (22.15 ng/ml); this comparison is statistically significant as $P\text{-value} \leq 0.05$. On the other hand, serum AFP showed steady increase with increasing the grade of liver pathology, but the comparison between mean AFP at different liver pathology grading was statistically insignificant. Although, there is a higher mean serum AFP level among cases with steatosis (10.54ng/ml) compared to cases without steatosis (7.53ng/ml) but the difference is statistically insignificant.

Using ROC analysis in this study, revealed that AFP can be used to differentiate chronic HCV infection from controls, and at a cut-off level of 2.27 ng/mL, the sensitivity was 75.4% and specificity was 85.7%. Also, AFP is seen to be a significant predicting factor for advanced fibrosis among CHC patients, and at a cut-off level of 5.17 ng/mL, the sensitivity was 69.7% and specificity was 83.8% (Figure 3).

Multivariate analysis for Logistic Regression model was performed; factors with a univariable $P < 0.05$ were entered into the multivariate model through purposeful forward selection. Factors entered into the multivariate model were: AST, Serum Albumin, Total Bilirubin and advanced stages of liver fibrosis. Ranking of these variables

from the more important to the less important to predict higher AFP showed that, the most important variable is total bilirubin ($p=0.008$), followed by serum albumin ($p=0.038$). All other variables show no relationship to AFP level

($p>0.05$). This means that total bilirubin and serum albumin levels – respectively - were the most two independent factors associated with rise of AFP among CHC patients (Table 4) .

Tables:

Table (1): The Laboratory findings of the two studied groups:

Variables	Control Group N=20		Study Group N=70		Test-Value***	P-value	Sig.
	Mean	SD	Mean	SD			
ALT Up to(45 IU/L)	28.39	10.29	56.22	47.39	**352.00	0.001	HS
AST Up to(45 IU/L)	26.77	5.44	52.26	46.23	**295.50	<0.001	HS
S. Albumin (3.5-5.5g/dl)	4.37	0.43	4.24	0.49	*1.092	>0.05	NS
T. Bili. Up to (1.2 mg/dl)	0.69	0.17	0.81	0.30	**558.00	.166	NS
D. Bili. Up to (0.3 mg/dl)	0.23	0.09	0.28	0.15	**564.00	.183	NS
INR	1.06	0.06	1.12	0.11	*-3.219	<0.01	HS
W. B. C. x 1000 (4 -11/mm ³)	6.69	1.69	6.50	1.88	*0.048	>0.05	NS
Hemoglobin (12-16g/dl)	14.34	1.45	14.34	1.80	*0.399	>0.05	NS
Platelets x 1000 (150 - 400/mm ³)	237.80	52.70	223.57	108.67	**557.00	>0.05	NS
PCR RNA (IU/L) x10 ⁶	--	--	0.82	1.41	--	--	--
AFP Up to (10ng/ml)	1.70	1.61	9.72	20.40	**223.50	<0.01	HS

*=T- value , **=Mann-Whitney U value, S= Significant, HS= Highly Significant, NS= Not Significant.

Table (2): Correlation between AFP level and patients characteristics in different stages of liver fibrosis:

Variables	F 0		F 1		F 2		F 3		F 4	
	"R"	P value	"R"	P value	"R"	P value	"R"	P value	"R"	P value
AGE	0.273	0.391	0.110	0.719	0.351	0.263	-0.399	0.141	-0.130	0.606
B.M.I	0.208	0.517	0.309	0.304	0.087	0.787	-0.135	0.632	-0.335	0.174

ALT	-0.25	0.43	-0.43	0.15	0.15	0.64	0.15	0.59	0.100	0.693
AST	-0.25	0.43	-0.23	0.45	-0.02	0.96	0.39	0.15	0.275	0.269
S. Alb.	-0.533	0.075	-0.676	0.111	-0.041	0.900	0.099	0.727	0.124	0.623
T. Bili	-0.448	0.145	0.357	0.231	0.484	0.111	0.543	0.037*	0.681	0.002**
D. Bili	-0.087	0.789	0.161	0.599	0.474	0.120	0.180	0.522	0.664	0.003**
INR	0.042	0.896	-0.337	0.261	-0.041	0.900	-0.415	0.124	0.253	0.311
WBC	-0.196	0.541	-0.211	0.488	0.599	0.051	0.004	0.990	-0.293	0.238
Hb.	-0.237	0.458	0.375	0.206	0.278	0.381	0.262	0.345	-0.099	0.696
Plt	-0.461	0.131	0.061	0.844	-0.079	0.808	0.039	0.891	-0.591	0.010**
PCR	0.319	0.289	0.604	0.083	-0.229	0.411	-0.112	0.657	0.026	0.936

R= Correlation Coefficient, *. Correlation is significant at the P-value ≤ 0.05 level (2-tailed),

***. Correlation is highly significant at the P-value ≤ 0.01 level (2-tailed).

Table (3): Comparison between mean AFP at different liver pathology findings among the study group:

Fibrosis	F 0		F 1		F 2		F 3		F 4		*test	P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
	2.90	1.47	4.44	3.91	6.88	4.37	7.19	7.69	22.15	37.33	2.55	.047
Grading	A 0		A 1		A 2		A 3		*test	P value		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
	3.59	2.74	8.21	6.51	11.91	16.83	12.40	28.52	.658	.581		
Steatosis	Steatosis		No Steatosis		**test	P value						
	Mean	SD	Mean	SD								
	10.54	23.74	7.53	4.79	.545	.587						

*= ANOVA Test , **= T-Test

Table (4): Multivariate analysis for the independent factors associated with elevated AFP levels:

Variables	P-value	OR	95% C.I. for OR	
			Lower	Upper
AST	0.061	1.020	0.999	1.041
S. Albumin	0.038	0.132	0.019	0.893
T. Bilirubin	0.008	27.879	2.394	324.678
Advanced fibrosis (F3-F4)	0.458	0.410	0.039	4.319

OR= Odds Ratio C.I.= confidence interval

Correct classification = 93.3 "Ability of model to predict the outcome by factors entered in the model the best is closer to 100%". **Significance of the model = <.001**

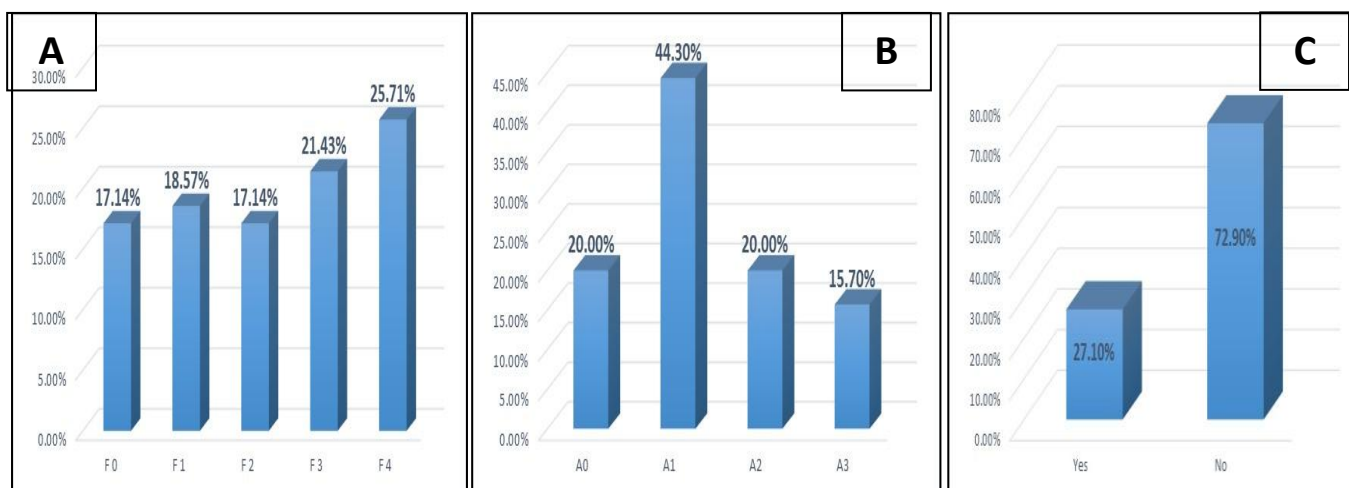


Figure (1): Liver pathology findings (fibrosis stage (A), grade (B) and steatosis (C)) among the study group.

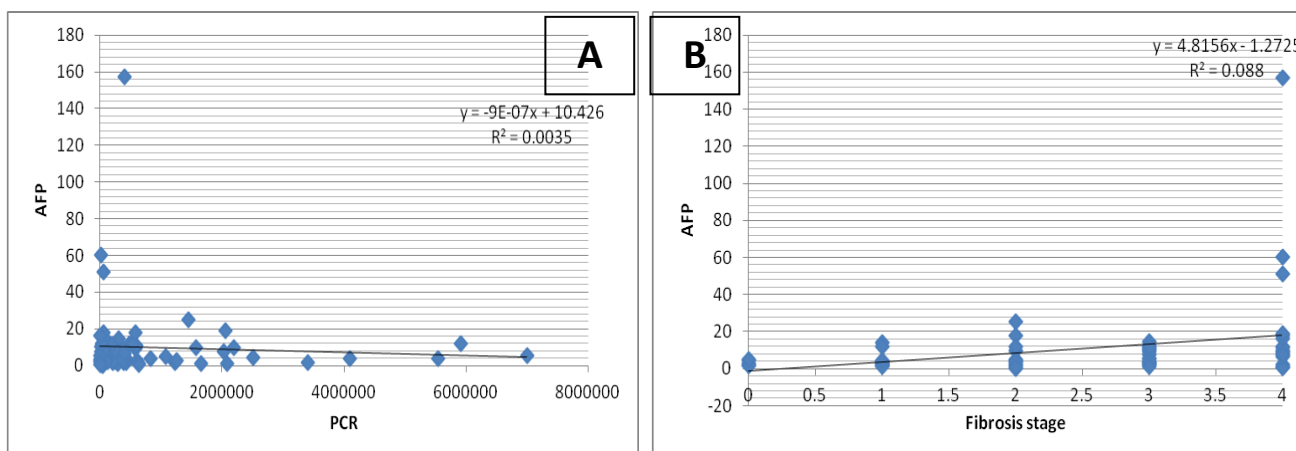


Figure (2): Correlation between AFP level and:

- A- PCR in different stages of liver fibrosis among the study group**
- B- Different stages of liver fibrosis in the study group**

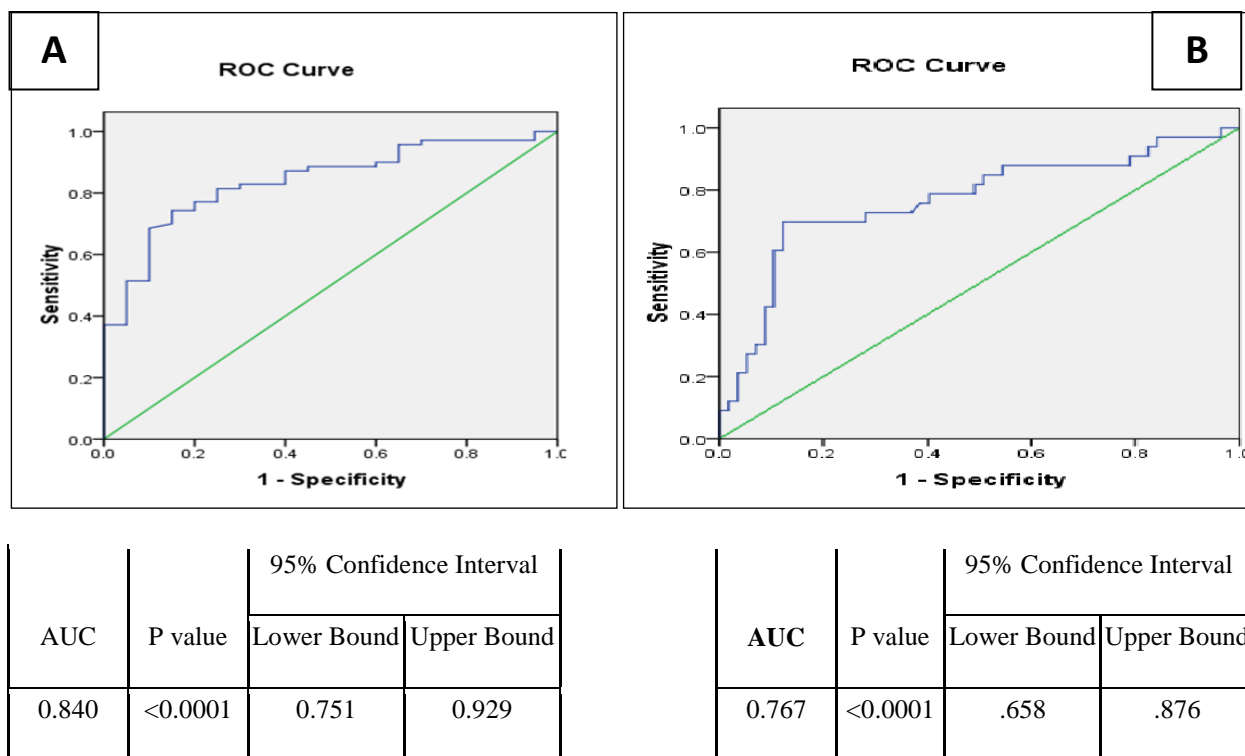


Figure (3): ROC curve to determine AFP level

A- in predicting cases of chronic HCV.

B- in predicting advanced stages of fibrosis “F3 and F4”

Discussion

Hepatitis C virus remains a large health care burden to the world. Chronic hepatitis C virus (HCV) infects approximately 170 million people worldwide (Ravazi et al., 2013) ¹⁰.

Over 15,000 deaths were attributed to chronic hepatitis C virus (HCV) infection in 2007 (Ly et al., 2012) ¹¹. Chronic hepatitis C is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) (Razavi et al., 2013) ¹⁰, which are major indications for liver transplantation in the United States and Europe (Andrade et al., 2009) ¹² with the highest prevalence rate among Egyptians (14% - 18%; approximately 10 fold greater than in the United States and Europe) ¹³.

HCV transmission is ongoing in Egypt, and incidence rates have been estimated at 2.4 per

1,000 person per year (165,000 new infections annually) ^{14,15,16}.

Elevations of serum AFP greater than 20 µg/L were present in patients with HCV related cirrhosis but without HCC with a prevalence ranging from 10% - 43% ¹⁷. This wide discrepancy can be attributed to the difference in the definition of the normal AFP range (10-30ng/ml), patient population, ethnicity and sample size ⁴. Diagnostic Level of AFP for HCC is ≥ 200 ng/ml ^{18,19}. AFP can be re-expressed not only during periods of uncontrolled cell growth, e.g. liver cancer, but also after hepatic injury, including chronic viral hepatitis and cirrhosis ²⁰. Elevated AFP levels are found in patients with viral hepatitis without HCC, especially in those with CHC and liver cirrhosis ²¹.

Few Egyptian studies had assessed the role of alpha- fetoprotein (AFP) levels in chronic hepatitis C patients.

The aim of the current study was to evaluate the clinical significance of Alpha-Fetoprotein (AFP) levels in chronic hepatitis C patients without hepatocellular carcinoma (HCC).

AFP levels in the current study showed higher levels among the study group (9.72 ng/mL) compared to controls (1.7 ng/mL). This is consistent with El-Attar et al. ²²; who found a significant rise of AFP levels among chronic HCV patients compared to healthy controls. It was suggested that elevated serum AFP values among CHC patients without HCC may be the result of altered hepatocyte-hepatocyte interaction associated with a loss of normal architectural arrangements.

In the current study, the correlation between AFP and different lab investigations among the control group and the stages of fibrosis of the study group were none significant, with the exception of total bilirubin level, which showed significant positive correlation with AFP levels among stages F3 and F4; and platelet counts, which showed negative significant correlation with AFP level only among F4 stage patients. This is consistent with Kobesy et al. ²³ who stated that there was a significant negative correlation between platelet counts and AFP level. However, they did not find a significant correlation between total bilirubin level and AFP levels. Also, Hu et al. ¹⁷ found a non significant correlation between AFP levels and total bilirubin levels. On the other hand, Tai et al.

²⁴ found significant correlation between AFP and all liver functions; including total bilirubin levels. ALT and AST levels showed none significant correlation with AFP in this study. ALT levels were similar to those of Chu et al. ²⁵ who reported that in CHC patients ALT levels are mildly elevated and are non significantly associated with AFP. However, these findings were different from those reported by Hu et al. ¹⁷ who found a significant correlation between AFP and liver functions namely AST, ALT and AST/ALT ratio. On the other hand, Richardson et al. ²¹ revealed a highly significant correlation between AFP and ALT levels. Also, Kobeisy et al. ²³ found a significant correlation between ALT and AFP levels.

Regarding viral load association with AFP, PCR showed none significant correlation with AFP level using Pearson correlation test. This is in agreement with both Hu et al. (2004)⁷ and Chu et al. (2001)⁷ studies' in the United States and in Taiwan, respectively, who reported that HCV viral load was not correlated with elevated serum AFP levels.

In the present study, the correlation between AFP and different stages of liver fibrosis was done and revealed a positive highly significant correlation. Using ANOVA test, we found that the mean AFP level increases steadily with increasing the stage of fibrosis, and this result was statistically significant. These findings were consistent with those seen by Kobeisy et al. ²³, Bruce et al. ²⁶, Peng et al. ²⁷, Chen et al. ³, Hu et al. ¹⁷ and Chu et al. ²⁵.

Kobeisy et al.²³ found that the independent variable associated with elevated serum AFP level was the advanced fibrosis stages (F3 and F4), with a significant correlation ($p=0.01$). Bruce et al.²⁶ reported that, elevated AFP level had a high positive predictive value (78%) for advanced stages of fibrosis compared to other stages.

Peng et al.²⁷ reported that liver fibrosis (fibrosis stage F4) is associated with hepatic progenitor cell activation. Furthermore, AFP gene activation is associated with hepatic progenitor cell activation and results in increased AFP production in patients with advanced fibrosis. Hu et al.¹⁷ indicated that elevated serum AFP level was strongly associated with F3 & F4 hepatic fibrosis.

Chu et al.²⁵ found that the severity of fibrosis/cirrhosis was a significant predictor of elevated serum AFP and that higher serum AFP levels were significantly correlated with advanced fibrosis /cirrhosis in patients with chronic HCV.

Concerning the association between AFP and different grades of liver histopathology, there was no significant statistical relation between the mean AFP levels and different grades of histopathological examination. This is in contrast to Chen et al.³ study which revealed a significant statistical relation between both. This may be explained by the higher number of cases that had been studied by Chen et al.³, and the limited percentage of A3 grades in our cases, as it is known that the significance increases with increasing the number of cases.

This study assessed the level of AFP between the steatosis positive and negative cases, steatosis showed positive correlation with higher AFP

levels but this finding was statistically non significant. This finding was similar to that revealed by Mouse et al.²⁸ who found that patients with chronic HCV and steatosis have a higher AFP levels than those without steatosis. Balbi et al.²⁹ found a significant correlation between AFP level and the development of steatosis, and also they found a highly significant correlation between AFP level and the degree of steatosis.

Although predictors for CHC patients with elevated AFP are diverse, advanced fibrosis stages and higher AST levels or low platelet counts are the most common and consistent with most previous studies^{4,17,25}.

Regarding the possible role of AFP as a predictive factor for both chronic liver affection and advanced liver fibrosis in our study, using ROC analysis in our study, we found that AFP can be used to differentiate chronic HCV infection from controls, and when we set a cut-off level of 2.27 ng/mL, the sensitivity was 75.4% and specificity was 85.7%.

Moreover, AFP is seen to be a significant predicting factor for advanced fibrosis among CHC patients, and when we set a cut-off level of 5.17ng/mL, the sensitivity was 69.7% and specificity was 83.8%. These findings were somewhat similar to those of Bruce et al.²⁶ and Hu et al.¹⁷.

Bruce et al.²⁶ revealed that AFP level can be a significant predictor for advanced fibrosis (Ishak stages 3-6) with a sensitivity of 39% and a specificity of 95% when a level of 8 ng/mL is used as a cut-off point.

In the study done by Hu et al.¹⁷, an AFP level 15 ng/mL was used as cut-off value and this revealed a sensitivity of 22.8% and a specificity of 94.5% for detecting advanced stages of fibrosis (F3 & F4). But when they set an AFP level >6 ng/mL as the cut-off value, the sensitivity and specificity for predicting advanced fibrosis was 74.3% and 68.4%, respectively.

According to Bayati et al.³⁰, elevated serum AFP level (more than 17.8ng/ml) was highly specific for the diagnosis of cirrhosis among patients with chronic hepatitis C. AFP value of 17.8ng/mL is 35% sensitive and 98.6% specific for diagnosis of cirrhosis, with a positive predictive value of 97.7%.

These findings indicated that hepatic fibrosis/cirrhosis is more important than necroinflammation in causing an elevation of serum AFP in patient with chronic hepatitis C³⁰.

Using Multivariate logistic regression analyses in this study, advanced fibrosis stages, along with elevated AST, elevated total bilirubin and decreased serum albumin are the most common predictors for elevated AFP. These results are in agreement with those of Chu et al.²⁵ who stated that there was a significantly lower mean serum albumin level in patients with elevated serum AFP when compared with patients without elevated serum AFP and that serum albumin of less than 4.2gm/dl was significantly independent predictor associated with elevated serum AFP and this may be explained by progression of the disease to cirrhosis.

Also, our results are in agreement with those of Di Bisceglie et al.⁴ and Hu et al.¹⁷ who stated that in

patients with chronic HCV elevated serum AFP is independently associated with elevated level of AST.

So, Using multivariate logistic regression analysis for ranking of these variables from the more important to the less important to (predict) higher AFP showed that the most important variable is total bilirubin levels (p=0.008) followed by serum albumin levels (p=0.038). AST, liver echo and advanced fibrosis showed no (causal) relationship to AFP level (p>0.05). This is different from the results seen by Kobeisy et al.²³ who found that, using multivariate analysis; the only significant factor was advanced liver fibrosis stages in predicting higher AFP levels; and this may be explained by the higher number of cases enrolled in their study. Mousa et al.²⁸ which revealed that in chronic HCV with steatosis, elevated AFP levels correlated positively with HAI and negative significant correlation with albumin level.

Serag,³¹ study suggests that serum alpha fetoprotein has significant association with liver damage. The level of alpha fetoprotein may serve as a useful sensitive marker for detection of hepatocellular carcinoma especially at level higher than 400 ng/dl and to differentiate between chronic HCV without cirrhosis and without ascites and between HCV with cirrhosis and with ascites. Alpha fetoprotein may serve as useful marker for follow up the progression of liver damage

The current study proved that determination of serum AFP levels may be useful as a non invasive indicator of severity of liver staging, as it is associated with increased levels of Metavir staging. So serum AFP levels could be routinely

screened in parallel with image studies in HCV positive patients.

Conclusions: • Serum AFP levels are significantly correlated with the serum bilirubin level and platelet count in chronic HCV infection.

• Serum AFP levels increase with advanced stages of liver fibrosis in chronic hepatitis C infection, even without hepatocellular carcinoma.

• Serum AFP levels may be used as a marker for prediction of chronic liver affection and staging of fibrosis.

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