Alpha 1 Acid Glycoprotein Level as a Diagnostic Factor in Patients with Hepatocellular Carcinoma

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Abstract: Background: Hepatocelular carcnoma (HCC) considered the common liver-cancer and the leading to death. The early diagnosises of HCC are the main benefits of HCC screening and α-1-acid glycoprotein (A1AG). The level of A1AG is marker for diagnosing HCC. **Objective**: Evaluation of the clinical utilites of AGP in HCC patients specially in attempt to find its role in diagnosing HCC in early stage. **Methods**: This study was performed on 85 patients recruited from Gastroenterology and Hepatology outpatient clinics and Internal Medicine Departments of Alahrar Zagazig Teaching Hospital, during the period from January2017 to January 2018 after obtaining a written consent from all subjects. **Results**: This study was performed on 85 patients. Group (I): (Healthy individuals) consists of 22 subjects included 10 males (45%) and 12 females (55%) with mean age 55.85±7.74 years. Group (II): (CLD-non HCC group) consists of 26 with cirrhosis included 19 males (73.1%) and 7females (26.9%) with mean age 58.4±4.7years. Group (III): (HCC group) consists of 37 HCC patients included 24 males (64.9%) and 13 females (35.1%) with mean age 60.45 ± 4.6 years. **Conclusion**: AGP is a sensitive and specific tumor marker for detection of HCC, especially for low AFP HCC. Combination between AGP and AFP increases the sensitivity and specificity of the diagnosis of HCC.

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Key words; HCC, diagnosis, cirrhosis, tumor, liver, 1-acid glycoprotein, fucosylation, glycoforms, diagnosis, prognosis.

1. Introduction

Hepatocelular carcnoma (HCC) is the most common malignancies in the world [1], the second cause of death from cancer worldwide, who estimated to be responsible for nearly 746,000 deaths in 2012 (9.1 % of the total) [2].

In most of the cases, HCC is diagnosed in its advanced stage so that the treatment options are limited with lower survival rate is less than 5%[3].

Currently, AFP was used as tumor marker for detection of HCC and considerable more advanced stages would be missed unless another diagnostic tools are used [4].

Several biomrkers are promising, but none of these markers has been validated for clinical use [5].

Another potential biomarker for HCC is alpha one acid glycoprotein (AGP). Cytokines can cause plasma AGP level to increase as part of an inflammatory response [6]. AGP has been suggested to be apotential marker for diagnosiing cirrhosis and HCC [7]. It will improve acc.uracy of diagnosis of HCC. So, AGP may be a useful tumour marker for HCC.

2. Materials and Methods

This study was performed on 85 patients recruited from Gastroenterology and Hepatology outpatient clinics and Internal Medicine Departments of ALAHRAR ZAGAZIG TEACHING HOSPITAL, during the period from January2017 to January 2018 after obtaining a written consent from all subjects.

Exclusion criteria:

- Age < 18 years.
- Alcohol use.
- HIV co infection.
- Autoimmune hepatitis.
- Known cases of malignancy (ovary, breast, pancreas).
- Asthmatic patients.
- Pregnant.

Methods:

All patients were subjected to: History taking, Physical examination and laboratory investigations: [Liver function tests (ALT.AST. total bilirubin, PT, PTT, serum albumin), Measurement of serum level of

Alpha fetoprotein (AFP) by ELISA technique, Measurement of serum level of alpha 1 acid glycoprotein (AAG) by ELISA technique]. A multidisciplinary approach includes clinical, abdominal image, and laboratory modalities with or without liver biopsy (in certain cases) to establish the diagnosis of HCC was applied. HCC was diagnosed by abdominal ultrasonography showing hepatic focal lesion (s), characteristic of HCC and serum level of alpha fetoprotein (AFP) > 250ng/dl.

3. Results

See the following Tables 1-8.

Table (1): Age distribution among studied groups

		N	Mean	Std. Deviation	Minimum	Maximum	F	P
Age	Control	**22**	**55.8273**	**7.74555**	**52.00**	**68.00**	**1.841**	**0.091**
	Cirrhosis	**26**	**58.4615**	**4.75168**	**51.00**	**67.00**		
	HCC	**37**	**60.4595**	**4.67020**	**52.00**	**68.00**		

No significant difference among groups regarding age.

Table (2): Sex distribution among studied groups

			Group			Total	X^2	P
			Control	Cirrhosis	HCC			
Sex	Male	N	**10**	**19**	**24**	**53**	**4.04**	**0.13**
		%	**45.5%**	**73.1%**	**64.9%**	**62.4%**		
	Female	N	**12**	**7**	**13**	**32**		
		%	**54.5%**	**26.9%**	**35.1%**	**37.6%**		
Total		N	**22**	**26**	**37**	**85**		
		%	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

Regarding the Age and sex there were no statistically significant difference between group (I), (II) and group (III) which means that their age and sex were matched.

Table (3): CBC distribution among studied groups

		N	Mean	Std. Deviation	Minimum	Maximum	F/ Kruskal Wallis	P
HB	Control	**22**	**13.1136**	**1.67710**	**10.90**	**18.20**	**17.399**	**0.00****
	Cirrhosis	**26**	**12.2385**	**1.87895**	**8.20**	**15.40**		
	HCC	**37**	**10.5541**	**1.56642**	**8.10**	**14.40**		
WBCs	Control	**22**	**7.2227**	**.86681**	**5.60**	**9.10**	**4.241**	**0.018***
	Cirrhosis	**26**	**7.0731**	**1.92116**	**4.20**	**10.50**		
	HCC	**37**	**5.8432**	**2.55523**	**1.90**	**10.30**		
SPLT	Control	**22**	**367.0909**	**67.24292**	**220.00**	**501.00**	**160.653**	**0.00****
	Cirrhosis	**26**	**172.7385**	**59.03479**	**86.00**	**291.00**		
	HCC	**37**	**100.4324**	**44.62034**	**22.00**	**205.00**		

In this study we found that there were statistically significant difference between the three groups regarding HB, WBCs and platelets. We found that HCC group is lower regard HB and WBCS and cirrhotic group is lower than control. At the same time HCC group is lower than both of them regard platelets.

Table (4): Liver and kidney function distribution

		N	Mean	Std. Deviation	Minimum	Maximum	F/ Kruskal Wallis	P
Albumin	Control	22	4.3727	.36798	3.80	5.00	107.834	0.00**
	Cirrhosis	26	3.3615	.51542	2.50	4.40		
	HCC	37	2.4108	.55367	1.50	3.40		
INR	Control	22	.9636	.10022	.80	1.10	45.106	0.00**
	Cirrhosis	26	1.3115	.27904	1.00	2.20		
	HCC	37	1.7432	.40107	1.00	3.20		
PT	Control	22	10.8909	.29262	10.00	11.30	77.094	0.00**
	Cirrhosis	26	11.5769	.90213	10.30	14.00		
	HCC	37	14.6892	1.75844	10.40	17.00		
APTT	Control	22	30.0273	.74908	29.00	31.20	41.253	0.00**
	Cirrhosis	26	31.3385	2.22604	29.00	39.60		
	HCC	37	34.5811	2.30625	29.80	38.00		
T bilirubin	Control	22	.8591	.17088	.40	1.10	13.784	0.00**
	Cirrhosis	26	1.2769	1.29161	.10	5.50		
	HCC	37	3.0676	2.40394	.70	14.10		
D bilirubin	Control	22	.4273	.17777	.10	.70	8.227	0.001**
	Cirrhosis	26	.8000	.56639	.10	2.30		
	HCC	37	1.2405	1.03399	.20	5.60		
AFP	Control	22	6.1364	1.88466	3.00	9.00	55.302	0.00**
	Cirrhosis	26	8.4231	4.51817	2.00	22.00		
	HCC*	37	432.0405	278.53965	4.90	1120.00		
AST	Control	22	23.3182	4.68418	15.00	31.00	30.631	0.00**
	Cirrhosis	26	24.9231	8.89460	12.00	41.00		
	HCC*	37	55.1081	26.00297	11.00	150.00		
ALT	Control	22	24.4545	5.22564	15.00	31.00	10.124	0.00**
	Cirrhosis	26	25.0385	9.21946	11.00	46.00		
	HCC*	37	38.4054	19.03864	12.00	100.00		
Cr	Control*	22	.7955	.25908	.30	1.20	18.710	0.00**
	Cirrhosis	26	1.0231	.20260	.70	1.50		
	HCC	37	1.1973	.26192	.50	1.60		

There is high significant difference between three groups regarding Albumin, Bilirubin, PT, PTT, INR, AST and Creatinine with high disturbance of all liver function tests among HCC group.

Table (5): AGP distribution among studied groups

	N	Mean	Std. Deviation	Minimum	Maximum	Kruskal Walis	P
Control	22	83.8636	36.66748	40.00	190.00	60.45	0.00**
Cirrhosis	26	595.0385	316.64876	103.00	1200.00		
HCC	37	2712.4595	1171.24599	750.00	5672.00		

HCC group is significant higher than other groups regarding AGP.

Table (6): Ascites distribution among studied groups

			Group			Total	X^2	P
			Control	Cirrhosis	HCC			
Ascites	No	N	**22**	**23**	**6**	**51**	**53.8**	**0.00****
		%	**100.0%**	**88.5%**	**16.2%**	**60.0%**		
	Mild	N	**0**	**1**	**8**	**9**		
		%	**0.0%**	**3.8%**	**21.6%**	**10.6%**		
	Moderate	N	**0**	**2**	**11**	**13**		
		%	**0.0%**	**7.7%**	**29.7%**	**15.3%**		
	Tense	N	**0**	**0**	**12**	**12**		
		%	**0.0%**	**0.0%**	**32.4%**	**14.1%**		
Total		N	**22**	**26**	**37**	**85**		
		%	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

Moderate and Tense ascites is highly associated with HCC group. Mild and Moderate ascites occurred in cirrhotic group but also less than occurring among HCC group.

Table (7): HE Distribution

			Group			Total	X^2	P
			Control	Cirrhosis	HCC			
HE	.00	N	**22**	**26**	**17**	**65**	**33.92**	**0.00****
		%	**100.0%**	**100.0%**	**45.9%**	**76.5%**		
	1.00	N	**0**	**0**	**10**	**10**		
		%	**0.0%**	**0.0%**	**27.0%**	**11.8%**		
	2.00	N	**0**	**0**	**9**	**9**		
		%	**0.0%**	**0.0%**	**24.3%**	**10.6%**		
	3.00	N	**0**	**0**	**1**	**1**		
		%	**0.0%**	**0.0%**	**2.7%**	**1.2%**		
Total		N	**22**	**26**	**37**	**85**		
		%	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

There is significant association of hepatic encephalopathy with HCC group.

Table (8): Association and agreement of AGP:

			Group		Total	X^2	P	Kappa agreement
			Control	Cirrhosis				
AGP	< 907.5	N	**44**	**2**	**46**	**62.6**	**0.00****	**0.85**
		%	**91.7%**	**5.4%**	**54.1%**			
	> 907.5	N	**4**	**35**	**39**			
		%	**8.3%**	**94.6%**	**45.9%**			
Total		N	**48**	**37**	**85**			
		%	**100.0%**	**100.0%**	**100.0%**			

Significant association and agreement with Sensitivity 94.6% Specificity 91.7%
PPV 89.7% NPV 95.6%

4. Discussion

Hepatocellular carcinoma (HCC) is estimated to be responsible for nearly 746,000 deaths in 2012 (9.1 % of the total).

As the five-year survival rate after diagnosis at an advanced stage is less than 5%, novel diagnostic techniques allowing for detection at early stage HCC are in high demand.

Currently, AFP serum AFP is not for a diagnostic level in all patients, particularly small HCC, and advanced stages would be missed diagnostic tools are used.

All patients were neither Alcoholic, nor asthmatic and non pregnant, also negative for HIV, Cancer ovary, Cancer breast and Cancer pancreas by clinical examination and pelvi-abdominal CT.

Regarding the Age and sex there were no statistically significant difference between group (I), (II) and group (III) which means that their age and sex were matched. In this study we found that there were statistically significant difference between the three groups regarding the CBC, BUN, Albumin, PTT, PT, AST and Bilirubin. We found that HCC group is lower regard HB and WBCS and cirrhotic group is lower than control. At the same time HCC group is lower than both of them regard platelets.

As regards the median levels of AGP, there was statistically significant difference between the three groups with levels reported as median because of skewed data distribution (non parametric), the median level of AGP in group (I) was (83.8, 40-190)µg/ml while for group (II) (595, 103-1200)µg/ml and for group (III) (3373, 750-7173) µg/ml this result agrees with Bachtiar et al., (2010), who stated that the median levels of AGP in the HCC group were for AFP high group (950.4,387.2-2748.8) µg/ml and AFP low group (1501.2,395.6-4419.5) µg/ml and for control group (cirrhotics and chronic hepatitis) (369.5,108.2-883.9) µg/ml.

There were positive significant correlation between AGP and age, INR, PT, PTT and ASTwhile it showed no significant correlation with CBC, kidney functions and other liver function tests, (and this may be explained by presence of HCC affecting the biliary tree) these correlations were not discussed in the study of Bachtiar et al., (2010) or Kang et al., (2010).

Regarding the levels of AFP there was highly significant difference between the first two groups (control) and the third one (HCC) with mean level (6.1± 1.88) ng/ml for health group (I) and (8.4±4.5) ng/ml for the cirrhotic group (II) and (432±278.5) ng/ml for HCC group (III), this agrees with Bachtiar et al., (2010) who stated that the levels of AFP shows was highly significant difference between the two groups (P<0.001) with median levels (2.9,0.4-151.8)) ng/ml and (29,0.4-444550) ng/ml for the cirrhotic and HCC group respectively and also it agrees with Gomaa et al., (2012), who stated that mean level of AFP in HCC group was (987.1±752.4ng/ml), cirrhosis group (32.7±19.2ng/ml) with highly significant difference between the two groups (P<0.001) and also agrees with Mohamed et al., (2013) who stated that there was highly significant difference between AFP levels in HCC group and cirrhotic group with mean levels (266.5±200) ng/ml and (49.6±50) ng/ml.

For the AGP at cut-off value (907.5µg/mL) it has sensitivity 94.6% and specificity 91.7% with PPV (89.7%) & NPV (95.6%), this agrees with Bachtiar et al., (2010) who stated that at cut off level 800µg/ml AGP shows sensitivity 71% and specificity 95% with PPV 95% & NPV 72%, and also agrees with Kang et al., (2010) who stated that at cut off level 716.7µg/ml AGP shows sensitivity 70% and specificity 90%, noting that the higher sensitivity and specificity in our study is obtained at higher cut off value.

Conclusion

AGP is a sensitive and specific tumor marker for detection of HCC, especially for low AFP HCC. Combination between AGP and AFP increases the sensitivity and specificity of the diagnosis of HCC. The use of AGP will improve the sensitivity and accuracy of diagnosis of HCC and so, AGP can be used with U/S in screening of HCC. Further, multicentre studies with larger number of HCC and cirrhotic patients are needed for the exact validation of the sensitivity and specificity of AGP in the diagnosis and screening of HCC.

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