International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
DOI: 10.22192/ijarbs Coden: IJARQG(USA) Volume 4, Issue 3 - 2017

Research Article

DOI: http://dx.doi.org/10.22192/ijarbs.2017.04.03.009

Evaluation of Alpha One Acid Glycoprotein as a biological Marker in Hepatocellular Carcinoma

Rady H[1], Mohy- eldin M[2], Abdo M[2], Saleh M[3], Gad, A[2]
Internal Medicine Department; Mansoura new hospital [1], Internal Medicine Department; Suez Canal University Hospital[2], Clinical Pathology Department; Suez Canal University Hospital [3]
Faculty of Medicine_Suez Canal University
Corresponding Author: Gad A ,
Associate professor, Internal Medicine Department, Suez Canal University School of Medicine,
Al- Nouras city, Blok 29, group 2, Ismailia, Egypt.
E-mail: *amalahgad@gmail.com*
Tel. +96565935445, +201097226108, Fax +96522469628

Abstract

Background: Hepatocellular carcinoma (HCC) is the most common liver cancer and the third leading cause of cancer death. The early diagnosis of HCC and the subsequent chance to select suitable treatment are the main benefits of HCC screening. α-1-acid glycoprotein (A1AG) is a member of the lipocalins and is an acute phase reactant protein. The level of A1AG has been suggested to be a potential marker for diagnosing HCC. **Aim:** The present study aimed to evaluate the role of A1AG in diagnosis of HCC. **Methods:** The study recruited 38 HCC and 38 age/sex matched liver cirrhosis patients. All patients were subjected to careful history taking, thorough clinical examination and laboratory investigations including AFP and AGP. **Results:** HCC patients had significantly higher A1AG when compared with cirrhosis patients. However, no significant correlation was found between A1AG and the various laboratory data. Our study also showed that At a cut-off 1550, A1AG has a sensitivity, specificity, positive predictive value and negative predictive value of 81.6 %, 74.3 %, 77.0 % and 78.0 % respectively with an area under the ROC of 0.85, P=0.042 which suggests that A1AG is a good diagnostic marker for HCC. **Conclusion:** A1AG is a reliable marker for diagnosis of HCC.

Keywords: diagnosis, cirrhosis, tumor, liver

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer related deaths worldwide (El-Serag et al., 2008). Approximately 80% of HCC cases arises in the developing countries. In Egypt, there is a rising trend of HCC, as there is a two fold increase in the proportion of HCC among chronic liver disease patients over the last decade (El-Zayadi et al., 2005).

If hepatocellular carcinoma diagnosed at an early stage, patients could be subjected to any of the available therapeutic options that may provide a high rate of complete response.(Peng et al, 2004). Therefore, it is very important to detect HCC and its recurrence at an early stage. The primary marker for hepatocellular carcinoma is alpha- fetoprotein (AFP)

Generally, alpha-fetoprotein shows acceptable sensitivity, however, it is not secreted in all cases of hepatocellular carcinoma and may be normal in 40% of patients with early hepatocellular carcinoma (Nakatsura et al., 2003). Moreover, equivocal alpha-fetoprotein concentrations are common in non-malignant chronic liver diseases (CLD) and its sensitivity for hepatocellular carcinoma in this setting tends to be low (Giannelli G et al., 2007). Alpha-1-acid glycoprotein (AAG) is an acute phase protein, synthesized predominantly in the liver. Cytokines can cause plasma AAG level to increase as a part of inflammatory response. (Fournieret al, 2000). The plasma level of AAG has been suggested to be a potential marker for diagnosing cirrhosis and HCC. (Paul et al, 2006). It is also known as orosomucoid (ORM), synthesized mainly by hepatocytes and circulates in the blood at concent-rations between 0.6 and 1.2 mg/ml, which corresponds 1 -- 3% of the total proteins in the blood of a healthy person (Allen et al., 1977). Since AGP blood concentration increases with certain pathologic processes, it has been tested for possible diagnostic applications. Promising results were obtained by (Bachtiar et al., 2010) compared AGP with des–carboxyprothrombin (DCP); and showed that AGP is more sensitive when AFP levels are low, while DCP is a better indicator under high AFP levels. In the study of (Kim et al., 2006), the authors measured the serum AGP concentration of patients with a variety of hepatic diseases or non-hepatic diseases and evaluated . Serum AGP value was moderately increased in patients with active chronic hepatitis but only slightly increased in inactive chronic hepatitis cases compared to the outstanding increase in liver cirrhosis (LC) and hepatocellular carcinoma (HCC) cases. These results indicate that AGP may be positively correlated with a progression of hepatic disease to an advanced state. Similarly,(Bachtiar et al., 2009) demonstrates that AGP is increased in patients with HCC in comparison to chronic liver disease (CLD). Interestingly, 83.3% among HCC patients who had AFP concentration below diagnostic concentration (20 ng/ml) demonstrated higher AGP values. Since some HCC patients even have low or negative AFP concentration in the terminal stage of their disease. By using serum AGP in combination with AFP, a diagnostic model for HCC detection with high sensitivity and specificity has been generated with a specificity of 90%, sensitivity of 89.0%. ROC analysis of AFP in combination with AGP yielded higher AUC of 0.943 compared to 0.750 for AFP alone (Bachtiar et al., 2009) All these findings gave us a rationale to further study the validity of AGP stratified according to AFP concentration and to evaluate in the hope that this could be a potential diagnostic test of HCC.

Materials and Methods

This is a cross sectional study, performed in the Internal Medicine Department of both Suez Canal university and Mansoura new general hospital, including 76 adults (> 18 years), with cirrhosis; of them 38 were non- HCC cirrhotic and 38 were HCC-liver cirrhotic

Exclusion criteria:

Pregnant women, previous intervention (surgical or non-surgical) for HCCl

Ethical consideration: All patients and controls signed an informed written consent after explanation of the aim of the study.

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 (Kim et al., 2012). HCC was diagnosed by abdominal ultrasonography showing hepatic focal lesion(s), characteristic of HCC and serum level of alpha fetoprotein (AFP) > 250ng/dl (Gan Y et al., 2014).

Results

This study , included 76 adults (>18 years), with cirrhosis; of them 38 were HCC cirrhotic and 38 were non- HCC- liver cirrhotic, with a mean± SD age of 47.4 ± 5.7 vs.46.2 ± 5.5respectively, p=0.35 and female n(%) of 12 (31.6 %) vs.14 (36.8 %) respectively, p= 0.63. There was no statistically significant differences between the studied groups regarding their demographic background.

HCC patients were found to have a significantly higher serum albumin and lower bilirubin levels when compared with cirrhosis patients (table 1).

Table-1 Comparison between the studied groups regarding liver functions

	HCC n= 38	Cirrhosis n=38	Student t test	
			t	p
Albumin	3.2 ± 0.7	2.6 ± 0.4	4.8	0.0001*
Bilirubin	1.4 ± 0.9	3.5 ± 5.3	-2.37	0.022*
SGPT	63.1 ± 30.9	54.5 ± 23.4	1.37	0.17
SGOT	99.1 ± 65.4	79.2 ± 49.3	1.49	0.13
Creatinine	0.97 ± 0.3	1.09 ± 0.3	-1.55	0.12
Platelets	130.7 ± 70.3	126.1 ± 29.7	1.79	0.17
INR	1.26 ± 0.31	1.24 ± 0.42	-1.6	0.11

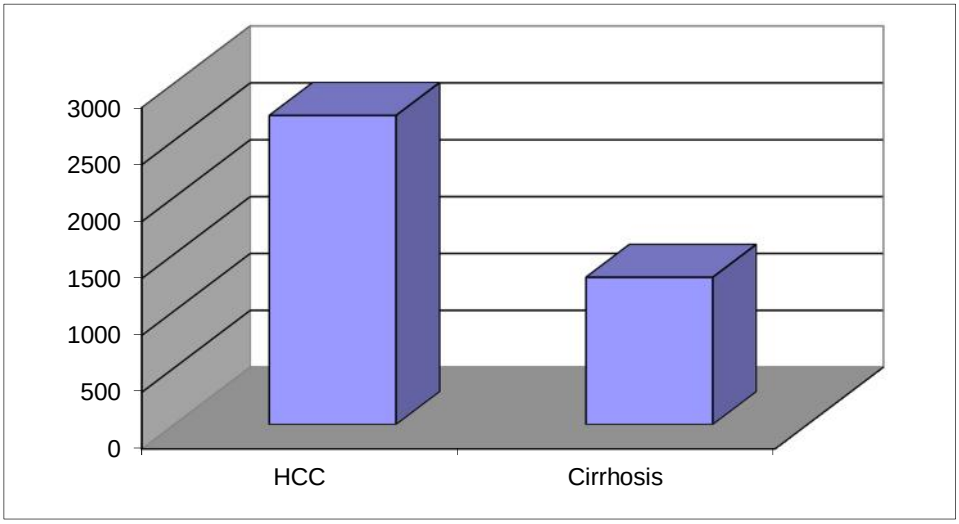
*This table shows that HCC patients had significantly higher albumin and lower bilirubin levels when compared with cirrhosis patients.

HCC patients had significantly higher AFP when compared with cirrhosis patients. Similarly, HCC patients had a significantly higher serum A1AG when compared with non- HCC cirrhotic patients (table 2, figure 1).

Table-2 Comparison between the studied groups regarding their serum level of both AFP and A1AG

	HCC n= 38	Cirrhosis n=38	Student t test	
			t	p
AFP	597.08 ± 563.1	5.9 ± 2.8	6.47	0.0001*
A1AG	2717.3 ± 1336.6	1294.2 ± 475.2	46.2	0.001*

Figure 1: Serum A1AG level in HCC compared with non- HCC cirrhotic patients.



Multivariate analysis showed that A1G1 is a good diagnostic marker for HCC At a cut-off of 1550, it has a sensitivity, specificity, positive predictive value and negative predictive value of 81.6 %, 74.3 %, 77.0 % and 78.0 % with AUC = 0.85 and P=0.042 (table 5, figure 2)

Table-3 Correlation between AFP and other variables in HCC patients

	AFP	
	r	p
Albumin	0.09	0.58
Bilirubin	0.027	0.87
SGPT	-0.007	0.96
SGOT	0.05	0.74
Creatinine	0.024	0.88
Platelets	-0.07	0.66
INR	0.05	0.75
A1AG	0.21	0.18

This table shows no statistically significant correlation between AFP and the laboratory data

Table-4 Correlation between serum A1AG and other variables in HCC patients

	A1AG	
	r	p
Albumin	0.074	0.65
Bilirubin	0.17	0.3
SGPT	0.14	0.39
SGOT	-0.023	0.88
Creatinine	0.17	0.27
Platelets	-0.09	0.58
INR	-0.039	0.81

This table shows no statistically significant correlation between A1AG and the laboratory data.

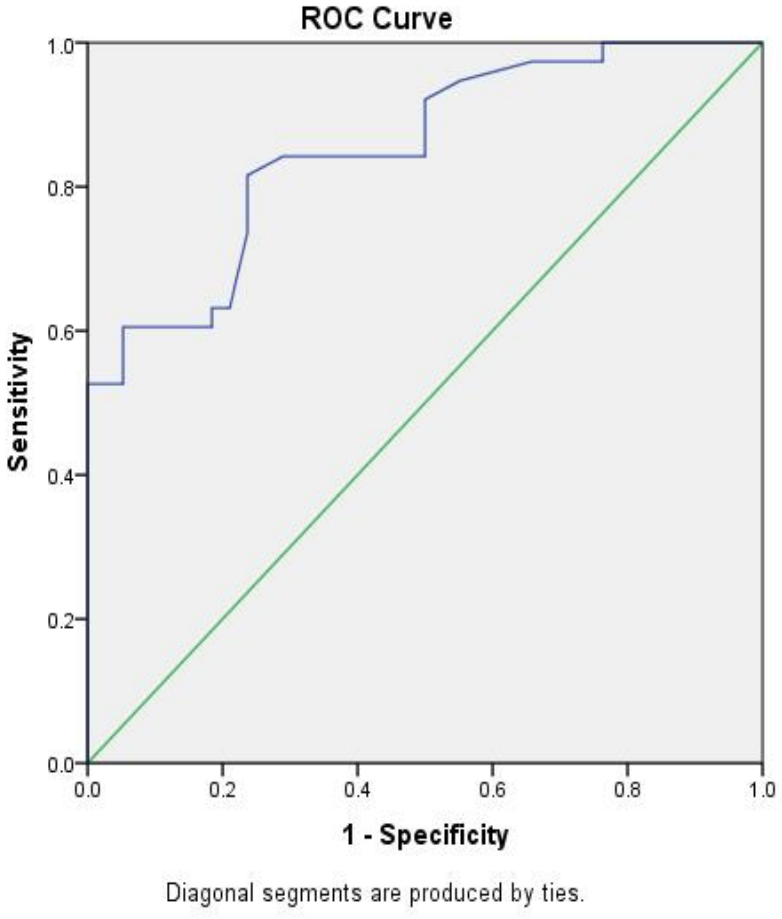
Table-5 Value of A1G1 in diagnosis of HCC

AUC	0.85
P	0.042*
Cut off	1550
Sensitivity	81.6 %
Specificity	74.3 %
Positive predictive value	77.0 %
Negative predictive value	78.0 %

This table shows that A1G1 is a good diagnostic marker for HCC At a cut-off of 1550, it has a sensitivity, specificity, positive predictive value and negative predictive value of 81.6 %, 74.3 %, 77.0 % and 78.0 % with AUC = 0.85 and P=0.042

.

Fig. (2) ROC curve for A1G1



Discussion

AFP has limited sensitivity for HCC diagnosis ***(Chen and Lee, 2011).*** In addition, several other biomarkers like human hepatocyte growth factor, and insulin-like growth factor-1, are promising, but none of these markers has been validated for clinical use ***(Spangenberg et al., 2006).*** A1AG has been suggested to be a potential marker for diagnosing HCC ***(Mooney et al., 2006).*** The present study aimed to evaluate the role of A1AG in diagnosis of HCC. The study recruited 38 HCC compared to 38 liver cirrhosis patients. Both groups were matched for age and sex.

In our study, HCC patients had significantly higher AFP when compared with cirrhosis patients. These results are in agreement with the study of ***Mital et al., (2013)*** who found that AFP is markedly elevated in HCC patients when compared with cirrhotic patients and control group, while no statistically significant differences was noted between cirrhotic patients and controls.

Our results showed a significantly higher A1AG in the HCC compared with non- HCC cirrhotic patients. Our study also showed a sensitivity, specificity, positive predictive value and negative predictive value of 81.6 %, 74.3 %, 77.0 % and 78.0 % with AUC = 0.85 and P=0.042 for A1AG as a diagnostic marker for HCC. These data are in agreement with the study of ***Kim et al., (2006)*** who found that Serum A1AG concentration in 83% of patients with liver cirrhosis (LC) and 89% of patients with hepatocellular carcinoma (HCC) was increased with a cutoff value (1.33 microg/ml). The area under ROC was 0.919 for LC and 0.946 for HCC. The authors concluded that Serum A1AG concentration exhibited good diagnostic accuracy as a biochemical marker for LC and HCC. In another study; ***Bachtiar et al., (2009)*** evaluated the diagnostic value A1AG alone and in combination with AFP in HCC patients. The expression of AAG was significantly higher in HCC patients than chronic liver disease with a sensitivity of (77%) and accuracy of (83%) with an area under the

ROC of 0.907. Furthermore, the study of ***Bachtiar et al., (2010)*** determined the performances of AAG and des-γ-carboxy prothrombin (DCP) for the diagnosis of HCC, especially for low AFP HCC patients. In their study, 124 had HCC, and 61 (49%) of them were AFP-low HCC (AFP ≤ 20 ng/mL). The remaining 96 patients, including 49 with chronic hepatitis B or C and 47 with cirrhosis, were considered as control. When all patients with HCC were evaluated, the area under ROC curve for AAG was 0.94 (95% CI: 0.91-0.97). The sensitivity of AAG was higher in AFP-low HCC than in AFP-high HCC (82% and 62%, respectively).

Moreover, the study of ***Gani et al., (2015)*** evaluated the use of AAG alone for diagnosing HCC and in combination with AFP as part of routine examination in liver cirrhosis patients. A hundred and six patients were included in this study. In their study, the accuracy was 76.5%.

References

Allen PC, Hill EA, Stokes AM. Alpha 1-acid glycoprotein in plasma proteins: analytical and preparative techniques. Blackwell Scientific; Oxford (UK): 1977. p. 207-9

Bachtiar I, Kheng V, Wibowo GA, Gani RA, Hasan I, Sanityoso A, Budhihusodo U, Lelosutan SA, Martamala R, Achwan WA, Soemoharjo S, Sulaiman A, Lesmana LA, Tai S. Alpha-1-acid glycoprotein as potential biomarker for alpha-fetoprotein-low hepatocellular carcinoma. BMC Res Notes. 2010 Nov 23;3:319.

Bachtiar I, Santoso JM, Atmanegara B, Gani RA, Hasan I, Lesmana LA, Sulaiman A, Gu J, Tai S: Combination of α-1-acid glycoprotein and α-fetoprotein as an improved diagnostic tool for hepatocellular carcinoma. Clin Chim Acta 2009, 399:97-101.

Chen, C.J.; Lee, M.H. Early diagnosis of hepatocellular carcinoma by multiple microRNAs: validity, efficacy, and cost-effectiveness. J Clin Oncol. 2011, 29, 4745-4747.

El-Serag H, Marrero J, Rudolph, et al., (May 2008). Diagnosis and treatment of hepatocellular carcinoma. Volume 134: 1752-1763.

el-Zayadi AR, Badran HM, Barakat EM, Attia Mel-D, Shawky S, Mohamed MK, Selim O, Saeid A. Hepatocellular carcinoma in Egypt: a single center study over a decade. *World J Gastroenterol* 2005; 11: 5193-5198

Fournier T, Medjoube N, Porquet Alpha-1-acid glycoprotein. Biochim Biophys Acta, D 2000; 1482:157-171.

Gan Y, Liang Q, Song X. Diagnostic value of alpha-L-fucosidase for hepatocellular carcinoma: a meta-analysis. *Tumour Biol* 2014; 35: 3953-3960

Gani RA, Suryamin M, Hasan I, Lesmana CR, Sanityoso A. Performance of Alpha Fetoprotein in Combination with Alpha-1-acid Glycoprotein for Diagnosis of Hepatocellular Carcinoma Among Liver Cirrhosis Patients. Acta Med Indones. 2015 Jul;47(3):216-22.

Giannelli G, Fransvea E, Trerotoli P. Clinical validation of combined serological biomarkers for improved hepatocellular carcinoma diagnosis in 961 patients. Clin Chim Acta 2007;383:147–52.

Kim BK, Kim SU, Park JY, Kim do Y, Ahn SH, et al.,. Applicability of BCLC stage for prognostic stratification in comparison with other staging systems: single center experience from long-term clinical outcomes of 1717 treatment-naïve patients with hepatocellular carcinoma. *Liver Int* 2012; 32: 1120-1127

Kim KA, Lee EY, Kang JH. Diagnostic accuracy of serum asialo-α1-acid glycoprotein concentration for the differential diagnosis of liver cirrhosis and hepatocellular carcinoma. Clin Chim Acta 2006;369:46–51.

Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. *J Clin Gastroenterol* 2013; 47 Suppl: S2-S6

Mooney P, Hayes P, Smith K. The putative use of alpha-1-acid glycoprotein as a non-invasive marker of fibrosis. Biomed Chromatogr. 2006 Dec;20(12):1351-8.

Nakatsura T, Yoshitake Y, Senju S, et al. (2003): Glypican-3 overexpressed specifically in human hepatocellular carcinoma, is a novel tumor marker Biochem Biophys Res Commun. 2003; 306:16-25.

Paul M, Peter H Kevin S The putative use of -1-acid glycoprotein as a noninvasive marker of fibrosis. Biomed Chromatogr 2006; 20:1351-1358.

Peng SY, Chen WJ, La PL et al., High alpha-fetoprotein level correlates with high stage, early recurrence and poor prognosis of hepatocellular carcinoma: significance of hepatitis virus infection, age, p53 and beta-catenin mutations. Int J Cancer 2004; 112(1):44-50.

Spangenberg, H.C.; Thimme, R.; Blum, H.E. Serum markers of hepatocellular carcinoma. Semin Liver Dis. 2006, 26,385-390.

Access this Article in Online	
	Website: www.ijarbs.com
Quick Response Code	Subject: Medicine
DOI:10.22192/ijarbs.2017.04.03.009	

How to cite this article:
Rady H, Mohy- eldin M, Abdo M, Saleh M, Gad, A. (2017). Evaluation of Alpha One Acid Glycoprotein as a biological Marker in Hepatocellular Carcinoma. Int. J. Adv. Res. Biol. Sci. 4(3): 86-92.
DOI: http://dx.doi.org/10.22192/ijarbs.2017.04.03.009