HEPATOCELLULAR CARCINOMA: CORRELATION OF ALPHA-FETOPROTEIN WITH TUMOUR CHARACTERISTICS

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ABSTRACT

Objective: To determine the correlation of alpha-fetoprotein (AFP) levels with tumour characteristics in hepatocellular carcinoma (HCC).

Study Design: Cross sectional study.

Place and Duration of Study: Pak Emirates Military Hospital Rawalpindi, from Oct 2014 to Feb 2016.

Methodology: It was a cross sectional study in which all patients with a diagnosis of hepatocellular carcinoma presenting to Pak Emirates Military Hospital (PEMH) Rawalpindi, from Oct 2014 to Feb 2016 were enrolled. They underwent testing for alpha-fetoprotein levels and investigations were carried out to determine Barcelona Clinic Liver Cancer (BCLC) staging and Child-Pugh classification. Patients' age, gender, underlying aetiology of liver disease, alpha-fetoprotein levels, number and size of hepatocellular carcinoma lesions, Child–Pugh class and Barcelona Clinic Liver Cancer stage and vascular invasion by the tumour were noted in a proforma. Alpha-fetoprotein levels were categorised into within normal limit, 8.5-100 ng/ml, 100-1000 ng/ml and >1000ng/ml. Data were entered in SPSS version 22 and descriptive statistics were used to calculate frequencies, means and standard deviation. Spearman correlation was used to find correlation between alpha-fetoprotein levels and other variables.

Results: Out of 100 patients 67 (67%) were men and 33 (33%) were women. Mean age was 58.23 yrs (SD ± 10.355). Majority (seventy nine, 79%) of patients had chronic liver disease due to hepatitis C virus. In majority (sixty, 60%) of patients size of the tumour was more than 5 cm, and hepatocellular carcinoma was mono-nodular in 62 patients. Positive correlation was seen between alpha-fetoprotein levels and Barcelona Clinic Liver Cancer stage of the tumour. Positive correlation was also seen between alpha-fetoprotein level and number and size of the tumour although it wasn't statistically significant.

Conclusion: Alpha-fetoprotein levels are positively correlated with Barcelona Clinic Liver Cancer stage of the tumour.

Keywords: Alpha-fetoprotein, Cirrhosis, Hepatocellular carcinoma.

INTRODUCTION

Alfa fetoprotein (AFP) is a glycoprotein which is normally produced during gestation by foetal hepatocytes and yolk sac. It also serves as a tumour marker for several malignancies which include hepatocellular carcinoma (HCC), gastric carcinoma, and tumours of gonadal origin. Higher than normal levels of AFP may also be seen in acute or chronic viral hepatitis[1] and cirrhosis of liver but in a high-risk patient a level of greater than 500mcg/L is considered diagnostic for HCC[2]. HCC is a fairly common tumor in Pakistan with an age adjusted rate of 7.6/100000 for men and 2.8/100000 for women[3]. Similar gender trends have been reported in other studies as well[4,5]. HCC in Pakistan mainly occurs on back-ground of cirrhotic liver due to chronic viral hepatitis[6,7], and has a poor prognosis if left untreated[8].

It has been debated if AFP levels correlate with tumour characteristics such as size, number, stage and aetiology and various studies have reported conflicting results. Many studies report that there is no such correlation[9] but recently few local studies have reported significant correlation between levels of AFP and tumour size and poor prognosis[10-12]. In present study, we tried to determine if any such correlation exists.

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METHODOLOGY

It was a cross sectional study. A sample size of 100 was calculated by using a prevalence of 5.2 per 100000 (7.6 for men and 2.8 for women[13]) and keeping the confidence level at 95% and margin of error at 5%. Patients were selected by non-probability convenience sampling. All HCC patients presenting at Pak Emirates Military Hospital (PEMH) Rawalpindi from Oct 2014 to Feb 2016 were enrolled in this study. Patients were either diagnosed after presenting in gastroenterology/ hepatology OPD in PEMH Rawalpindi or were referred to this hospital after being diagnosed elsewhere. After being worked up as outdoor/ indoor patients, cases of all patients were discussed in multi disciplinary team meeting at Army Liver Transplant Unit held once every week. History was obtained and clinical examination was done and findings recorded. Functional status of the patients was recorded according to the Eastern Cooperative Oncology Group (ECOG) scoring system.

Following investigations were done in all cases

Complete blood counts, liver function tests including albumin, Prothrombin time and INR, renal function tests, hepatitis serology, alfa fetoprotein (AFP) levels, ultrasonography and contrast enhanced CT scan of abdomen.

Following investigations were done in those patients where it was required;

Upper GI endoscopy, polymerase chain reaction (PCR) for HBV and/or hepatitis C virus (HCV), MRI abdomen, liver biopsy, Doppler sonography for vascular involvement, tumour markers (CA-19-9, CA-125, CEA).

Patients were categorised according to Barcelona Clinic Liver Cancer (BCLC) and Child-Pugh classification systems. Data were entered in SPSS-22, descriptive statistics were used to calculate frequencies, means and standard deviation while correlation of AFP levels with different tumour characteristics was derived by using Spearman correlation calculation.

RESULTS

A total of 100 patients with new diagnosis of HCC were enrolled in this study. Sixty seven (67%) were men and thirty three (33%) were women. Mean age of the patients was 58.23 years with a range from 27 to 84 years (SD ± 10.355). An overwhelming majority of 79 (79%) patients had underlying chronic liver disease due to chronic viral hepatitis C followed by eleven (11%) patients suffering from hepatitis B. Three (3%) patients were co-infected with HBV and HCV while rest of the patients (seven, 7%) had other underlying aetiologies which included cryptogenic cirrhosis (two, 2%), NASH (three, 3%) and

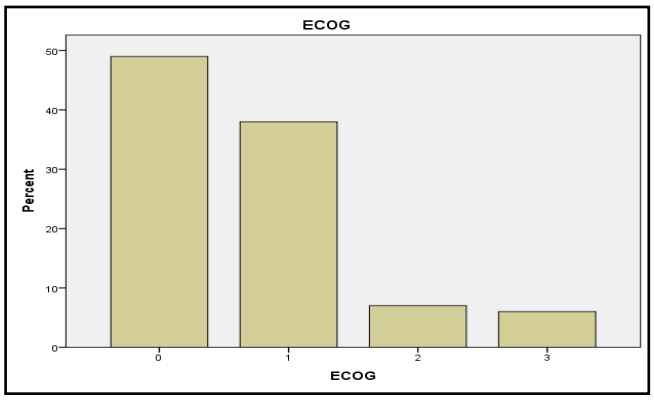

Figure-1: Frequency of ECOG performance scores.

alcoholic cirrhosis (one, 1%). Mean AFP level was 404 ng/ dl (SD ± 668) with a mean value of 38.5. Most patients had good ECOG performance status in this study (fig-1). Patients were divided into three groups as regards size of the tumour. Group I was tumour size less than 3 cm, group II 3 to 5cm and group III more than 5 cm. Seventeen (17%) patients belonged to group I, 23 (23%) to group II and 60 (60%) to group III. Majority of patients (62, 62%) had a single tumour, eleven (11%) had two lesions and 27 (27%) patients had 3 or more tumour nodules. Vascular involvement was found in fifteen (15%) patients. Main portal vein was involved by tumour in 4 (4%) patients while a branch of portal vein was involved in 9 (9%) patients. Inferior vena cava and mesenteric vein, along with main portal vein were involved in one (1%) patient each. Alfa fetoprotein level was normal (<8.5ng/ml) in forty two (42%)

patients and was raised in the other fifty eight (58%). Mean AFP level was 404.4 ng/ml with an SD of 668. Patients were divided into 4 groups as regards alpha fetoprotein levels. Group I was normal AFP level (<8.5ng/ml), group II 8.5-100ng/ml, group III 100-1000ng/ml and group IV >1000ng/ml. There was small positive correlation between AFP levels and the tumour size (r=0.172) but it was not statistically significant (p=0.088). Similarly, there was a small but statistically insignificant, positive correlation between AFP levels and number of HCC lesions (r=0.173, p=0.85).

Table-I: Descriptive statistics of patient variables and AFP levels.

Variables			n (%)	AFP Level (ng/ml)			
				<8.5	8.5-100	100-1000	>1000
Gender		Male	67 (67)	26	18	8	15
		Female	33 (33)	16	6	7	4
Aetiology		HCV	79 (79)	32	19	11	17
		HBV	11 (11)	6	4	0	1
		HCV+HBV	3 (3)	1	-	2	-
		Others	7 (7)	3	1	2	1
BCLC Stage		0	1 (1)	1	-	-	-
		A	34 (34)	17	8	6	3
		B	42 (42)	18	8	6	10
		C	18 (18)	5	6	2	5
		D	5 (5)	1	2	1	1
Tumour size	**Mean ± SD**						
	6.0 ± 2.7	<3cm	17 (17)	7	6	3	1
		3-5cm	23 (23)	13	4	4	2
		>5cm	60 (60)	22	14	8	16
No. of HCC lesions	1.65 ± 0.8 (Median 1.0)	1	62 (62)	29	14	10	9
		2	11 (11)	6	2	2	1
		≥3	27 (27)	7	8	3	9

Table-II: Spearman correlation between AFP levels and other variables.

Variable	Spearman Coefficient (r)	p-value
Tumour size	0.172	0.088
No. of HCC lesions	0.173	0.085
BCLC stage	0.203	0.044

Patients ECOG performance status did not bear any significant correlation with AFP levels (r=-0.062, p=0.540). There was however a small positive but significant correlation between AFP level and the BCLC stage of HCC (r=0.203, p=0.044).

DISCUSSION

HCC is a common liver malignancy in our country owing to high burden of chronic viral hepatitis predominantly HCV which is also reflected in this study. AFP is a tumour marker long associated with HCC and few recent studies reported a correlation between AFP levels and tumour size and prognosis. Rationale of this study was to find strength of association between different tumour characteristics i.e. size, number, stage etc with the levels of AFP. If strong association could be demonstrated, then AFP could have been used as representative of the HCC disease severity or as a predictor of morbidity and/or mortality in a given patient.

This analysis has shown a positive correlation between degree of AFP rise and number of tumour lesions which is however; insignificant statistically. A positive correlation has also been found between AFP level and tumour size but it is again statistically insignificant. An earlier study by Wu *et al* did not report a clear role of tumour size with prognosis in HCC[14], while another study by Dai *et al*[15] suggested that 5 year mortality was higher for tumours >5cm as

compared to smaller ones. Abbasi *et al*[10] reported a significant correlation between AFP level and tumour size. Our study also suggests a positive correlation between these two variables, nevertheless it is statistically insignificant.

A significant correlation between AFP levels and BCLC tumour stage is an important finding. Since BCLC stage depends on performance status, underlying liver disease and HCC characteristics collectively, significant correlation between all these important characteristics and AFP is logical. Even within the same stage AFP levels may predict prognosis after a particular form of treatment. Ma *et al*[8] and Lai *et al*[9] reported that pre-op AFP levels may be useful in predicting prognosis after surgery in HCC patients with resectable tumours (BCLC stage 0 or A). The latter study also suggests that Des Gamma carboxy Prothrombin (DCP) and an isoform of AFP called AFP–L3 can be useful as predictors of survival and tumour recurrence in surgically treated patients. This however was not evaluated in our study and needs further research in our country with studies properly designed to assess this correlation. Another recent large study by Bai *et al*[10] found correlation between pathological grade, TNM-7 stage and survival of patients with AFP positive tumours associated with less differentiated tumours, more advanced TNM stage, larger tumour size and lower survival as compared to AFP negative disease. Studies like this with very large number of patients are also needed in Pakistan to determine local trends in HCC.

Most commonly used staging system for HCC is BCLC which guides appropriate treatment options for a given stage as well. It can therefore be rightly assumed that higher the AFP level worse is the disease. Future studies with larger number of patients may further validate our findings and may also evaluate the role of newly discovered markers like AFP-L3 and DCP in predicting stage of disease and survival after treatment.

CONCLUSION

AFP levels are positively correlated with BCLC stage of HCC, tumour size and number of lesions. The correlation of the latter two however is not statistically significant. We recommend that future researchers design their studies with larger number of patients with HCC so as to find further evidence to this correlation especially focusing on correlation of AFP levels with patient survival with or without treatment.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Sterling RK, Wright EC, Morgan TR, Seeff LB, Hoefs JC, Di Bisceglie AM, et al. Frequency of elevated hepatocellular carcinoma (HCC) biomarkers in patients with advanced hepatitis C. Am J Gastroenterol 2012; 107(1): 64-74.
2. Collier J, Sherman M. Screening for hepatocellular carcinoma. Hepatol 1998; 27(1): 273-78.
3. Bhatti ABH, Dar FS, Waheed A, Shafique K, Sultan F, Shah NH. Hepatocellular Carcinoma in Pakistan: National Trends and Global Perspective. Gastroenterol Res Pract 2016; 2016: 5942306.
4. Liu P, Xie SH, Hu S, Cheng X, Gao T, Zhang C, et al. Age-specific sex difference in the incidence of hepatocellular carcinoma in the United States. Oncotarget 2017; 8(40): 68131-37.
5. Hefaiedh R, Ennaifer R, Romdhane H, Ben Nejma H, Arfa N, Belhadj N, et al. Gender difference in patients with hepatocellular carcinoma. La Tunisie Medicale 2013; 91(8-9): 505-8
6. Butt AS, Abbas Z, Jafri W. Hepatocellular carcinoma in pakistan: where do we stand? Hepat Mon 2012; 12(10 HCC): e6023-e
7. Butt AS, Hamid S, Wadalawala AA, Ghufran M, Javed AA, Farooq O, et al. Hepatocellular carcinoma in Native South Asian Pakistani population; trends, clinico-pathological characteristics & differences in viral marker negative & viral-hepatocellular carcinoma. BMC Res Notes 2013; 6(1): 137-41.
8. Giannini EG, Farinati F, Ciccarese F, Pecorelli A, Rapaccini GL, Di Marco M, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology (Baltimore, Md) 2015; 61(1): 184-90.
9. Kumar R, Sarswat MK, Sharma BC, Sakhuja P, Sarin SK. Characteristics of hepatocellular carcinoma in India: retrospective analysis of 191 cases. Q J Med 2008; 101(1): 479-85.
10. Abbasi A, Bhutto AR, Butt N, Munir SM. Corelaion of serum alpha fetoprotein and tumor size in hepatocellular carcinoma. J Pak Med Assoc 2012; 62(1): 33-36.
11. Gill ML, Atiq M, Sattar S, Khokhar N. Treatment outcomes with long acting octreotide in inoperable hepatocellular carcinoma: a local experience and review of literature. J Pak Med Assoc 2005; 55(4): 135-38.
12. Abbas Z, Siddiqui AR, Luck NH, Hassan M, Mirza R, Naqvi A, et al. Prognostic factors of survival in patients with non-resectable hepatocellular carcinoma: Hepatitis C virus versus miscellaneous etiology. J Pak Med Assoc 2008; 58(1): 602-07.
13. Abbas Z. Hepatocellular carcinoma in Pakisan. J Coll Physicians Surg Pak 2013; 23(10): 769-70.

14. Wu G, Wu J, Wang B, Zhu X, Shi X, Ding Y. Importance of tumor size at diagnosis as a prognostic factor for hepatocellular carcinoma survival: a population-based study. Cancer Manag Res 2018; 10(1): 4401-10.
15. Dai CY, Lin CY, Tsai PC, Lin PY, Yeh ML, Huang CF, et al. Impact of tumor size on the prognosis of hepatocellular carcinoma in patients who underwent liver resection. J Chinese Med Assoc 2018; 81(2): 155-63
16. Ma WJ, Wang HY, Teng LS. Correlation analysis of preoperative serum alpha-fetoprotein (AFP) level and prognosis of hepatocellular carcinoma (HCC) after hepatectomy. World J Surg Oncol 2013; 11(1): 212-23.
17. Lai Q, Melandro F, Pinheiro RS, Donfrancesco, Fadel BA, Sandri GBL, et al. Alpha-fetoprotein and novel tumour biomarkers as predictors of hepatocellular carcinoma recurrence after surgery: A brilliant star rises again. Intl J Hepatol 2012; 1(1): 1-9.
18. Bai DS, Zhang C, Chen P, Jin SJ, Jiang GQ. The prognostic correlation of AFP level at diagnosis with pathological grade, progression, and survival of patients with hepatocellular carcinoma. Sci Rep 2017; 7(1): 12870-77.

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