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Elevated Serum Alpha-Fetoprotein as A Prognostic Factor for Hepatocellular Carcinoma in Patients with Chronic Liver Disease

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ABSTRACT

Objective: To determine the elevated Serum Alpha-Fetoprotein level in Hepatocellular Carcinoma patients with chronic liver disease at Isra University Hospital Hyderabad. **Study Design:** cross sectional study. **Settings:** Gastroenterology Department at Isra University Hospital, Hyderabad. **Duration:** Six month from April 2017 to September 2017. **Methodology:** All the patients of hepatocellular Carcinoma caused by hepatitis B virus and hepatitis C virus with tumor size ≥3cm, of either gender were included. Ultrasound abdomen was done for diagnosis of hepatocellular carcinoma. Blood samples were collected to measure alpha-fetoprotein levels through Isra University Hospital Laboratory; in all those patients who were admitted to gastroenterology department at the time, of being enrolled to this study. Cirrhosis severity was evaluated by child pugh scoring. Relevant data was collected via proforma. **Results:** Total 160 patients were studied; their mean age was 52.7±5.3years. Males were found in majority as: 65.47%**.** HCV was a commonest infection 46%, after that HBV and HBV+HCV were found among 45% and 9% cases respectively. Majority of patients 73/ (43.45%) were found with size of tumor >7cm. (47.61%) cases had elevated serum Alpha fetoprotein more than 400 IU/ml. Old age people, hepatitis C virus and child Pugh group C were significantly associated with elevated Alpha fetoprotein respectively; P-value 0.001. There was no significant difference in Alpha fetoprotein levels according to gender; P-value 0.07. **Conclusion:** It was concluded that elevated level of serum Alpha fetoprotein is an invasive and reliable indicator of hepatocellular carcinoma.

Keywords: CLD, Serum alpha-fetoprotein, HCC.

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INTRODUCTION

Hepatocellular carcinoma is a 5th most common neoplasm globally, and represents 5.6% cancers of all human-related malignancies.[1,2] Primary hepatic cancers, around 75% to 80% are attributable to chronic viral diseases with hepatitis B or C viruses.[3] Hepatitis B is the major etiological factor of Hepatocellular carcinoma.[4] Alpha fetoprotein is a valuable biomarker for Hepatocellular carcinoma diagnosis; since 1970, when majority of hepatocellular carcinoma's patients were detected at an end stage along with clinical symptoms. Alpha fetoprotein levels beyond the reference range of 10 ng/L take place in around 75% of hepatocellular carcinoma subjects.[5] It is yet regarded as a significant biomarker for hepatocellular carcinoma diagnosis.[3,6] Alpha fetoprotein co-localizes as well as interacts with Retinoic acid receptors-β within the cytoplasm and contributes in preventing the shifting of Retinoic acid receptors-β into the nucleus through bidding to Retinoic acid receptors-β with all-trans-retinoic acid.[7] Therefore, cytoplasmic Alpha fetoprotein acts as an inhibitor within the retinoic acid receptor signaling pathway and is most likely at least partially accountable for resistance of retinoid in cancer chemotherapy.[8] Recommendations of American Association for Study of Liver Diseases suggested just ultrasonography to screen for hepatocellular carcinoma and have remarked sub-optimal sensitivity of Alpha fetoprotein to screen for hepatocellular carcinoma.[9] There are a few small scale studies from this region about validity of Alpha fetoprotein has been conducted.[10] Alpha fetoprotein is an important indicator of Hepatocellular carcinoma, and is useful in evaluating issues in administration of hepatocellular carcinoma and monitoring therapy regimes. Additionally, in a study reported that Alpha fetoprotein is, a marker of hepatocellular carcinoma's risks, frequently in cases with Hepatitis B or C and cirrhosis,[11] and out of 480 male patients, (8.13%) showed raised Alpha fetoprotein levels. Likewise, 7 (5.34%) women out of 131 having raised Alpha fetoprotein levels were diagnosed having hepatocellular carcinoma.[11] This study aimed to assess the raised level of serum alpha-fetoprotein as a prognostic factor among chronic liver disease patients of Hepatocellular Carcinoma.

METHODOLOGY

Study Design: Cross sectional study.

Setting: The study was held at Gastroenterology Department of Isra University Hospital, Hyderabad.

Duration: Six months from April 2017 to September 2017.

Sample size: The Rao soft software was used for "Sample size calculation" via proportion (elevated Alpha fetoprotein levels, found in 7.58% of the subjects diagnosed with hepatocellular

carcinoma)[11] With 95% confidential level and 4% power of test, the sample size stands to be n=168.

Methods: All the patients with hepatocellular Carcinoma resulting from hepatitis B virus and hepatitis C virus with tumor size ≥3cm on ultrasound and both female and male genders with age range of 35 -70 years were enrolled in the study. Chronic hepatic infection was defined as progressive damage to hepatic parenchyma over >6 months of period resulting in cirrhosis and fibrosis assessed by ultrasound. All the patients who were unwilling to take part in current study and hepatocellular carcinoma not caused by hepatitis C and hepatitis B were excluded. Patients were enrolled into current study following a well-versed consent. Complete medical history along with ultrasound abdomen was done. Ultrasound was performed for tumor size and blood samples were collected to measure serum alpha-fetoprotein level by diagnostic laboratory of Isra University Hospital Hyderabad, in all those patients who were admitted to Gastroenterology Department. Relevant data was collected via proforma. Researcher collected all the data including demographic profile, levels of serum alpha-fetoprotein.

Data analysis: The data analysis was performed by 16.0 version of statistical program SPSS. Mean standard deviation were computed for age, alpha fetoprotein level and tumor size. Simple frequencies and percentages were computed for gender, hepatitis B, hepatitis C, and child Pugh groups A, B and C. Stratification was done for alpha fetoprotein level in terms of age, gender, tumor size, etiology and child Pugh classes; chi square test was performed and P-value < 0.05 was considered as significant.

RESULTS

Total 168 patients were studied and patients mean age was found as 52.7±5.3 years with range of 40 to 70 years. Mostly partakers were males as 65.47% contrasted to females 34.53%.

Table 1: Demographic characteristics of patients (n = 168)

	Variables	Frequency (%)
Gender	Male	115(65.47%)
	Female	53(34.53%)
	Total	168(100.0%)
Viral hepatitis	HCV	123(73.21%)
	HBV	37(22.02%)
	HCV+HBV	8(4.76%)
	Total	168(100.0%)
Tumor size	3–5 cm	40/(23.80%)
	5-7cm	55/(32.73%)
	> 7cm	73/(43.45%)
	Total	168(100.0%)
Child Pugh Classification	Class-A	26/(15.47%)
	Class-B	42/(25.0%)
	Class-C	90(53.57%)
	Total	168(100.0%)
	Mean age (mean±SD)	52.7±5.3 years

Hepatitis C (73.21%) was commonest, followed by hepatitis B and co-infection of (hepatitis B + hepatitis C) 22.02% and 4.76% respectively. Most of the patients, 73/(43.45%) were found with size of tumor >7cm. child Pugh class C was most common among 90(53.57%) cases, followed by class B, and A in 42/(25.0%) and 26/(15.47%) cases respectively. Table 1

In this series 33/(19.64%) patients were noted with elevated serum Alpha fetoprotein level <20IU/ml, 45/(26.78%) patients had Alpha fetoprotein levels ranging from 20IU/ml to 400IU/ml, while most cases 80/(47.61%) had raised Alpha fetoprotein >400 IU/ml. Table 2

Table 2: Serum alpha fetoprotein level of the patients (n=168)

SERUM Alpha fetoprotein LEVEL	# of pt/(%)
< 20IU/ml	33/(19.64%)
20-400IU/ml	45/(26.78%)
> 400 IU/ml	80/(47.61%)

Old age, HCV infection and child Pugh class C were significantly associated with Alpha fetoprotein elevation; P-value 0.004. While there was no significant association of Alpha fetoprotein elevation with gender, P-value 0.07. Table 3

Table 3: Serum Alpha fetoprotein level according to age, gender, viral hepatitis and child Pugh classification (n=168)

Variables Level	Serum Alpha fetoprotein IU/ml			P-value
Age groups	< 20	20-400	>400	
40-50 years	13	10	15	0.004
51-60 years	10	23	35	
> 60 years	10	12	40	
Total	33	45	90	
Gender				
Male	20	35	60	0.076
Female	13	10	30	
Total	33	45	90	
Viral hepatitis				
HCV	23	30	70	0.001
HBV	08	11	18	
HCV+HBV	02	04	02	
Total	33	45	90	
Child Pugh Classification				
Class-A	15	09	02	0.001
Class-B	10	16	26	
Class-C	08	20	62	
Total	33	45	90	

DISCUSSION

Favorable outcomes in hepatocellular carcinoma are further likely if identified at an initial stage. Therefore, effective screening intends to detect preclinical hepatocellular carcinoma. To this end, several combinations of Alpha fetoprotein testing and imaging with computer topography, ultrasound and/or magnetic resonance imaging, are suggested. The contribution of persistent viral hepatitis in carcinogenesis of liver is established. Chronic hepatitis B and C infects around 170

million individuals globally, it is a key factor of cirrhosis and hepatocellular carcinoma, and accounts for the most common reason for hepatic-transplantation within the Europe and US.[12] Levels of Alpha fetoprotein is a routine examination tool for Hepatocellular carcinoma in patients with chronic liver diseases because raised Alpha fetoprotein concentrations is a marker of raised risk of Hepatocellular carcinoma,[13] and this was confirmed by our study. Patients' mean age in current study was found to be 55.7±5.3 years and males in dominance as 65% contracted to 35% females. Likewise, Abbasi A et al[14] documented mean age of patients 53.89±12.511 years and 70.4% males and 29.6% female. Generally, males are believed to be further susceptible to hepatocellular carcinoma in contrast to females, because among males, smoking and alcohol consumption is higher, and have increased iron stores. Increased genetic susceptibility and androgenic hormones have also been suggested as the causative factors. In this series, we found that hepatitis B and C were equally the commonest factors of hepatocellular carcinoma, whereas; hepatocellular carcinoma's duration was 9.5±6.2 months. Phulpoto JA et al[16] documented an etiologic distribution as: hepatitis B 71 (36.6%), hepatitis C 54 (27.8%), dual infection with hepatitis B and hepatitis C 12 (6.2%). In several studies from Pakistan; 43-83.3% Hepatocellular carcinoma cases have been noticed to have anti-hepatitis C antibody positive.[15,17] According to Butt; 67.9% of hepatocellular carcinoma cases were hepatitis C positive.[18]

Abbasi A et al[14] documented that tumor sized below 3cm was among 17.3%, 3-5cm of tumor among 35 35.7% and tumor sized above 5cm was among 49.9% cases. Whereas; we noticed most of the cases 58.0% with tumor size above 7cm, followed by 27.0% patients had tumor size 5-7cm; whereas, 15.0% cases were noticed with tumor size 3–5 cm.

After this study elevated Alpha fetoprotein level is considered as prognostic factor for HCC. Similarly, others reported that elevated Alpha fetoprotein level can identify the high-risk HCC.[19,20] Though, clinicians ought to bear in mind that some cases with primary liver carcinoma will have typical levels of Alpha fetoprotein, and moderately or normal raised levels ought not to be practiced to exclude the hepatocellular carcinoma diagnosis. As per Abbasi A et al[14] positivity of Alpha fetoprotein was examined to check its correlation with the tumor size and 22.44% cases had Alpha fetoprotein blow 20ng/ml, 25.5% had levels ranging from 20 to 399 ng/ml and 52% were found with levels ≥ 400 ng/ml. Greatest level of Alpha fetoprotein was 66408 ng/ml. In our study; 13.0% cases had Alpha fetoprotein < 20IU/ml, 34.0% cases were found with serum Alpha fetoprotein of 20-400IU/ml, whereas majority of patients 53.0% were found to have above 400 IU/ml. Similarly, another study has found that Alpha fetoprotein was normal (<8.5 ng/ml) among 20%, moderately raised (8.5-300 ng/ml) among 48%, and considerably raised (>300 ng/ml) among 32% cases.[21] In one more study from south India, raised levels of Alpha fetoprotein were noticed among 47.4% cases with hepatocellular carcinoma.[22]

In our study; large tumor size was found significantly associated with serum Alpha fetoprotein elevation; P-value 0.002, and elevated serum Alpha fetoprotein > 400 IU/ml was found significantly associated with child Pugh class C; P-value 0.001. Abbasi A et al[14] reported that Alpha fetoprotein positivity was examined to check its correlation with tumor size. Abbasi A et al[14] established that 22.44% were found with levels of Alpha fetoprotein blow 20ng/ml, 25.5% were found with levels ranging 20 to 399 ng/ml and 52% were found with levels ≥400 ng/ml. Others have examined histopathologically confirmed hepatocellular carcinoma patients and found that Alpha fetoprotein is normal (<8.5 ng/ml) among 20%, moderately raised (8.5-300 ng/ml) among 48%, and substantially raised (>300 ng/ml) among 32% of patients. In a study from north India, levels of Alpha fetoprotein were elevated among 65% patients of hepatocellular carcinoma, the greatest levels found were 580 ng/ml.[22] These data advocate that in cases believed to have hepatocellular carcinoma on clinical level, Levels of alpha fetoprotein around 400 ng/ml must strongly confirm the existence of hepatocellular carcinoma via tissue diagnosis.

CONCLUSION

In was concluded that elevated serum Alpha fetoprotein is a useful, non-invasive and reliable indicator of hepatocellular carcinoma. It should be assessed routinely among patients of hepatitis C and hepatitis B for early diagnosis of HCC. Further studies are required to correlate the serum levels of Alpha fetoprotein with the size, tumor, and degree of differentiation of hepatocellular carcinoma.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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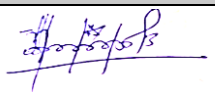
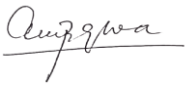
Dr. Nadeem Bajkani Gastroenterologist, Gastroenterology Isra University Hospital, Hyderabad-Pakistan	Data collection, manuscript writing	
Dr. Muhammad Akram Bajwa Assistant Professor, Gastroenterology Liaquat University of Medical and Health Sciences, Hyderabad-Pakistan	Review the manuscript	
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