ASSOCIATION OF SERUM ALPHA FETOPROTEIN (AFP) LEVELS WITH SIZE OF HEPATOCELLULAR CARCINOMA

Khawar Shabbir, Asim Shehzad, Mehdi Naqvi, Muhammad Sohail Khalid, Nadeem Zia*, Ehtesham Haider, Asif Farooq

Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To determine the association between high levels of serum Alpha Fetoprotein (AFP) and tumor size in hepatocellular carcinoma (HCC).

Study Design: Cross-sectional analytical study.

Place and Duration of Study: Department of Gastroenterology and Hepatology, Pak Emirates Military Hospital, Rawalpindi from June 2015 to June 2017.

Material and Methods: Two hundred and thirty six patients diagnosed with HCC were enrolled in the study, out of which 175 provided the required data to perform the association. All demographic data and clinical information was recorded on a predesigned proforma, after taking proper informed consent. The cases were divided into three groups for each variable to evaluate. Concerning the serum alpha fetoprotein levels, they were divided as group 1 (normal level: <20 UI/ml), group 2 (higher level: 21 to 399 UI/ml) and group 3 (extremely high level: >400 UI/ml). According to the size of their tumors, the group A contains patients with less than 3 cm. tumors; in group B the tumors are 3 to 5cm. and the group C is formed by patients whose tumors were larger than 5 cm. Other variables such as number of lesions (tumors), Child Pugh and BCLC scores were considered as additional information.

Results: Total 175 patients took part in final data analysis. The age range was from 30 to 85 years old. Considering their AFP levels, there were 61 in group 1, 75 in group 2 and 39 in group 3. In addition, according to their size of tumor, there were 28, 56 and 91 for group A, B and C respectively. A clear relationship between the AFP levels and the size of the tumors was noticed, especially for the group 2 and 3 with 55.4% and 56.4% respectively, in concordance with group B & C.

Conclusion: No significant association was seen between Serum AFP levels and the size of tumor in HCC (*p*-value = 0.72).

Keywords: Hepatocellular Carcinoma, Serum Alpha Fetoprotein, Tumor size.

INTRODUCTION

Hepatocellular Carcinoma, also called malignant hepatoma, accounts for 80-90% of the primary malignant tumors in the liver, being the third commonest reason of deaths related to cancer[1]. It is closely related to liver cirrhosis, which is considered almost a direct cause of HCC. Cirrhosis may appear either with a viral infection like hepatitis C virus, Delta virus or hepatitis B virus (though this last one often leads to cancer without even developing cirrhosis), or for non-viral reasons as excessive alcohol drinking or related to non-alcoholic steato-hepatitis[2].

Because HCC is a cancer that does not manifest clear signs until it is too late, its mortality is much higher than it should be and, when detected on time, has much more healing opportunities. This is the main reason why developing detection and diagnostics tools has to be a priority in order to revert its mortality and morbidity[3].

In order to achieve that target, periodic screening of high risk patients is the necessary. The periodic screening methods includes measures like the Child Pugh score (which

Correspondence: Dr Khawar Shabbir, Department of Gastroenterology, PEMH Rawalpindi Pakistan
Email: khawarshabbir@yahoo.com
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assesses prognosis in chronic liver diseases using the levels of Bilirubin, serum Albumin, Prothrombin time, Ascites and Hepatic Encephalopathy); or the Barcelona clinic for liver cancer (BCLC) stage (a staging system evaluator for liver cancer based on the number and size of tumors, the patient's performance status and liver functions, according to Child Pugh Score). Imaging technique examinations (like ultrasound, MRI or computer tomography) and serum tumor marker tests are part of these screening methods as well[4].

Tumor markers are produced either by the neoplastic cells, or as a body response for their invasion, which allows determining the prognosis of a cancer or the efficacy of its treatment. The tumor marker for the Hepatocellular Carcinoma is the serum Alpha Fetoprotein (AFP).

AFP is a glycoprotein produced by the fetal yolk sac after the seventh week of gestation, and later on by the fetus gut and liver. After birth, its level decreases being usually lower than 20 IU/ml[5].

People with serum AFP levels greater than 20 IU/ml should be closely examined as higher levels are usually related to liver cancer. There are other neoplasia that might increase AFP levels as well as other liver diseases implying that the marker might not be so reliable as a

Table-I: Demographic and clinical data of patients in relation with serum AFP levels

Features	Group 1 AFP<20IU/ml	Group 2 AFP20-399IU/ml	Group 3 AFP> 400IU/ml
Number of Patients	61	75	39
Gender (M/F)	42 / 19	55 / 20	24 / 15
Age (<65/>65)	40 / 21	51 / 24	29 / 10
Etiology: HCV HBV/Coinf./Neg	44 / 9 / 1 / 3 *1	57 / 11 / 3 / 1	34 / 2 / 0 / 2
Child Pugh Score (A/B/C)	44 / 12 / 0	51 / 22 / 0	23 / 13 / 1
Perform Status 0 / 1 / 2 / 3	26 / 28 / 3 / 2	35 / 32 / 2 / 6	13 / 19 / 4 / 2
BCLC System A / B / C / D	14 / 16 / 8 / 0	16 / 28 / 12 / 2	4 / 13 / 3 / 1
PT/INR: Y / N Coagulopathy	8 / 57	7 / 65	4 / 32
Vascular Invasion Y/N	10 / 51	12 / 63	5 / 34
Lymph Nodes Y / N	3 / 58	7 / 68	2 / 37
Metastases Y / N	1 / 60	3 / 72	1 / 38
Renal Profile Severe/Mild/No	0 / 2 / 55	1 / 3 / 67	0 / 2 / 35
Size of tumor <2 / 3-5 / >6 cm	11 / 23 / 28	12 / 22 / 41	5 / 12 / 22
N° of Tumors 1 / 2-5 / > 5	31 / 26 / 4	37 / 32 / 6	19 / 19 / 1
*1 – Two cases of Delta Virus			

diagnostic tool. A recent local study by Samiullah *et al*[6] concluded that there is significant correlation between serum AFP and tumor size in HCC (r=0.668). Abbasi *et al*[7] previously demonstrated significant correlation of serum AFP level with tumour size in hepatocellular carcinoma. (r=0.472, 0.0001). In contrast Sharieff *et al*[8] reported no significant correlation between tumor size and AFP levels (r=-0.155; *p*=0.129). Keeping in view the conflicting conclusions we decided to conduct this study with principal aim of determining correlation between serum AFP levels and tumor size in HCC.

Table-II: Correlation of serum AFP and size of tumors in HCC (no other variable considered).

Serum AFP Size of Tumor	GROUP 1 (<20 IU/ml) Total: 62	GROUP 2 (21-399 IU/ml) Total: 74	GROUP 3 (>400 IU/ml) Total: 39
GROUP A (< 3 cm) Total: 28	11 (A: 39,2% - 1: 17.7%)	12 (A: 42,8% - 2: 16.2%)	5 (A: 17,8% - 3: 12.8%)
GROUP B (3-5 cm.) Total: 56	23 (B: 41% - 1: 37%)	21 (B: 37,5% - 2: 28.3%)	12 (B: 21,4% - 3: 30.7%)
GROUP C (> 5 cm) Total: 91	28 (C: 30,7% - 1: 45.1%)	41 (C: 45% - 2: 55.4%)	22 (C: 24,1% - 3: 56.4%)

PATIENTS AND METHODS

This cross-sectional analytical study was undertaken from a total of 236 patients diagnosed with HCC who attended to the Pak Emirates Military Hospital (Rawalpindi, Pakistan) from June 2015 till June 2017. Only 175 of them had substantial data recorded to apply for this research (AFP levels and size of tumor registered). The sample size was calculated using statistical assumptions of α=0.05 and β=0.20 taking value of r to be 0.4727 and came out to be at least 33 patients for this study.

Non probability consecutive sampling technique was used to enroll the patients. Patients included were at all stages of the disease, either with only one, or with multiple tumors, with or without metastases, vascular invasion, lymph nodes involved or coagulopathy.

Their demographical data and clinical parameters were considered as a whole, but not directly related. They all had a record of their serum AFP levels measures gotten by different laboratory tests, and the sizes of the tumors taken from imaging techniques. All other variables were obtained by its regular methods. Some of them have some data missing, but were incorporated anyway, as the missing data was not relevant for the relation we mean to prove in this study.

Taking the tumor size parameter, they were divided into three groups (A, B, and C, with less than 3cm, 3 to 5 cm. and more than 5 cm. respectively). On the Serum AFP levels basis, they were separated into groups 1 (with serum levels lower than 20 IU/ml), 2 (serum from 20 to 399 IU/ml) and 3 with serum levels higher than 400 IU/ml.

Data had been analyzed using SPSS version 17. Descriptive statistics were used to describe the results. Chi-square test was used to study the significance of the association between AFP level and size of tumor. A *p*-value <0.05 was considered as significant.

RESULTS

A sample of 175 patients with hepatocellular carcinoma was taken with all the information needed. They comprised 121 male and 54 female. The age range was from 30 to 85 years old. Of them, there were 61 in the group 1, 75 in the

group 2 and 39 in the group 3 (table-I). In addition, according to the size of their tumor, there were 28, 56 and 91 for group A, B and C respectively (table-III). Of the 175 patients, 68.5% were under 65 years old, HCV was the etiology of 77.1%; 49.7% had only one tumor and most of them were in level 0 or 1 of performance status. Although a relationship between the AFP levels and the size of tumor was observed, especially for the group 2 with 55.4% of the patients in group C, and the group 3, with 56.4% of patients in group C but this was statistically insignificant (*p*-value=0.92). Overall there was no significant difference in percentage of people present among the different groups thereby indicating no significant correlation exists (*p*-value = 0.72).

Table-III: Demographic and clinical data of patients in relation with the size of their tumors.

Features	Group A <3 cm.	Group B 3-5 cm.	Group C >5 cm.
Number of Patients	28 (16%)	56 (32%)	91(52%)
Gender: (M/F)	17(60.7%) / 11(39.3)	36(64.3%) / 20(35.7%)	68(74.7%) / 23(25.3%)
Age: (<65 / >65)	20(71.4%) / 8(28.6%)	43(76.8%) / 13(23.2%)	57(62.6%) / 34(37.4%)
Etiology: HCV HBV/Coinf./Neg	20 / 3 / 2 / 2 *1	47 / 4 / 1 / 2	68 / 15 / 1 / 3
Child Pugh Score (A/B/C)	17 / 10 / 0	34 / 19 / 0	67 / 18 / 1
Perform Status 0 / 1 / 2 / 3	9 / 17 / 0 / 2	28 / 22 / 1 / 2	37 / 40 / 8 / 6
BCLC System A / B / C / D	15 / 3 / 0 / 0	17 / 16 / 4 /	2 / 38 / 19 / 3
PT/INR: Y / N Coagulopathy	7 / 20	7 / 46	5 / 80
Vascular Invasion Y/N	2 / 26	1 / 55	24 / 67
Lymph Nodes: Y / N	0 / 28	5 / 51	7 / 84
Metastases: Y / N	0 / 28	0 / 56	5 / 86
Renal Profile Severe/Mild/No	1 / 0 / 25	0 / 4 / 51	0 / 3 / 81
Serum AFP: <20 / 21-399 / >400	11 / 12 / 5	23 / 21 / 12	28 / 41 / 22
N° of Tumors 1 / 2-5 / > 5	16 / 11 / 1	23 / 31 / 2	48 / 35 / 8

*1 – One case of Delta Virus

DISCUSSION

Pakistan has the 2nd highest prevalence of HCV in the world[10]. All these patients are at an increased risk of developing HCC in future. Therefore it is critically important to screen these patients periodically to detect any tumor as soon as it shows up. Ultrasound and serum alpha fetoprotein levels are currently the mainstay of screening. EASL and AASLD recommend 6 monthly Ultrasounds for this purpose. Asian Pacific Association for the Study of the Liver recommends both 6 monthly ultrasound and serum alpha fetoprotein levels for screening purposes[11].

Our study showed no significant correlation between serum AFP level and tumor size. This was in line with the findings of Sharieff *et al*[8]. All the other three local studies reported a significant correlation[9-18]. A possible reason could be the different classification criteria used by us to categorize the patients into the three groups based on tumor size.

Our study found serum AFP levels to be raised in 64.5% of HCC cases. This was lower compared to Samiullah *et al*[6] and Abbasi *et al*[7] who reported raised AFP level in 77.7% and 77.5% of the patients respectively. In our study,

HCV was present in 77.1% of the cases whereas Abbasi *et al*[7] and Haque *et al*[9] reported HCV to be present in just 48% and 54.5% of the patients respectively. Only 39 (22.3%) of our patients had a serum AFP level >400 IU/ml. In contrast Samiullah *et al*[6] reported 69% of patients with serum AFP levels of greater than 400 IU/ml/. More than half of the patients had a tumor size of >5 cm.

There were certain limitations to our study. Dynamics of AFP levels i.e. how fast the levels change with time were not taken into consideration. All high risk patients for HCC, in whom AFP ranges change, should be monitored more closely as it may be related to a developing tumor that will gain size quickly. Serum AFP levels should always be correlated with sensitive imaging techniques in order to avoid missing out on a small tumor.

CONCLUSION

This study showed that no significant correlation exists between serum AFP levels and the size of tumour in HCC. Therefore, we cannot rely on AFP solely for screening purpose rather it should only be used in conjunction with ultrasound. Newer diagnostic modalities like triphasic CT need to be embraced.

CONFLICT OF INTEREST

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

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