IJRMC Vol 1 (Issue 1) https://doi.org/10.37939/jrmc.v1i1.1988

Correlation of Serum Alpha-Fetoprotein (AFP) Levels with the size of Hepatocellular carcinoma on Triphasic CT scan: A study in patients with the heterotrophic viral infection

Javeria Khan[1], Maria Khaliq[2], Tayyub Saeed[3], Muhammad Imran[4], Nasir Majeed[5], Rabia Khan[6], Muhammad Umar[7], Bushra Khaar[8], Tanveer Hussain[9], Sadia Ahmed[10], Misbah Noureen[11], Saima Ambreen[12]

Abstract

Objective: To determine the association between serum Alpha-Fetoprotein (AFP) levels with different variables including Hepatocellular tumor size.

Materials and Methods: This cross-sectional study was conducted in the Center of Liver and Digestive Diseases, Holy Family Hospital, Rawalpindi. Three hundred and thirty-four liver cirrhosis patients complicated with HCC were participants. Different variables such as diabetes, hypertension, ischemic heart disease, smoking, jaundice, fever, lethargy, weight loss, anorexia, pain right hypochondrium, abdominal distention, ascites, encephalopathy, biochemical tests (Bilirubin levels, serum albumin levels, prothrombin time(PT) (<4 /4-6 / >6 sec prolonged), child Turcotte class (A, Band C), PST(performance status), Barcelona Clinic liver cancer staging system (0/A/B/C/D) and tumor size in 3 Groups (Group I size <3 cm, Group II size 3-5cm, and Group size III >5cm size) were compared with serum Alpha Feto Proteins (AFP) levels(Group I AFP level >20 and <200ng/mL, Group II AFP level 200-400 ng/mL, while Group III AFP level was >400ng/mL). Data were analyzed through SPSS Statistics version 23.0 (IBM, Armonk, NY), Spearman's rank is used for P-value.

Results: The AFP (Group-I/II/III)association with diabetes (P 0.121), HTN (P 0.811), IHD (P 0.546), HBsAg positive patients (all P 0.186), HCV positive patients (all P 0.131), pain right hypochondrium (P 0.599), fever (P 0.065), lethargy (P 0.388) and Encephalopathy (all P 0.075) were identified as non-significant association while biochemical levels such as Bilirubin (P 0.000), Albumin (P 0.000), Prothrombin Time (P 0.038) creatinine (all P 0.001) , Child Turcotte Class A, B and C (P 0.000),smoking (P 0.023), weight Loss (P 0.002), Anorexia (P 0.007), Jaundice (P 0.012), Ascites (P value 0.000), ECOG (P 0.000), Barcelona Clinic for liver cancer (BCLC) staging system (P 0.000), lesion I (P 0.000) and lesions II (P 0.006) on CECT had significant association.

Conclusion: We hereby, conclude that there is a noteworthy correlation between Alpha Feto Proteins with different variables including an increase in the size of the tumor. Hence Alfa Feto protein is not only helpful for the diagnosis of HCC but also has a pivotal role in predicting tumor burden and disease level.

Keywords: Serum Alpha-Fetoprotein (AFP) Levels, hepatocellular carcinoma, heterotrophic viral infection.

[1,3,7,8,9,10,11] Gastroenterologist at Center for Liver & Digestive Diseases, Holy Family Hospital, Rawalpindi; [2] Radiologist, Department of Radiology, Holy Family Hospital, Rawalpindi; [4] Department of Biological Sciences, International Islamic University Islamabad (IIUI), Islamabad; [5] Section on Gastroenterology and Hepatology, Department of Internal Medicine, Wake Forest University School of Medicine, Winston Salem, NC, United States; [6] Paediatric Gastroenterology Fellow at the Hospital for the Sick Children, Toronto, Canada; [12] Associate Professor of Medicine, Rawalpindi Medical University, Rawalpindi. **Correspondence:** Dr. Javeria Khan, Gastroenterologist, Centre for Liver & Digestive Disease, Holy Family Hospital, Rawalpindi. **Email:** docjaveriakhan@hotmail.com

Cite this Article: Khan, J., Khaliq, M., Saeed, T., Imran, M., Majeed, N., Khan, R., Umar, M., Khaar, B., Hussain, T., Ahmed, S., Noureen, M., Ambreen, S. Correlation of Serum Alpha-Fetoprotein (AFP) Levels with the size of Hepatocellular carcinoma on Triphasic CT scan: A study in patients with the heterotrophic viral infection. International Journal of Rawalpindi Medical College. 30 Jun. 2022; 1(1): 36-43.

Received March 9, 2022; accepted May 30, 2022; published online June 30, 2022

1. Introduction

Today, Hepatocellular carcinoma (HCC) is a pressing health issue for the globe, due to late diagnosis, high morbidity, and mortality rate. Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer worldwide and is associated with liver primary malignancy. It is one of the most frequent causes of death that is associated with cancer. Cases of HCC are constantly rising worldwide.[1-3]

Multiple risk factors are identified for HCC such as chronic hepatitis B& C, non-alcoholic fatty liver disease, and alcohol consumption are the most common while the less common factors are hereditary hemochromatosis, primary biliary cirrhosis, autoimmune hepatitis, Wilson's disease, and alpha1-antitrypsin deficiency. In Pakistan, the prevalence of Hepatocellular carcinoma malignant tumors is 3.7%-16% while the common causes are viral hepatitis B and C-related cirrhosis.[4] The burden of disease and hospital admissions of this disease is also continuously increasing. Most HCC patients have been diagnosed at a late stage limiting the cure

options. Delayed diagnosis is associated with disease being either asymptomatic initially or present with vague and non-specific symptoms. Patients are presented with different types of symptoms that are related to chronic liver diseases such as skin and eyes yellowish discoloration, right upper abdominal pain, abdomen swelling, weakness, fever, and weight loss.[5,6]

In recent decades, more asymptomatic patients are diagnosed due to active monitoring and awareness of HCC in high-risk patients, particularly in cirrhosis. Hepatocellular carcinoma diagnostic tools such as blood alpha-fetoprotein (AFP) and imaging studies are being used for screening after every six months in cirrhotic patients. In patients with chronic liver disease (CLD) increased AFP level is considered a risk factor for HCC which is helpful for chronic liver disease subgroup identification. In this regard, Alpha-fetoprotein (AFP) level fluctuation reflects acute on chronic hepatic injury, liver disease progression, or HCC.[7,8]

People with serum AFP levels > 20 ng/mL should be monitored because of their ability to predict liver cancer. Higher serum AFP level is linked with tumor size, bilobar involvement, portal vein tumor thrombus, and massive or diffuse tumor types.[9,10] In addition, a high level of AFP is linked to tumor recurrence and metastasis.[11,12]

The Definitive Hepatocellular carcinoma diagnostic tool is an image-based diagnosis such as contrast-enhanced Computed Tomography (CT) based on the arterial enhancement of the tumor followed by washout in venous and delayed phases.[13-16]

Our study's main aim was to check the association of liver size with serum AFP protein levels, which may be helpful in the future for HCC diagnosis. Pakistan is a developing country, hence, offering expensive and advanced tools for the diagnosis of cancer is beyond our capacity.

2. Materials & Methods

Ethical approval of this study was taken from the Rawalpindi Medical University institutional board. A cross-sectional study was conducted at the Center of Liver and Digestive Diseases, Holy Family Hospital, Rawalpindi, which is a tertiary care facility. Subjects with known chronic liver disease secondary to chronic hepatitis B and Hepatitis C complicated by Hepatocellular Carcinoma patients were included. This study was started in January 2017 and was completed in January 2022. Demographic characteristics, Hepatitis B or C infection, size, and the number of Hepatocellular carcinoma lesions detected on ultrasound and confirmed by Triphasic CT scan were compared with serum Alpha Feto Proteins (AFP). Based on Alfa fetoprotein level, we divided patients into 3 groups; Group I patient's AFP levels were >20ng/ml but <200ng/mL, Group II AFP levels were 200-400 ng/mL, while Group III AFP levels were >400ng/mL. While based on tumor size we divided them into three Groups (such as <3 cm, 3-5cm, and >5cm size). In cases of multiple tumor nodules, the size of the largest lesion was considered.[17]

Different signs and symptoms were recorded such as associated co-morbidities like diabetes, hypertension, ischemic heart disease, smoking, and symptoms at presentation (jaundice, fever, lethargy, weight loss, anorexia, pain right hypochondrium, and abdominal distention), presence of ascites and encephalopathy. In addition, biochemical tests such as serum bilirubin levels, serum albumin levels, prothrombin time(PT) (<4 /4-6 / >6 sec prolonged), child Turcotte class (A, B, and C), PST (performance status), Barcelona Clinic liver cancer staging system (0/A/B/C/D), presence or absence of lymph nodal involvement and vascular metastasis was noted.

Data were analyzed through SPSS Statistics version 23.0 (IBM, Armonk, NY). Association of serum AFP levels with different variables was analyzed, Spearman's rank correlation is used for P-value, and a value <0.05 was considered a significant outcome.

3. Results

Baseline patients' characteristics:

The patients sample size was 334, all patients were confirmed cases of Hepatocellular carcinoma. Among these patients, 214(64%) were males while 120 (36%) were females. On the basis of age groups; 1(0.2%) were in 1-10 years age group, 2(0.5%) were in 11-20 and 21-30 years, 8(2.3%) were in 31-40 years, 59(17.6%) were in 41-50 year, 143(42.8%) were in 51-60 year, 92(27.5%) were in 61-70 year, 22(6.5%) were in 71-80 years, 4(1.1%) were in 81-90 year while 1(0.2%) were in 91-100 years age group shown in Figure 1.

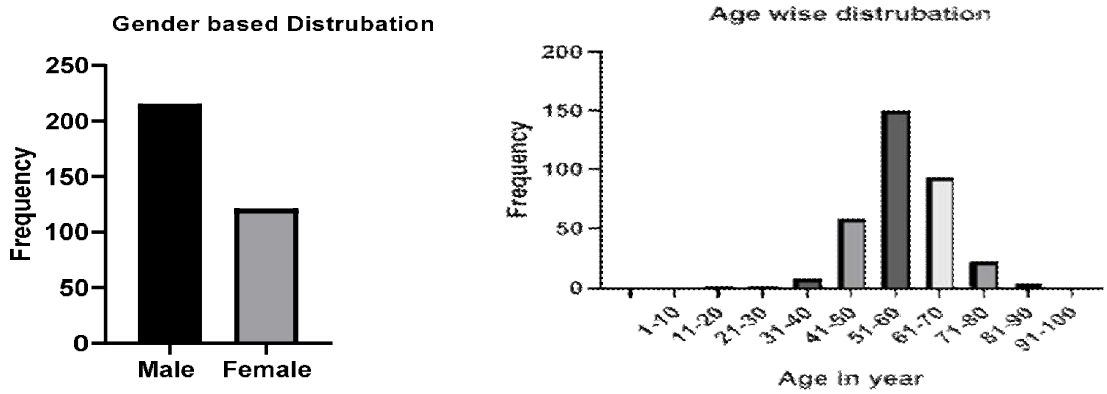

Figure 1: Gender and age-wise based distribution (right to left)

Based on Alpha-fetoprotein (AFP) level we divided into 3 groups; Group I AFP levels were >20 but < 200 ng/mL, Group II AFP levels were 200-400 ng/mL while Group III AFP levels were > 400 ng/mL. In Group I men's participants were 23.6% while women were 14.1%, in group II men's participants were 15.6%, while women were 8.9%, in group III men's participants were 24.8% while women's proportion was 13%. The proportions of both sexes were not significant.

We analyzed the basic characteristic in all the three groups; in Group-I/II/III proportion revealed diabetes 12.6%/ 7.5%/ 24.5% (P 0.121), HTN 11.9%/ 4.8%/ 12.3(P 0.811), IHD 3.5%/ 2.7%/ 2.7% (P 0.546), HBsAg positive proportion was 5.7%/ 2.2%/ 3.5 while negative cases were 32.1%/ 22.4%/ 34.3% (all P 0.186), HCV positive proportion was 32.6%/ 23.3%/ 35.3% while negative case were 4.8%/ 1.2%/ 2.8% (all P 0.131), pain right hypochondrium 24%/14.3%/25.1% (P 0.599), fever 13.8%/7.1%/18.3%(P 0.065), lethargy 29%/ 20.3%/ 31.2% (P 0.388) and Encephalopathy mild 5.7 %/ 6%/ 8.3% while marked was 0.2%/ 0.9%/ 0.9% (all P 0.075) were identified as non-significant risk factors for AFP levels.

We analyzed biochemical test according to lower-high level; in all groups bilirubin < 2 mg/dL, 2-3 mg/dL and > 3 mg/dL (P 0.000), Albumin <2.8mg/dL, 2.8-3.5 g/dL and >3.5g/dL (P 0.000), Prothrombin Time < 4sec ,4-6 sec and >6 sec prolonged (P 0.038) child turcotte Class A, B and C (P 0.000), creatinine <1.2 mg/dL and1.2-3.0 mg/dL(all P 0.001) compared with AFP groups were identified as significant association .Other characteristics such as smoking (P 0.023), Weight Loss (P 0.002), Anorexia (P 0.007), Jaundice (P 0.012), abdominal Mass (P 0.000), Ascites (P value 0.000) were also identified as significant association with AFP level mentioned in Table: 1.

Table: 1: Baseline characteristics of Hepatocellular carcinoma (HCC) patients

Variable		*AFP 20-200 ng/mL*	*AFP 200-400 ng/mL*	*AFP >400 ng/mL*	*Total*	*P-Value*
Gender	***Male***	*79(23.6%)*	*52(15.6%)*	*83(24.8%)*	*214(64%)*	*0.544*
	Female	*47(14.1%)*	*30(8.9%)*	*43(13%)*	*120(36%)*	
Diabetes		*42(12.6%)*	*25(7.5%)*	*82(24.5%)*	*149(44.6%)*	*0.121*
HTN		*40(11.9%)*	*16(4.8%)*	*41(12.3%)*	*97(29.0%)*	*0.811*
IHD		*12(3.5%)*	*9(2.7%)*	*9(2.7%)*	*30(8.9%)*	*0.546*
Smoking		*24(7.1%)*	*22(6.5%)*	*43(12.8%)*	*89(26.4%)*	*0.023*
HBsAg	***positive***	*19(5.7%)*	*7(2.1%)*	*12(3.5%)*	*38(11.3%)*	*0.186*
	Negative	*107(32.1%)*	*75(22.4%)*	*114(34.2%)*	*296(88.7%)*	
HCV	***positive***	*109(32.6%)*	*78(23.3%)*	*118(35.3)*	*306(91.2%)*	*0.131*
	Negative	*16(4.8%)*	*4(1.2%)*	*9(2.8%)*	*29(8.8%)*	

Pain Right Hypochondrium		*80(24%)*	*48(14.3%)*	*84(25.1%)*	*212(63.4%)*	*0.599*
Weight Loss		*68(20.3%)*	*54(16.1%)*	*90(27%)*	*212(63.4%)*	*0.002*
Fever		*46(13.8%)*	*24(7.1%)*	*61(18.3%)*	*131(39.2%)*	*0.065*
Lethargy		*97(29%)*	*68(20.3%)*	*104(31.2%)*	*269(80.5%)*	*0.388*
Anorexia		*87(26.0%)*	*67(20.1%)*	*105(31.4)*	*259(77.5%)*	*0.007*
Jaundice		*19(5.7%)*	*9(2.7%)*	*34(10.1%)*	*62(18.5%)*	*0.012*
Abdominal Mass		*53(15.9%)*	*47(14%)*	*88(26.3%)*	*188(56.2%)*	*0.000*
Ascites		*34(10.1%)*	*32(9.6%)*	*52(15.6%)*	*118(35.3%)*	*0.000*
Encephalopathy	***Mild***	*19(5.7%)*	*20(6%)*	*28(8.3%)*	*67(20%)*	*0.075*
	Marked	*1(0.2%)*	*3(0.9%)*	*3(0.9%)*	*7(2.0%)*	
Bilirubin	***< 2 mg/dL***	*93(27.9%)*	*46(13.7%)*	*68(20.3%)*	*208(61.9%)*	*0.000*
	2-3 Mg/dL	*18(5.4%)*	*29(8.7%)*	*28(8.3%)*	*75(22.4%)*	
	>3 mg/dL	*15(4.49%)*	*7(2.1%)*	*30(9%)*	*52(15.5%)*	
Albumin	***<2.8 g/dL***	*10(3%)*	*12(3.5%)*	*35(10.5%)*	*57(17%)*	*0.000*
	2.8-3.5 g/dl	*59(17.7%)*	*31(9.3%)*	*57(17%)*	*147(44%)*	
	>3.5 g/dL	*56(16.7%)*	*39(11.7%)*	*35(10.5%)*	*130(38.9%)*	
Prothrombin Time	***< 4 sec prolonged***	*71(21.2%)*	*45(13.5%)*	*57(17.1%)*	*173(51.8%)*	*0.038*
	4-6 sec prolonged	*43(12.9%)*	*33(9.9%)*	*50(15%)*	*126(37.8%)*	
	>6 sec prolonged	*12(3.6%)*	*4(1.2%)*	*19(5.6%)*	*35(10.4%)*	
Child Turcotte Class	***Class A***	*58(17.5%)*	*24(7.1%)*	*34(10.1%)*	*116(34.7%*	*0.000*
	Class B	*44(13.3%)*	*41(12.2%)*	*40(11.9%)*	*125(37.4%)*	
	Class C	*22(6.59%)*	*18(5.39%)*	*53(15.87%)*	*93(27.8%)*	
Creatinine	***<1.2 mg/dL***	*116(34.7%)*	*69(20.6%)*	*100(30%)*	*285(85.3%)*	*0.001*
	1.2-3.0 mg/dL	*10(3%)*	*13(3.9%)*	*26(7.8%)*	*49(14.7%)*	

Association between AFP levels with ECOG, BCLC, lesion number, and size:

The association of AFP levels with ECOG Performance Status Scale Grade 0, 1, 2, 3, 4 (P 0.000) and Barcelona Clinic liver cancer (BCLC) staging system (P 0.000) was highly significant. The association of AFP levels with lesion size and the number of nodules was analyzed via ultrasonography and contrast-enhanced computed tomography (Triphasic), a total of 334 patients were included in both techniques. On ultrasonography lesion, I/II/III/IV in all groups (P 0.784), on CECT I/II/III/IV in all groups (P 0.767) revealed no significant association. We divided lesion size into 3 groups such as < 3 cm, 3-5 cm, and > 5 cm, lesion I (P 0.000) on USG was significant while lesion II (P 0.356) was not significant. On CECT lesions I (P 0.000) and lesions II (P 0.006) had a highly significant association with AFP mentioned in Table 2 and Figures 2 & 3.

Table 2: Association between AFP levels with lesion number and size in USG and CECT

Lesion No and Size, ECOG, BCLC		***AFP 20-200 ng/mL***	***AFP 200-400 ng/mL***	***AFP >400 ng/mL***	***Total***	***P - value***
No of lesion USG	***I***	*125(37.4)*	*83(25%)*	*126(37.6%)*	*334*	*0.784*
	II	*45(13.4%)*	*34(10.6%)*	*47(13.7%)*	*126(37.7%)*	
	III	*15(4.5%)*	*18(5.3%)*	*20(6%)*	*53(15.8%)*	
	IV	*3(0.9%)*	*6(1.8%)*	*5(1.4%*	*14(4.1%)*	
No of Lesions on CECT	***I***	*126(37.7%)*	*83(24.8%)*	*125(37.5%)*	*334*	*0.767*
	II	*50(14.9%)*	*33(9.8%)*	*51(15.2%)*	*134(40.1%)*	
	III	*18(5.3%)*	*14(4.1%)*	*22(6.7%%)*	*54(16.1%)*	
	IV	*8(2.4%)*	*7(2%)*	*8(2.4%)*	*23(6.8%)*	

Size of lesion 1 USG	***< 3 cm***	*58(17.6%)*	*13(3.8%)*	*17(5.0%)*	*88(26.4%)*	*0.000000*
	3-5 cm	*44(13.1%)*	*41(12.2%)*	*33(9.8%)*	*118(35.3%)*	
	>5cm	*23(6.8%)*	*28(8.3%)*	*77(23%)*	*128(38.3%)*	
Size of lesion 2 USG	***<3 cm***	*11(3.2%)*	*15(4.4%)*	*10(3.1%)*	*36(10.7%)*	*0.356*
	3-5 cm	*6(1.7%)*	*3(0.8%)*	*5(1.6%)*	*14(4.1%)*	
	>5cm	*4(1.1%)*	*2(0.6%)*	*3(0.9%)*	*9(2.6%)*	
Size of Lesions CECT 1	***< 3 cm***	*56(16.8%)*	*12(3.6%)*	*17(5.0%)*	*85(25.4%*	*0.000*
	3-5 cm	*42(12.6%)*	*41(12.3%)*	*31(9.2%)*	*114(34.1%*	
	>5cm	*28(8.4%)*	*29(8.7%)*	*78(23.4%)*	*135(40.5%)*	
Size of lesion 2	***< 3 cm***	*20(6%)*	*12(3.5%)*	*7(2.1%)*	*39(11.6%)*	*0.006*
	3-5 cm	*6(1.8%)*	*5(1.5%)*	*17(5%)*	*28(8.3%)*	
	>5cm	*3(0.8%)*	*5(1.5%)*	*6(1.8%)*	*14(4.1%)*	
PST performance status (ECOG)	***0***	*73(21.8%)*	*26(8%)*	*20(6%)*	*119(35.6%)*	*0.000*
	1	*25(7.5%)*	*24(7.1%)*	*38(11.4%)*	*87(26%)*	
	2	*6(2%)*	*15(4.4%)*	*36(10.7%)*	*57(17.0%)*	
	3	*21(6.3%)*	*12(3.6%)*	*26(7.8%)*	*59(17.7%)*	
	4	*1(0.3%)*	*4(1.2%)*	*7(2.2%)*	*12(3.7%)*	
Barcelona Clinic for liver cancer (BCLC)	***0***	*4(1.2%)*	*1(0.2%)*	*0*	*5(1.4%)*	*0.000*
	A	*64(19.4%)*	*25(7.4%)*	*13(3.8%)*	*102(30.6%)*	
	B	*25(7.4%)*	*26(7.8%)*	*40(12%)*	*91(27.2%*	
	C	*7(2.1%)*	*10(3%)*	*18(5.4%)*	*35(10.5%)*	
	D	*25(7.4%)*	*21(6.2%)*	*56(16.7%)*	*101(30.3%)*	

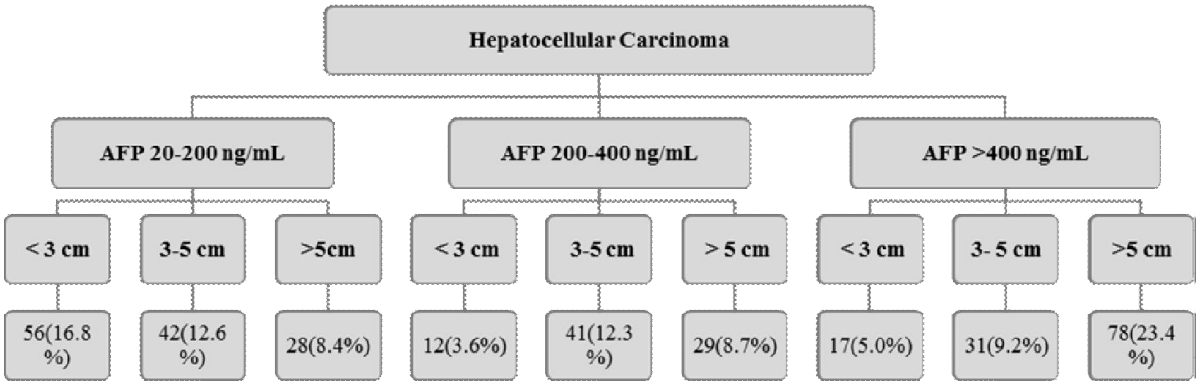

Figure 2: Association of AFP with lesion 1 size via CECT (P 0.000)

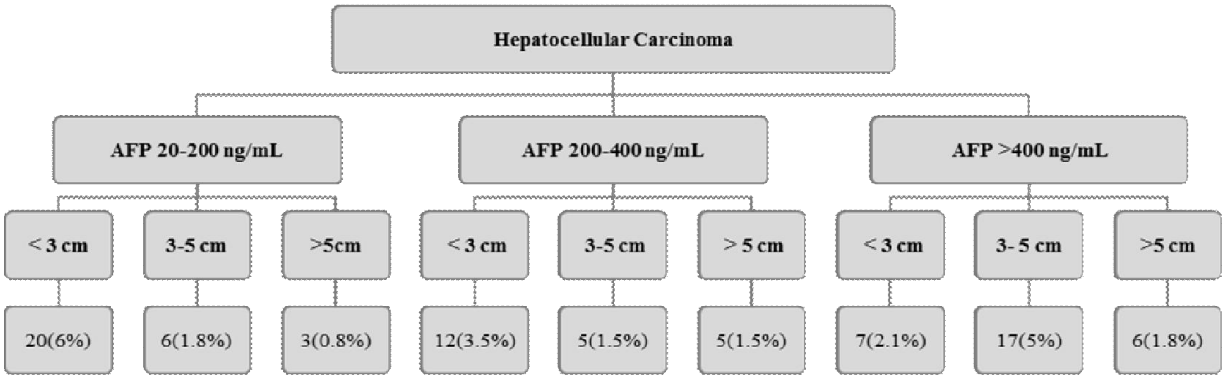

Figure 3: Association of AFP with lesion II size via CECT (P 0.006)

4. Discussion

HCC being the leading primary hepatic malignancy is the 4th most fatal tumor worldwide.[18,19] Although the etiology of HCC varies globally the increasing burden of Hepatitis C in Asian countries is becoming the leading cause of this tumor. Pakistan the 2nd most prevalent country as far as Hepatitis C is concerned is putting on a huge health burden due to HCC [20]. Our study also suggests a significant contribution of HCV (109 patients) as compared to HBV (19 patients) in our part of the world which is contrary to the global association where still HBV leads as a causative agent.[21] One likely explanation for this disparity can be the major mode of transmission of HBV in our part of the world. As globally it is the vertical transmission of HBV that not only increases the risk of chronicity of the disease as well as the chances of developing HCC, but in Pakistan, the major likely mode of transmission can still be horizontal.[22]

We also don't find any significant difference between AFP levels or the size of the tumor between these two viral etiologies. Spiros P Hiotis et al. in a study had shown much higher AFP levels (median level of AFP: HBV-1000 ng/ml vs. HCV-37 ng/ml; $p = 0.002$) as well as tumor size (HBV-78% >5 cm vs HCV-28 % >5 cm; $p < 0.001$) amongst patients with HBV as an etiology as compared to HCV.[23]

AFP is a tumor marker of HCC, being widely in use for several decades. Multiple studies have been conducted in the past to establish its correlation with Tumor size, number, and disease burden. Our study shows a significant association between AFP levels and Tumor size on CECT of not only the 1st lesion ($p = 0.000$) but also with the 2nd lesion ($p = 0.006$) if identified on a CT scan. A similar significant association can be seen with the size of 1st lesion on ultrasound and AFP ($p = 0.000000$) however the significance is not well established for the 2nd lesion on ultrasound ($P = 0.356$). S. Sharieff et al.[24] Khawar Shabbir et al[25] and Laura et al[26] in their studies are unable to prove a significant association between AFP and tumor size. Whereas studies by Aman Ullah Abbasi et al[27] and Rafi ud Din et al[28] have shown a positive correlation between AFP with tumor size. The study by S.Sharieff[24] is an older study published in 2001 and the tumor size is determined through ultrasound instead of CECT. However, in our study even the ultrasound correlation of tumor size of 1st lesion and AFP are significant. Khawar Shabbir et al. though unable to determine a significant association but in the higher AFP groups with values of 21-399 IU/ml and >400 IU/ml a clear correlation between AFP and the size of the tumor was observed.

A study was conducted by Laura et al[26], there is a weak but insignificant relationship between tumor size and HCC and the author calls this an accidental association which is contrary to our study and several other studies[27,28] where it seems to be a pathologic correlation between AFP and tumor size. AFP is a 591 amino acid glycoprotein produced by the fetal yolk sac, liver, and intestine and is associated with several tumors including HCC. A larger size of tumor means more cells producing the glycoprotein and hence a positive correlation is well anticipated.[29]

There have been additional statistically significant findings with AFP levels. There was a statistically significant association of AFP groups with various child Turcotte Pugh classes as well as with bilirubin, albumin, and prothrombin time. Of note, all these abnormalities serve as prognostic indicators for liver dysfunction in various scoring systems like the Model for End-Stage Liver Disease (MELD) Score, etc.

So, a positive association of AFP groups likely indicates worsening liver disease that is expected with the increasing size of the tumor. This appears in synchronization with our hypothesis that higher AFP levels are an indicator of worsening disease burden. This is further evident by the significant association of AFP levels with ECOG Performance Status Scale grades and Barcelona Clinic for liver cancer (BCLC) staging. These evaluations are used to assess stages as well as the impact of HCC relating to the quality of life of the patients before making treatment decisions. So, a positive association of AFP groups again shows that rising AFP levels are an indicator of worsening oncologic burden including tumor size.

Certain limitations of our study must be acknowledged when we consider its results in implications. Due to the cross-sectional study design, temporality and residual confounding could be considered study limitations. Additionally, it is a single-center study with small data set so generalizability may be limited. The strength of our study is that the database is from a tertiary care referral center so the results can be representative of a larger

population across various sociodemographic groups. The study does raise the need for further studies in the area to further establish the link in more rigorous clinical trials.

5. Conclusion

Alfa Feto Protein is a well-recognized tumor marker for Hepatocellular Carcinoma. Based on our study findings, we hereby, conclude that there is a noteworthy correlation between Alpha Feto Proteins and the increase in the size of the tumor. Hence Alfa Feto protein is not only helpful for the diagnosis of HCC but also has a pivotal role in predicting tumor burden and disease level. Though more tumor markers including PIVKA-II have been introduced in the market for the diagnosis of Hepatocellular Carcinoma, Alfa Feto protein, being the old one, still is being extensively used throughout the world as a diagnostic and prognostic indicator of stage progression of the disease and survival.

CONFLICTS OF INTEREST- None

Financial support: None to report.
Potential competing interests: None to report

Contributions:

J.K, T.S- Conception of study
J.K- Experimentation/Study conduction
M.I, S.A- Analysis/Interpretation/Discussion
J.K, M.K, R.K, T.H, S.A, M.N- Manuscript Writing
J.K, N.S, M.U, B.K- Critical Review
J.K- Facilitation and Material analysis

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018 Nov;68(6):394-424.DOI:https://doi.org/10.3322/caac.21492.

[2] GRADE Working Group. Grading quality of evidence and strength of recommendations. Bmj. 2004 Jun 19;328(7454):1490.DOI: https://doi.org/10.1136/bmj.328.7454.1490.

[3] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015 Mar;65(2):87-108.DOI: https://doi.org/10.3322/caac.21262.

[4] Munaf A, Memon MS, Kumar P, Ahmed S, Kumar MB. Comparison of viral hepatitis-associated hepatocellular carcinoma due to HBV and HCV-cohort from liver clinics in Pakistan. Asian Pacific Journal of Cancer Prevention. 2014;15(18):7563-7.DOI: https://doi.org/10.7314/APJCP.2014.15.18.7563.

[5] Butt AS, Hamid S, Wadalawala AA, Ghufran M, Javed AA, Farooq O, Ahmed B, Haq TU, Jafri W. Hepatocellular carcinoma in Native South Asian Pakistani population; trends, clinico-pathological characteristics & differences in viral marker negative & viral-hepatocellular carcinoma. BMC research notes. 2013 Dec;6(1):1-3.

[6] Parkash O, Hamid S. Next big threat for Pakistan hepatocellular carcinoma (HCC). Journal of Pakistan Medical Association. 2016;66(6):735.

[7] Yurie H, Ikeguchi R, Aoyama T, Kaizawa Y, Tajino J, Ito A, Ohta S, Oda H, Takeuchi H, Akieda S, Tsuji M. The efficacy of a scaffold-free Bio 3D conduit developed from human fibroblasts on peripheral nerve regeneration in a rat sciatic nerve model. PloS one. 2017 Feb 13;12(2):e0171448.DOI: https://doi.org/10.1371/journal.pone.0171448.

[8] Patil M, Sheth KA, Adarsh CK. Elevated alpha fetoprotein, no hepatocellular carcinoma. Journal of Clinical and Experimental Hepatology. 2013 Jun 1;3(2):162-4.DOI: https://doi.org/10.1016/j.jceh.2013.02.246

[9] ur Rehman K, Samiullah M, Sharif S, Farhat S. HEPATOCELLULAR CARCINOMA: CORRELATION OF SERUM ALPHA FETOPROTEIN AND TUMOR SIZE. The Professional Medical Journal. 2016 Feb 10;23(02):209-12.

[10] Song PP, Xia JF, Inagaki Y, Hasegawa K, Sakamoto Y, Kokudo N, Tang W. Controversies regarding and perspectives on clinical utility of biomarkers in hepatocellular carcinoma. World journal of gastroenterology. 2016 Jan 1;22(1):262.DOI: 10.3748/wjg.v22.i1.262.

[11] Chang SK, Hlaing WW, Yu RQ, Lee TW, Ganpathi IS, Madhavan KK. Value of alpha-foetoprotein for screening of recurrence in hepatocellular carcinoma post resection. Singapore medical journal. 2012 Jan 1;53(1):32.

[12] Tangkijvanich P, Anukulkarnkusol N, Suwangool P, Lertmaharit S, Hanvivatvong O, Kullavanijaya P, Poovorawan Y. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. Journal of clinical gastroenterology. 2000 Dec 1;31(4):302-8.

[13] Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. Journal of hepatology. 2001 Sep 1;35(3):421-30.DOI: https://doi.org/10.1016/S0168-8278(01)00130-1.

[14] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology (Baltimore, Md.). 2011 Mar;53(3):1020.DOI: 10.1002/hep.24199

[15] Kim KW, Lee JM, Klotz E, Park HS, Lee DH, Kim JY, Kim SJ, Kim SH, Lee JY, Han JK, Choi BI. Quantitative CT color mapping of the arterial enhancement fraction of the liver to detect hepatocellular carcinoma. Radiology. 2009 Feb;250(2):425-s34.

[16] Pang G, Duan Z, Shao C, Zhao F, Zhong H, Shao G. Heterogeneity analysis of triphasic CT scan perfusion parameters in differential diagnosis of hepatocellular carcinoma and hemangioma. Medicine. 2018 Sep;97(38).DOI: 10.1097/MD.0000000000012512

[17] Toader E, Bancu A, Mitrica DE, Constantinescu G, Stefanescu G, Balan GG. Interrelations between elevated alpha-fetoprotein levels and tumor morphology of patients with hepatocellular carcinoma. Rom J Morphol Embryol. 2019 Jan 1;60(1):181-7.

[18] Carcinoma H. Villanueva A. N Engl J Med. 2019;380:1450-62.

[19] World Health Organization. Liver Factsheet. Globocan https://gco.iarc.fr/ today/data/factsheets/cancers/11-Liver-fact-sheet.pdf (2018): DOI: https://gco.iarc.fr/today/fact-sheets-cancers.

[20] Lim AG, Qureshi H, Mahmood H, Hamid S, Davies CF, Trickey A, Glass N, Saeed Q, Fraser H, Walker JG, Mukandavire C. Curbing the hepatitis C virus epidemic in Pakistan: the impact of scaling up treatment and prevention for achieving elimination. International journal of epidemiology. 2018 Apr 1;47(2):550-60.DOI: https://doi.org/10.1093/ije/dyx270.

[21] Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP. Hepatitis B virus infection: epidemiology and vaccination. Epidemiologic reviews. 2006 Aug 1;28(1):112-25.DOI: https://doi.org/10.1093/epirev/mxj009.

[22] Ali SA, Donahue RM, Qureshi H, Vermund SH. Hepatitis B and hepatitis C in Pakistan: prevalence and risk factors. International journal of infectious diseases. 2009 Jan 1;13(1):9-19.DOI: https://doi.org/10.1016/j.ijid.2008.06.019.

[23] Hiotis SP, Rahbari NN, Villanueva GA, Klegar E, Luan W, Wang Q, Yee HT. Hepatitis B vs. hepatitis C infection on viral hepatitis-associated hepatocellular carcinoma. BMC gastroenterology. 2012 Dec;12(1):1-7.

[24] Sharieff S, Burney IA, Salam A, Siddiqui T. Lack of correlation between alpha fetoprotein and tumor size in hepatocellular carcinoma. J Pak Med Assoc. 2001 Mar 1;51(3):123-4.

[25] Sahbbir K, Shehzad A, Nqvi M, Khalid MS, Zia N, Haider E, Farooq A. ASSOCIATION OF SERUM ALPHA FETOPROTEIN (AFP) LEVELS WITH SIZE OF HEPATOCELLULAR CARSINOMA. PAFMJ. 2019 Feb 28;69(1):71-5.

[26] Laura S, Julija S, Laura M. Correlation of Serum Alpha Fetoprotein with Tumor Size and Number of Tumors in Hepatocellular Carcinoma. Laboratorine medicina. 2016.18(Nr. 1),p. 29 -32.

[27] Abbasi A, Bhutto AR, Butt N, Munir SM. Corelation of serum alpha fetoprotein and tumor size in hepatocellular carcinoma. JPMA-Journal of the Pakistan Medical Association. 2012 Jan 1;62(1):33.

[28] Din RU, Qadir A, Ali RS, Salamat A. Hepatocellular carcinoma: correlation of alpha-fetoprotein with tumour characteristics. PAFMJ. 2020 Apr 30;70(2):420-24.

[29] Aoyagi Y, Suzuki Y, Igarashi K, Saitoh A, Oguro M, Yokota T, Mori S, Suda T, Isemura M, Asakura H. Carbohydrate structures of human α-fetoprotein of patients with hepatocellular carcinoma: presence of fucosylated and non-fucosylated triantennary glycans. British journal of cancer. 1993 Mar;67(3):486-92.