

Raised Alpha-Fetoprotein Level and its Association with Hepatocellular Carcinoma

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ABSTRACT

Objective: To evaluate raised alpha feto-protein levels for socio-demographic and clinicopathological features in hepatocellular carcinoma.

Study Design: Cross-sectional study.

Place and Duration: Department of Medical Oncology, Jinnah Postgraduate Medical Center, Karachi Pakistan, from Jan 2019 to Jan 2020.

Methodology: Two hundred and thirty-six patients of age more than 20 years, of either gender diagnosed with hepatocellular carcinoma were included. Detailed demographic data, information regarding addiction and medical history were collected. According to The National Comprehensive Cancer Network, Hepatocellular carcinoma was diagnosed using a multiphasic liver protocol CT scan with intravenous contrast. The alpha-fetoprotein levels were checked after confirmation of hepatocellular carcinoma on a multiphasic CT scan. The cut-off value for elevated alpha feto-protein was ≥ 20 ng/mL.

Results: The median alpha protein levels were reported as 411 ng/mL. About 183(78%) patients had elevated alpha protein levels. In univariate analysis, age, gender, diabetes mellitus, hepatitis B, hepatitis C, portal vein thrombosis, number of lesions, cirrhotic liver, features of portal hypertension, anti-viral treatment status, cigarette smoking, and segment of the liver showed a statistically significant relationship with elevated alpha protein levels ($p < 0.05$). On the multivariate model, age, hepatitis C, number of lesions, portal vein thrombosis, and Child Pugh score showed statistically significant association with elevated alpha protein ($p < 0.05$).

Conclusions: The elevated alpha protein levels level was found to be higher among hepatocellular carcinoma and associated with age, hepatitis C, number of lesions, portal vein thrombosis and Child Pugh score.

Keywords: Alpha-fetoprotein, Child-Pugh score, Hepatocellular carcinoma, Hepatitis C, Hepatitis B, Liver cirrhosis.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth leading cause of death globally, with 782,000 deaths in the year 2018.¹ The incidence of HCC in males is higher than in females, and the risk increases with age and typically, cases diagnosed over the 75 years of age.² Due to the high incidences of hepatitis B and C infections, HCC is becoming widespread in Asia.³ In Pakistan, HCC is a frequent cancer. It comprises 10.7% of all the cases of cancer.⁴

The development of HCC is closely related to chronic liver diseases, especially in cirrhotic liver. The cirrhotic patients should be monitored regularly with computed tomography (CT) and ultrasound (US) in combination with serum alpha-fetoprotein (AFP) determination.⁵

Potentially curative treatments like resection, radiofrequency ablation and liver transplantation

showed better results, with a five-year overall survival rate greater than 70 percent in patients with small tumour size.⁶ Thus, HCC detected with adequate screening modality during an early stage is important for optimizing patient clinical outcomes.⁷ A screening modality should be accessible, cost-effective and have good sensitivity. According to "Asia Pacific Association for the Study of Liver Diseases (APASL)" guidelines, all cirrhotic patients should be screened with US and AFP for HCC.⁸ In a recent study by Sarwar *et al.* reported 86.2% specificity, 72.2% sensitivity and 77.4% overall accuracy of AFP for the diagnosis of HCC at a cut-off value of 20.85 ng/ml.⁹

Thus, the present study aimed to examine the significance of elevated alpha-fetoprotein levels for socio-demographic and clinicopathological features of patients presenting with hepatocellular carcinoma (HCC) at a tertiary care hospital in Karachi, Pakistan.

METHODOLOGY

The cross-sectional study was conducted at the Department of Medical Oncology of Jinnah Postgraduate Medical Center, Karachi, from January 2019

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to January 2020. Approval from the Ethical Review Committee (NO.F.2-81-IRB/2019-GENL/10082/JPMC). The sample size was estimated using an open epi online sample size calculator by taking the frequency of elevated AFP as 67% among HCC patients.¹⁰

Inclusion Criteria: Patients of age more than 20 years of either gender diagnosed with HCC were included in the study.

Exclusion Criteria: Patients with pregnancy, respiratory illness, chronic kidney failure, coronary artery disease and concomitant second malignancy were excluded from the study.

Informed consent was taken from all the eligible patients before data collection. Detailed demographic data, information regarding addiction and medical

history were collected from each patient. Liver cirrhosis was staged using the CHILD PUGH score. HCC was diagnosed using NCCN guidelines. Its imaging included the use of multiphasic liver protocol CT with IV contrast. HCC lesion was characterized by intense arterial uptake or enhancement followed by contrast washout or hypointensity in the delayed non-peripheral venous phase. AFP levels were checked after confirmation of HCC on a multiphasic CT scan. The cut-off value for elevated AFP was set as ≥ 20 ng/mL and AFP normal as < 20 ng/mL.¹¹

Statistical Packages for Social Sciences (SPSS) version 23 was used to analyze the data. Numeric variables were presented as mean and SD. Categorical/binary variables were presented as frequency and percentage. The Chi-square test was applied to see the association between elevated AFP levels and other

Table-I: Distribution of Study Variables (n=236)

Variables	n(%)
Age (years) Mean±SD	56.48±9.95
Gender	
Male	176(74.6%)
Female	60(25.4%)
Ethnicity	
Urdu	62(26.3%)
Sindhi	87(36.9%)
Punjabi	26(11%)
Pashto	27(11.4%)
Balochi	16(6.8%)
Other	18(7.6%)
Residence	
Urban	62(26.3%)
Rural	174(73.7%)
Education	
Illiterate	168(71.2%)
Literate	68(28.8%)
Marital status	
Married	162(68.6%)
Unmarried	74(31.4%)
Addiction	
Cigarette smoking	89(37.7%)
Alcohol consumption	8(3.4%)
Betel nut	18(7.6%)
Other	32(13.6%)
Co-morbid	
Hypertension	35(14.8%)
Diabetes mellitus	54(22.9%)
Hepatitis C	46(19.5%)
Hepatitis B	170(72%)
History of transfusion	
Yes	51(21.6%)
No	185(78.4%)
History of surgery	
Yes	41(17.4%)
No	195(82.6%)

Variables	n(%)
Child Pugh Score	
A	142(60.2%)
B	63(26.7%)
C	31(13.1%)
Portal Vein Thrombosis	
Yes	122(51.7%)
No	114(48.3%)
Segment of Liver	
Right lobe	125(53%)
Left lobe	30(12.7%)
Both	81(34.3%)
Number of lesion	
Single	43(18.2%)
Multi-centric	193(81.8%)
Cirrhotic liver	
Yes	158(66.9%)
No	78(33.1%)
Features of portal hypertension	
Yes	176(74.6%)
No	60(25.4%)
Treatment Naïve	
Yes	216(91.5%)
No	20(8.5%)
Clinical stage of cancer	
2	34(14.4%)
3	165(69.9%)
4	37(15.7%)
Metastasis	
None	211(89.4%)
Adrenal	1(0.4%)
Lungs	1(0.4%)
Bone	9(3.8%)
Pulmonary	11(4.7%)
Multiple sites	3(1.3%)

related variables. The multivariate logistic regression model adjusted potential effect modifiers in univariate analysis for elevated AFP levels. The *p*-value of ≤ 0.05 was taken as statistically significant.

RESULTS

Of 236 patients, the mean age was reported as 56.48±9.95 years. Eighty-three patients were of age 51-60 years (35.1%). The majority of the patients were males (n=176, 74.6%), Sindhi (n=87, 36.9%), belonged from rural areas (n=174, 73.7%), illiterate (n=168, 71.2%) and married (n=162, 68.6%). About 89(37.7%)

patients were smokers and 18 (7.6%) were betel nut consumers. About 142 (60.2%) HCC patients had child-pugh score A, and 122(51.7%) had portal vein thrombosis. More than half of the patients (n=125, 53%) had the right lobe involved, and 81(34.4%) had both lobes involved. Most patients had multi-centric lesions (n=193, 81.8%), and 158(66.9%) had cirrhotic liver. One seventy-six patients had features of portal hypertension (74.6%), 216 patients were anti-viral treatment naïve (91.5%), and 165 patients had clinical stage 3(69.9%). The most frequent site of metastasis was pulmonary (n=11, 4.7%), followed by bone metastasis (n=9, 3.8%) (Table-I).

Table-II: Association of Elevated Alpha-Fetoprotein with Independent Variables (n=236)

	Elevated Alpha-Fetoprotein		<i>p</i> -value
	Yes	No	
Age Groups			
<55 years	82(44.8%)	14(26.4%)	0.016
≥55 years	101(55.2%)	39(73.6%)	
Gender			
Male	144(78.7%)	32(60.4%)	0.007
Female	39(21.3%)	21(39.6%)	
Ethnicity			
Urdu	48(26.2%)	14(26.4%)	0.672
Sindhi	64(35%)	23(43.4%)	
Punjabi	22(12%)	4(7.5%)	
Pashto	20(10.9%)	7(13.2%)	
Balochi	13(7.1%)	3(5.7%)	
Other	16(8.7%)	2(3.8%)	
Area			
Urban	52(28.4%)	10(18.9%)	0.164
Rural	131(71.6%)	43(81.1%)	
Education			
Illiterate	128(69.9%)	40(75.5%)	0.434
Literate	55(30.1%)	13(24.5%)	
Marital status			
Married	128(69.9%)	34(64.2%)	0.423
Unmarried	55(30.1%)	19(35.8%)	
Hypertension			
Yes	26(14.2%)	9(17%)	0.617
No	157(85.8%)	44(83%)	
Diabetes Mellitus			
Yes	48(26.2%)	6(11.3%)	0.023
No	135(73.8%)	47(88.7%)	
Hepatitis C			
Yes	28(15.3%)	18(34%)	0.003
No	155(84.7%)	35(66%)	
Hepatitis B			
Yes	140(76.5%)	30(56.6%)	0.004
No	43(23.5%)	23(43.4%)	
History of Transfusion			
Yes	41(22.4%)	10(18.9%)	0.582
No	142(77.6%)	43(81.1%)	
History of Surgery			
Yes	32(17.5%)	9(17%)	0.932
No	151(82.5%)	44(83%)	

Child Pugh Score			
A	119(65%)	23(43.4%)	0.018
B	43(23.5%)	20(37.7%)	
C	21(11.5%)	10(18.9%)	
Portal Vein Thrombosis			
Yes	103(56.3%)	19(35.8%)	0.009
No	80(43.7%)	34(64.2%)	
No. of lesions			
Single	20(10.9%)	23(43.4%)	0.001
Multi-centric	163(89.1%)	30(56.6%)	
Cirrhotic liver			
Yes	129(70.5%)	29(54.7%)	0.032
No	54(29.5%)	24(45.3%)	
Features of Portal Hypertension			
Yes	144(78.7%)	32(60.4%)	0.007
No	39(21.3%)	21(39.6%)	
Treatment Naïve			
Yes	173(94.5%)	43(81.1%)	0.002
No	10(5.5%)	10(18.9%)	
Cigarette Smoking			
Yes	76(41.5%)	13(24.5%)	0.025
No	107(58.5%)	40(75.5%)	
Alcohol Consumption			
Yes	5(2.7%)	3(5.7%)	0.301
No	178(97.3%)	50(94.3%)	
Betel nut			
Yes	15(8.2%)	3(5.7%)	0.54
No	168(91.8%)	50(94.3%)	
Segment of Liver			
Right lobe	96(52.5%)	29(54.7%)	0.004
Left lobe	17(9.3%)	13(24.5%)	
Both	70(38.3%)	11(20.8%)	
Clinical Stage			
2	23(12.6%)	11(20.8%)	0.313
3	130(71%)	35(66%)	
4	30(16.4%)	7(13.2%)	
Metastasis			
No	163(89.1%)	48(90.6%)	0.647
Adrenal	1(0.5%)	0	
Lungs	1(0.5%)	0	
Bone	8(4.4%)	1(1.9%)	
Pulmonary	7(3.8%)	4(7.5%)	
Multiple sites	3(1.6%)	0	

The AFP level was not normally distributed. Therefore, the median AFP levels of HCC patients were reported as 411 ng/mL with an interquartile range of 25.45-1447.08 ng/mL and a range of 2-700000 ng/mL. About 78% of the patients had elevated AFP (Figure).

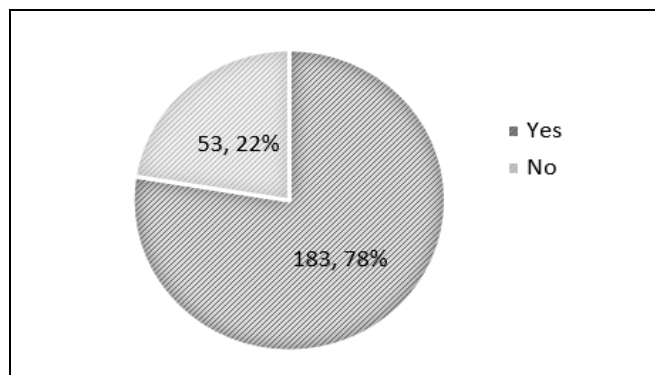


Figure: Elevated Alpha-Fetoprotein among Patients with Hepatocellular Carcinoma (n=236)

In univariate analysis, age, gender, diabetes mellitus, hepatitis B, hepatitis C, portal vein thrombosis, number of lesions, cirrhotic liver, features of portal hypertension, anti-viral treatment naïve, cigarette smoking, and segment of the liver showed a statistically significant relationship with elevated AFP ($p < 0.05$) (Table-II).

After adjusting odds in the multi-variate logistic regression model, only age ($p = 0.003$), hepatitis C ($p = 0.021$), number of lesions ($p = 0.016$), child-pugh score ($p < 0.05$), and portal vein thrombosis ($p = 0.021$) showed statistically significant association with elevated AFP (Table-III).

Table-III: Multivariate Analysis for Potential Effect Modifiers (n=236)

Variables	p-value	Adjusted OR	95% CI for OR	
			Lower	Upper
Age	0.003	0.938	0.900	0.978
Hepatitis C				
Yes	1	Reference		
No	0.021	3.669	1.211	11.110
No of Lesions				
Single	1	Reference		
Multi-centric	0.016	4.005	1.289	12.447
Child Pugh Score				
A	1	Reference		
B	0.003	0.266	0.110	0.643
C	0.045	0.321	0.106	0.973
Portal Vein Thrombosis				
Yes	1	Reference		
No	0.012	0.350	0.155	0.791

DISCUSSION

In the present study, we have evaluated the association between elevated AFP levels and different potential factors in subgroup analysis. We found that the median AFP levels of HCC patients were reported as 411 ng/mL, whereas a study by Baig *et al.* found the mean AFP levels as 421 ± 59 $\mu\text{g/ml}$.¹² In the present study, 78% of the HCC patients had elevated AFP levels (>20 ng/mL). In a previous study by Lalisang *et al.*, they found that 57.9% of the HCC patients had AFP levels >20 ng/mL.¹³

In our study, AFP levels were elevated in 65% of the patients with child-pugh score A followed by Child-Pugh score B (23.5%) and C (11.5%) and a statistically significant association was found between elevated AFP and Child-Pugh score ($p < 0.05$). In a previous study, 100% of the HCC patients had Child-Pugh score A; among them, 40.6% had AFP over 20 ng/mL.¹⁴ In another research, about 96% of the patients had a Child-Pugh score of A.¹⁵ Among them, more than 95% of the patients had an AFP level of more than 20 ng/mL, and a further statistically insignificant association was found between AFP levels and the Child-Pugh stage ($p > 0.05$).¹⁶

In another research conducted in Pakistan, it was found that 27 and 44 patients with Child-Pugh scores A and B had elevated AFP levels, respectively. However, it showed an insignificant relationship between AFP levels and Child-Pugh score ($p > 0.05$).¹⁷ In the present research, 91.5% of the patients were anti-viral treatment naïve and elevated AFP was significantly high in 94.5% of those patients ($p < 0.05$). A previous retrospective study included treatment patients with chronic hepatitis B who had positive AFP before initiating anti-viral treatment for 12 months and found that AFP levels normalised in 48 per cent of the patients after treatment.¹⁸ Other studies also found similar results that falsely raised AFP levels dramatically reduced after treatment with anti-viral. Hence, using anti-viral treatment and determining AFP may be useful in diagnosing HCC patients with cirrhosis-associated hepatitis B virus.^{19, 20}

Finally, multivariate analysis of the present study showed a clear association of age, hepatitis C, number of lesions, portal vein thrombosis and child-pugh score with elevated AFP (>20 ng/mL). Further large and multicenter studies should be conducted to see the correlation between levels of AFP with size, grade and histology of HCC.

CONCLUSION

The elevated alpha protein levels were higher among hepatocellular carcinoma and associated with age, hepatitis C, number of lesions, portal vein thrombosis and child Pugh score. The elevated AFP level has been increasingly recognized as a valuable marker in diagnosis and predicting HCC recurrence. It can be used for screening and monitoring of HCC to help in early detection of HCC before the clinical manifestation.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MH: & GH: Data acquisition, data analysis, critical review, approval of the final version to be published.

MD: & AH: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

RI: & KA: Concept, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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