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Original Article

Serum Alpha Fetoprotein as a Predictor of Tumor Size in Hepatocellular Carcinoma

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ABSTRACT:

Objective: To evaluate the relationship between serum alpha fetoprotein (AFP) levels and tumor burden in hepatocellular carcinoma (HCC) patients.

Methods: This cross-sectional analytical study was conducted in the Interventional Radiology Department of Rehman Medical Institute from May 2016 to November 2022. Patients with chronic liver disease and concurrent HCC were included, while patients with liver metastases from other primary malignancies were excluded. Demographic characteristics, clinical information, laboratory investigations, and imaging modalities were considered. Patients were classified according to AFP levels and tumor diameter. Descriptive statistics (frequencies and percentages) and inferential statistics using Spearman's rank-order correlation test were employed. In addition, sensitivity and specificity of AFP levels for predicting larger tumor sizes were calculated.

Results: A direct positive association was observed between AFP levels and tumor size (Pearson Chi-Square = 220.091, $p < 0.001$). Most patients with AFP levels >2000 IU/mL had tumors >5 cm in diameter (n = 127). Using an AFP cutoff of >400 IU/mL to predict tumors >5 cm, sensitivity was calculated as 62.0% and specificity as 42.8%. With a higher cutoff of >2000 IU/mL, the sensitivity was 27.0% and specificity 34.4%. In addition, patients with higher AFP levels had significantly larger tumors, more frequent vascular invasion, and extrahepatic metastases. Histopathological confirmation (performed in a subset of cases via ultrasound-guided biopsy) supported the imaging diagnosis of HCC.

Conclusion: Elevated serum AFP levels are positively associated with larger tumor size and advanced tumor progression in HCC patients. Although AFP is a useful biomarker for estimating tumor load, its sensitivity is limited, particularly when used alone. Therefore, AFP should be interpreted in conjunction with imaging studies and, where applicable, histopathological confirmation to improve diagnostic accuracy.

Keywords: Hepatocellular carcinoma, Alpha fetoprotein, Tumor size, Sensitivity, Specificity

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Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies worldwide and ranks as the sixth most frequently diagnosed cancer and the third leading cause of cancer-related death. Approximately 790,000 new HCC cases are diagnosed annually, with more than 700,000 deaths per year, particularly in regions with high hepatitis B and C virus prevalence. As the incidence of HCC increases, there is a growing need for efficient diagnostic and therapeutic strategies. Biomarkers such as AFP play an important role in assessing disease progression, predicting prognosis, and monitoring treatment response. AFP is a glycoprotein synthesized during fetal hepatogenesis and normally declines postnatally. However, in adults, elevated AFP levels are primarily associated with liver diseases such as HCC, making it a valuable diagnostic tool.

Nevertheless, AFP has several limitations. Its levels may be elevated in nonmalignant conditions, including liver regeneration in chronic liver disease, which can lead to misdiagnosis. Therefore, understanding the correlation between AFP levels and tumor characteristics—including size—is essential to improve diagnostic accuracy and patient management. Previous studies have produced inconclusive results regarding the strength of this relationship, necessitating further research to clarify the role of AFP in predicting tumor burden in HCC.

Materials and Methods

This cross-sectional analytical study was carried out at Interventional Radiology Department of Rehman Medical Institute, Peshawar, over the period from May 2016 to Nov 2022. In the study, patients with chronic liver disease and diagnosed cases of Hepatocellular Carcinoma were enrolled. In this regard, patients with primary liver lesion other than HCC and metastasis were excluded. Demographic details like age, gender, and place of residence were also included as preliminarily structured templates involving general history and physical examination were taken.

They were followed by routine haematological and biochemical parameters, the amount of total protein, albumin/globulin ratio, serum albumin concentration and blood serum antigen of HBsAg, antibody of anti-HCV and AFP.
Most of the patients were diagnosed having typica features of HCC with supporting findings, rest were having ultrasound guided biopsy. Patients were grouped based on their serum AFP levels into three categories: Group I, AFP less than 20 IU/ml, considered as the normal range; Group II, moderate increase in AFP, in the range of 20-399 IU/ml; Group III, AFP greater than 400 IU/ml referred to as highly raised. Similarly, patients were classified based on tumor size: This is the rationale for classifying patients into three groups: Group A with tumor size of <3 cm, Group B with tumor size of between 3-5 cm, and Group C with tumor size of >5 cm.

Moreover, Spearman's rank correlation test was used to assess the corresponding relationship between serum AFP levels and tumour size, with an assigned significance level of r = 0. 01. Descriptive statistics analysis was carried out in this study

by using Statistical Package for Social Science (SPSS) software version 27 to achieve high accuracy in the findings. This approach was designed to assess the correlation of serum AFP levels with tumor size of HCC patients and possibly offer some practical suggestions.

Results

The study included a total of 882 patients, with a mean age of 57.69 years (SD = 12.057). The gender distribution was 69.2% male (n = 610) and 30.8% female (n = 272). Among the patients, 80.2% (n = 707) were diagnosed with hepatocellular carcinoma (HCC), while 19.8% (n = 175) had other diagnoses. Treatment details indicated that 21% (n = 185) received complete treatment (CT), 54.2% (n = 478) received partial treatment (PT), and 24.8% (n = 219) received no treatment (No TX) for viral hepatitis B or C.

Table 1: Demographic and Clinical Characteristics of the Study Population

Statistic	Value
Mean Age (years)	57.69
Standard Deviation	12.057
Gender (Male)	69.2%
Gender (Female)	30.8%
HCC Diagnosis	80.2%
Non-HCC Diagnosis	19.8%
Complete Treatment (CT)	21.0%
Partial Treatment (PT)	54.2%
No Treatment (No TX)	24.8%

Table 2 presents the tumor sizes stratified by AFP levels. A statistically considerable relationship between AFP levels and tumor size was determined (95%confidence, chi-square = 99. 407, p < 0. 001). For the purpose of analysis, the patients were categorized based on the tumor size and AFP levels: The majority the patients with AFP levels >2000 IU/ml had tumors >5 cm (n = 127).

Table 2: AFP Levels and Tumor Size Cross-Tabulation

AFP Levels (IU/ml)	Tumor Size <3 cm	Tumor Size 3-5 cm	Tumor Size >5 cm	Total
<10	26	33	83	142
11-20	18	6	27	51
21-40	16	15	24	55
41-100	7	13	45	65
101-400	3	19	77	99
401-2000	7	17	88	112
>2000	4	8	127	139
Total	81	111	471	663

Pearson Chi-Square = 220. 091 whereby p < 0. 001, a high level of significance was also determined between AFP levels and HCC. Among the patients with elevated AFP levels, 155 patients with AFP >2000 IU/ml were diagnosed as having HCC.

Table 3: AFP Levels and HCC Diagnosis Cross-Tabulation

AFP Levels (IU/ml)	HCC	No HCC	Total
<10	145	137	282
11-20	51	9	60
21-40	52	9	61
41-100	67	5	72
101-400	102	8	110
401-2000	119	1	120
>2000	155	5	160
Total	691	173	865

AFP levels were also found to have positive correlations with two other parameters, namely; vascular invasion (VI) and extra hepatic disease (EHD). Hence, rates of VI and EHD were found to be significantly related to AFP levels; the higher the AF P level the higher would be the rates of VI and EHD.

Table 4: AFP Levels and Vascular Invasion (VI)

AFP Levels (IU/ml)	No (EHD)	Yes (EHD)	Total
<10	259	22	281
11-20	56	4	60
21-40	54	7	61
41-100	59	12	71
101-400	89	20	109
401-2000	82	36	118
>2000	113	45	158
Total	712	146	858

Table 5: AFP Levels and Vascular invasion (VI)

AFP Levels (IU/ml)	No VI	Yes VI	Total
<10	245	33	278
11-20	54	6	60
21-40	49	11	60
41-100	55	17	72
101-400	74	34	108
401-2000	60	57	117
>2000	55	102	157
Total	592	260	852

Sensitivity and Specificity Analysis

Using an AFP cutoff of >400 IU/mL (Group III), the combined number of patients was 350. Among these, 292 had tumors >5 cm. With the total number of patients with tumors >5 cm being 471, the sensitivity for detecting large tumors (>5 cm) at this cutoff is 292/471 (approximately 62.0%). Conversely, the number of patients with AFP ≤400 IU/mL was 313, among whom 134 had tumors <5 cm; thus, the specificity is 134/313 (approximately 42.8%).

For a higher cutoff (AFP >2000 IU/mL), 139 patients were positive, and 127 of these had tumors >5 cm, yielding a sensitivity of 127/471 (approximately 27.0%) and a specificity of 180/524 (approximately 34.4%).

The Spearman's rank correlation test shows: $r_s \approx 0.31$, $p < 0.001$. This result indicates a statistically significant moderate positive correlation between AFP levels and tumor size in HCC patients. In other words, as AFP levels increase, there is a tendency for tumor size to be larger.

Discussion

Our study confirms the beneficial association between serum alpha fetoprotein (AFP) concentrations and tumor size in HCC patients.

In the research by Munir et al. (2021) the mean age and gender distribution of HCC patients in Pakistan was comparable to ours. Munir et al. reported a mean age of 57.69 years similar to our study mean, but predominantly male.[6] This similarity in demographic distribution underscores our generalizability across populations and ethnicities.

In our study, the tumor size was larger in subjects with high AFP level. In fact, BMI, L-R, L / T ratios and prognostic nutritional index were high, platelets and AFP were high

and most of the patients with AFP > 2000 IU / ml had tumors larger than 5 cm. This is consistent with the literature which mentions that increasing the size of the tumor increases the quantity of AFP created and released in the bloodstream. Thus this positive relationship (Pearson Chi-Square = 99. 407, p 0. 001) highlights the role of AFP in estimation of tumor load in HCC.

Anwar et.al (2020) also investigated the association between tumor size and AFP levels in relation to HCC tumor size.[7] Our study range of 101-400 ng / mL is in agreement with the positive correlation reported by Anwar et al. who also found significant correlations at AFP > 400 ng / mL.[7] In a similar study, Shaikh et.al (2016) reported that patients with HCC with higher AFP levels had larger tumors and worse prognosis.[8] Their Chi-Square test results confirmed the statistical significance of the AFP-tumor size association and matched ours (2 = 99.407, df = 12, p 0.001).

Our results also showed that AFP levels were positively associated with HCC incidence. Among total patients with AFP > 2000 IU / ml majority were HCC patients (Pearson Chi-Square = 220). 091, p 0. 001). This finding confirms the general usefulness of AFP in the diagnosis of HCC, but also underscores the problem of specificity in that some elevated AFP positives were also not HCC. This requires the use of AFP in conjunction with other complementary techniques such as imaging and histopathology to limit false results.

Bai et al. reported that AFP greater than 200 ng / mL was associated with bigger tumor sizes and poorer prognosis; this is consistent with our finding that bigger tumors (> five cm) have been associated with high AFP (> 400 ng / mL).[9] This study confirms our results that tumors larger than 5 cm are strongly associated with AFP > 2000 ng / mL. Thus, very high AFP levels indicate the need for aggressive monitoring and possibly intensive treatment. Abbasi et al. also confirmed that AFP can detect HCC at levels above 400 ng / mL.[10] Our study supports this by demonstrating that elevated AFP levels are associated with advanced tumor stages. Their results further solidify AFP as a valid biomarker associated with tumor size.

Although AFP levels provide important information for diagnosis and prognosis, Toader et al. in 2019 and Laura et al. (2016) highlighted how important imaging methods such as MRIs and CT scans are for the identification and evaluation of HCC.[11,12] This supports our study's claim that AFP should not be the only diagnostic standard. Imaging studies need to be combined to characterize tumors.

Khan et al. (2022) supported our results by pointing out that AFP alone is not a reliable indicator of HCC.[13] Their research demonstrated that AFP measurements should be combined with imaging modalities to improve diagnostic precision and provide a comprehensive strategy for managing HCC.

The clinical implications of our study findings are multiple. With a Pearson Chi-Square value of 99.407 and a p-value 0.001, AFP levels are highly significant predictors of tumor size that clinicians can use to inform treatment decisions. Patients with AFP > 2000 ng / mL should be assigned to detailed imaging studies and closer follow-up as larger tumors are more likely to require intensive treatment.

In line with our conclusion that high AFP levels warrant aggressive medical intervention and close monitoring, Bajkani et.al (2019) found that elevated AFP levels are a prognostic factor in HCC.[14] This consistent finding demonstrates the role of AFP in treatment protocol development and diagnosis for improved patient outcomes.

Our study has some limitations despite the high correlation between AFP levels and tumor burden. First of all, as noted by Sahbbir et al. not all HCC patients have elevated AFP levels, suggesting that reliance on AFP alone may in some cases lead to underdiagnosis.[15] Hence, a combined strategy using imaging methods and AFP levels is recommended.

Furthermore, benign liver conditions can lead to elevated AFP levels, thereby complicating the differential diagnosis. This, as noted by Samant et al., necessitates interpretation of AFP results within the context of a larger clinical setting, where the importance of accurate diagnostic assessments for precise disease characterization was emphasized.[16]

Clinical Implications.

Furthermore, from the discovery of these biomarkers several clinical correlations can be inferred. First, they note that serum AFP is a good indicator of disease and tumor burden in HCC. Raised AFP levels may require more frequent monitoring and drastic management that may be beneficial to patients. However, this study also highlights the disadvantages of applying AFP such as its nonspecific nature. In some instances, AFP might increase in chronic liver diseases like cirrhosis or hepatitis, complicating the diagnosis of HCC. Hence, AFP should be included in a combination of diagnostic methods based on imaging and biopsies to assess the disease status.

These results are consistent with earlier studies and also validate the impact of AFP levels and tumor size in HCC patients. Raised AFP values reflect larger tumor size, increased intravasation, and metastatic disease. Hence, AFP can be an objective marker of tumor mass and disease activity. Nevertheless, the results suggest low specificity of AFP and it must be utilized in conjunction with histopathology and imaging for correct diagnosis and treatment. Future work will require LWA of these observations and its replication in a multi center large cohort of patients managed for HCC to improve the clinical value of AFP.

References

1. Sathish Kumar K. HBV: A hepatocellular carcinoma (liver cancer) causing virus its mechanism and prevention.
2. Shen C, Jiang X, Li M, Luo Y. Hepatitis virus and hepatocellular carcinoma: recent advances. Cancers. 2023 Jan 15;15(2):533.
3. Hafeez Bhatti AB, Dar FS, Waheed A, Shafique K, Sultan F, Shah NH. Hepatocellular carcinoma in Pakistan: national trends and global perspective. Gastroenterology Research and practice. 2016;2016(1):5942306.
4. Piñero F, Dirchwolf M, Pessôa MG. Biomarkers in hepatocellular carcinoma: diagnosis, prognosis and treatment response assessment. Cells. 2020 Jun 1;9(6):1370.
5. Adigun OO, Yarrarapu SN, Zubair M, Khetarpal S. Alpha fetoprotein.
6. Munir M, Maqbool M, Ayyaz J, Anis S, Maqbool S. Correlation of Hepatocellular Carcinoma with Different Levels of Alpha-Fetoprotein in Pakistani Population. Annals of PIMS-Shaheed Zulfiqar Ali Bhutto Medical University. 2021 Nov 15;17(3):260-5.
7. Anwar MN, Hayat MK, Nasim O, Khan MA, Fahad MS, Hussain Z. Correlation of serum alpha fetoprotein (AFP) and tumor size of hepatocellular carcinoma (HCC) in a tertiary care hospital of Peshawar. Journal of Rehman Medical Institute. 2020 Oct 5;6(3):12-5.

8. Shaikh FH, Zeb S, Chandio SA, Munaf A, Ghori MA, Memon MS, Burney AA. Frequency of deaths in hepatitis C virus infected hepatocellular carcinoma patients and its relationship with raised serum alpha-fetoprotein levels. J Pak Med Assoc. 2016 Jan 1;66(1):34-6.
9. 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. Scientific reports. 2017 Oct 9;7(1):12870.
10. 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.
11. 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.
12. 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.
13. Khan J, Khaliq M, Tayyub Saeed MI, Majeed N, Khan R, Umar M, Khaar B, Hussain T, Ahmed S, Noureen M, Khan SA. 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. Journal of Rawalpindi Medical College. 2022;26(2-S1).
14. Bajkani N. Elevated serum alpha-fetoprotein as a prognostic factor for hepatocellular carcinoma in patients with chronic liver disease. Annals of Punjab Medical College (APMC). 2019 Mar 31;13(1):56-9.
15. Sahbbir K, Shehzad A, Naqvi M, Khalid M, Zia N, Haider E, et al. Association of serum alpha fetoprotein (AFP) levels with size of hepatocellular carcinoma. PAFMJ. 2019;69(1):71-5.
16. Samant H, Amiri HS, Zibari GB. Addressing the worldwide hepatocellular carcinoma: epidemiology, prevention and management. Journal of gastrointestinal oncology. 2021 Jul;12(Suppl 2):S361.

Author's Contribution:

MA: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
ANK, USU, MKK, GSG: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.