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ORIGINAL ARTICLE

Relation of hypoalbuminemia with tumor parameters in hepatocellular carcinoma patients.

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ABSTRACT… Objective: To determine the frequency of hypoalbuminemia in patients with hepatocellular carcinoma (HCC) and its relation with tumor parameters. **Study Design:** Descriptive, Cross-sectional Study. **Setting:** Department of Medicine, Nishtar Hospital, Multan. **Period:** March 11th, 2025, to September 10th, 2025. **Methods:** A total of 118 cases of HCC of either gender were enrolled in the study. After informed consent and patient characteristics, all the patients underwent laboratory testing for serum albumin and tumor markers, and an ultrasound for the number of liver nodules and the size of the largest nodule. After descriptive statistics and prevalence of hypoalbuminemia, the relation of hypoalbuminemia with multifocality, tumor size groups, and serum alpha-fetoprotein groups was assessed through the chi-square test, and a p-value ≤0.05 was taken as significant. **Results:** The mean age was 56.58 ± 10.68 years. The mean duration of liver cirrhosis was 8.25±4.3 years. The average number of liver nodules was 2.94±1.44. Regarding the size of liver nodules, the mean size was 7.18±2.96 (cm). The mean serum AFP was 422.36±443.34 (ng/ml). The serum mean albumin was 3.26±0.72 (g/dl). The prevalence of hypoalbuminemia was present in 58.5% (n=69) of patients presenting with HCC. No statistically significant association was found between hypoalbuminemia and multifocality (p = 0.426), tumor size group (p = 0.716), or serum alpha-fetoprotein levels (p = 0.405), indicating that hypoalbuminemia was not significantly related to these tumor parameters in the study population. **Conclusion:** Hypoalbuminemia was frequent among patients with HCC in our setting. However, it showed no significant association with tumor multifocality, size, or AFP levels.

Key words: Alpha Fetoproteins, Hepatocellular Carcinoma, Hypoalbuminemia, Liver Neoplasms, Serum Albumin, Tumor Burden, Ultrasonography.

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INTRODUCTION

Hepatocellular Carcinoma (HCC) is the most common liver malignancy, and globally, it's the third most common cause of mortality due to cancer.[1] Common risk factors include hepatitis B&C, aflatoxins, and contaminated water, especially in rural regions.[2] HCC ranks among the primary causes of mortality in individuals with liver cirrhosis, with cirrhosis occurring in 80-90% of HCC patients.[3] Latest statistics indicate that Hepatitis C infection has risen in incidence and mortality of HCC, predominantly in industrialized countries. The estimated incidence in Pakistan is 8 per 100,000 annually.[4]

Patients with cirrhosis require regular imaging evaluations, such as ultrasound and computed tomography, alongside serum alpha-fetoprotein (AFP) measurement.[5,6] The fetal yolk sac, intestine, and liver mainly produce AFP. Increased levels indicate HCC in the relevant clinical context[7], which is observed in 60-70% of HCC patients. AFP is not just a marker of HCC presence but also a marker of the severity of tumor size.[8] In a study by Abbasi et al. there was a significant correlation was observed between serum AFP levels and tumor size in HCC ($r = 0.472$, $p < 0.0001$).[9] Apart from novel tumor markers in HCC, like Glypican-3, DCP (Des-gamma-carboxy prothrombin, etc.), albumin level is a traditional marker of cirrhosis, and has been correlated with HCC in a few studies. In a study by Carr et al. Hypoalbuminemia was observed in 45.7% (n=1889) of the HCC patients. HCC patients exhibiting lower serum albumin levels demonstrated significantly increased tumor diameters, multifocality, and elevated α-fetoprotein levels compared to those with higher albumin levels.[10]

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Keeping in view the disease burden of HCC that is commonly diagnosed at an advanced stage in South Punjab due to low levels of surveillance and the late presentation, serum albumin is a low-cost and readily available marker that depicts liver function in this population with a high burden of cirrhosis. Moreover, there is little local data related to this study available, especially in the South Punjab population. So, this is a study of the frequency of hypoalbuminemia and how it's associated with tumor parameters to produce the evidence that's local and relevant.

METHODS

After the approval of the institutional ethical review committee (3602/NMU; dated 10-03-2025), a descriptive, cross-sectional Study was done at the Department of Medicine, Nishtar Hospital, Multan, over a period of 6 months (March 11th, 2025, to September 10th, 2025) after approval of the synopsis. After the informed consent, a total of 118 patients were enrolled in the study, using the non-probability consecutive sampling technique. The Sample size was calculated through the WHO sample size calculator using the formula for a single proportion, where: frequency of hypoalbuminemia=45.7%[10], absolute precision=9%, confidence level = 95%. The minimum sample size was 118. The inclusion criteria of my study were: Patients 40 – 75 years of age, either male or female gender, cases of hepatocellular carcinoma ≤ 3 months. Patients with recent blood transfusion (≤ 4 weeks), on treatment with radiotherapy or chemotherapy, were excluded from the study. Patients with known cases of liver cirrhosis having liver nodules> 1cm and serum alpha protein levels > 20 ng/ml and triphasic CT showing a hypervascular lesion on hepatic arterial phase images that becomes iso- to hypoattenuating relative to the liver on portal venous images were deemed positive.

After informed consent, the patient characteristics, including age, gender, duration of liver cirrhosis, and Child-Pugh class, were recorded. All the patients underwent venipuncture aseptically, and 2 mL of blood was sent to a single laboratory for serum albumin and tumor markers assessment as per hospital protocol. Hypoalbuminemia was labelled as serum albumin levels <2.5 g/dL on presentation. Tumor parameters included were serum alpha fetoprotein ng/mL, categorized as < 40, 40 – 400, and > 400. All patients underwent an ultrasound by a consultant radiologist with ≥3 years of post-fellowship experience to document the number of liver nodules and the size of the largest nodule. Tumor was labelled as multifocal if >1 nodule on ultrasound and tumor size (cm) on USG abdomen, and categorized as <5-cm and ≥5-cm. All the data was recorded on a proforma.

SPSS version 23 was used for data analysis. Normality of numerical data was checked through the Shapiro-Wilk test. Age, duration of liver cirrhosis, number of liver nodules, size of the largest nodule, serum alpha protein, and serum albumin were presented as mean and standard deviation. Gender, Child-Pugh, hypoalbuminemia, multifocality, tumor size groups, and serum alpha fetoprotein groups were presented as frequencies and percentages. The correlation of hypoalbuminemia with multifocality, tumor size groups, and serum alpha-fetoprotein groups was assessed through the chi-square test. Data were stratified on age, gender, duration of cirrhosis, and Child-Pugh class to determine the effect on the relationship between hypoalbuminemia and tumor parameters. Post-stratification chi-square test was applied, and a p-value ≤0.05 was taken as significant.

RESULTS

A total of 118 patients were included in the study. The mean age was 56.58 ± 10.68 years. The mean duration of liver cirrhosis was 8.25±4.3 years. The average number of liver nodules was 2.94±1.44. Regarding the size of liver nodules, the mean size was 7.18±2.96 (cm). The mean serum AFP was 422.36±443.34 (ng/ml). Descriptive statistics are shown in Table-I. The serum mean albumin was 3.26±0.72 (g/dl). The prevalence of hypoalbuminemia was present in 58.5% (n=69) of patients presenting with HCC, as shown in Figure-1. No statistically significant association was found between hypoalbuminemia and multifocality (p = 0.426), tumor size group (p = 0.716), or serum alpha-fetoprotein levels (p = 0.405), indicating that hypoalbuminemia was not significantly related to these tumor parameters in the study population (Table-II).

TABLE-I

Baseline characteristics of patients with HCC (n = 118)

Variable	Category	n (%)	Variable	Category	n (%)
Age Groups	40-60 (years)	74 (62.7)	Multifocality	Yes	91 (77.1)
	61-75 (years)	44 (37.3)		No	27 (22.9)
Gender	Male	65 (55.1)	Tumor size group (cm)	<5-cm	34 (28.8)
	Female	53 (44.9)		≥5-cm	84 (71.2)
Child-Pugh class	1	42 (35.6)	Serum AFP (ng/ml)	<40	40 (33.9)
	2	37 (31.4)		40-400	33 (28.0)
	3	39 (33.1)		>400	45 (38.1)

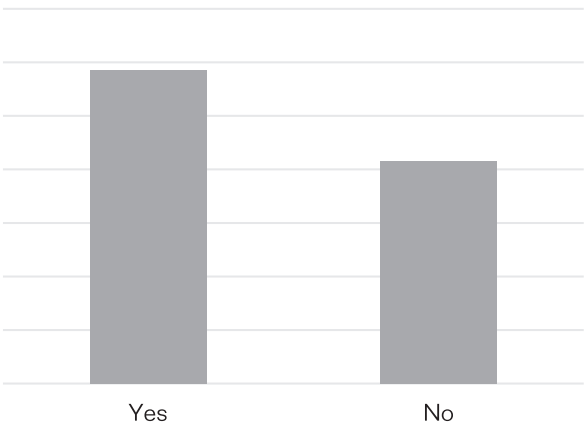
TABLE-III

Association of hypoalbuminemia with tumor multifocality, tumor size, and serum alpha-fetoprotein levels (n=118)

Variable	Category	Hypoalbuminemia		Test of sig.
		Yes	No	
Multifocality	Yes	55 (79.7%)	14 (20.3%)	χ^2=0.63, p=0.426
	No	36 (73.5%)	13 (26.5%)	
Tumor size (cm)	<5-cm	19 (27.5%)	50 (72.5%)	χ^2=0.132, p=0.716
	≥5-cm	15 (30.6%)	34 (69.4%)	
Serum AFP (ng/ml)	<40 (ng/ml)	20 (29%)	20 (40.8%)	χ^2=1.8, p=0.405
	40-400 (ng/ml)	21 (30.4%)	12 (24.5%)	
	>400 (ng/ml)	28 (40.6%)	17 (34.7%)	

FIGURE-1

Prevalence of hypoalbuminemia among patients with HCC (n=118)



DISCUSSION

This study evaluated the prevalence of hypoalbuminemia in HCC patients and its association with tumor characteristics. A descriptive cross-sectional design was employed; this is the design used in many prognostic biomarker studies. Similar designs have been employed in recent studies on a regional and international level to test nutritional and inflammatory markers in HCC patients.[11-13] The strength in the present methodology is the standardized laboratory testing and the ultrasound-based tumor evaluation by experienced radiologists. This helps in minimizing measurement bias and improving internal validity. However, unlike some cohort-based studies that evaluated survival outcomes, this study evaluated tumor burden parameters only.[14,15] This difference in methodology may in part explain differences in associations. Many of the recent studies have used longitudinal designs to assess albumin as a prognostic marker and not a variable of correlation.[16,17] Despite this, cross-sectional analysis is still valuable for estimating the burden of disease and producing evidence of local importance, especially in resource-limited tertiary care settings such as South Punjab.

The average age in this study was 56.6±10.7 years. This is similar to the data from Pakistan showing a mean age at diagnosis of 54-58 years.[18,19] Similar age distributions have been reported from China and Egypt, where HCC presents essentially in the sixth

decade of life.[20,21] The male predominance (55.1%) in our cohort is similar to data from other parts of the world where male-to-female ratios range from 1.5:1 to 3:1.[22] The mean duration of cirrhosis was more than eight years, which is similar to findings from cohorts in the region showing longstanding liver disease before diagnosis This pattern is similar to other tertiary care studies in Pakistan where delayed diagnosis is still common.[18,24]

Hypoalbuminemia was present in 58.5% of patients in our study. This frequency is higher than in Carr et al, who found hypoalbuminemia in 45.7% of the HCC patients.[25] Recently, Asian studies have shown a prevalence of 48%-62%, depending upon the cut-off value used.[16,20] This study from Karachi, Pakistan, seems to have a prevalence of hypoalbuminemia in 55% of the HCC patients, which is close to the results in our study.[19] The slightly higher frequency in our population may be due to advanced disease stage, poor nutritional status, and low access to early screening programs in rural South Punjab. These regional differences have also been underscored in recent national reports on cancer.[14,16]

In our study, there was no significant association of hypoalbuminemia with multifocality, tumor size, or alpha-fetoprotein. However, several international studies have reported a strong association between low albumin levels and multifocal disease.[10,15] One possible explanation is that serum albumin is a reflection of hepatic synthetic function and not solely a function of tumor biology. In patients with advanced chronic liver disease, albumin levels may be uniformly low in all cases, making discrimination difficult.[16,17] In a recent study from Pakistan, where ultrasound-based measurements have been used, results have also failed to show a consistent relationship between albumin levels and tumor size, supporting our results.[18,19] Studies with CT-based volumetric assessment have shown larger tumors in hypoalbuminemic patients.[20,25] The lack of association between hypoalbuminemia and AFP levels (p=0.405) is interesting. Several studies have reported an increased AFP level in patients with low albumin.[20,25] However, recent evidence suggests an elevation of AFP is not dependent on the liver synthetic function but depends on the differentiation of the tumor and molecular subtype.[13,16] A 2022 multicenter Asian study showed that serum albumin was not independently associated with serum AFP after adjusting for Child-Pugh class.[16] Similar results were observed in a study based in Lahore, where AFP levels varied considerably among the albumin strata.[24] These results support the present study observations.

CONCLUSION

Hypoalbuminemia was frequent among patients with hepatocellular carcinoma in our setting. However, it showed no significant association with tumor multifocality, size, or AFP levels. These findings differ from some international reports but align with recent regional data using similar methodologies. The results highlight the influence of underlying liver dysfunction and late disease presentation on biochemical markers. Further prospective studies using advanced imaging and survival outcomes are recommended.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Javeria Shamim:** Conception of idea, data collection.
2	**Shahzad Alam Khan:** Data analysis.
3	**Fatima Zuhra:** Interpretation, report writing.