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Original Article

Serum Albumin Levels Relation to Tumor Aggressiveness in Patients with Hepatocellular Carcinoma from a Tertiary Care Hospital in Pakistan

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Abstract

Background: Hepatocellular carcinoma (HCC) is a major cause of morbidity and mortality in patients with chronic liver diseases (CLDs). Studies have shown a correlation between low serum albumin levels and the aggressiveness of liver cancer. We aimed to determine the prevalence of hypoalbuminemia and its relationship with HCC aggressiveness in our patients.

Methods: This study was conducted retrospectively, and data were gathered from the gastroenterology unit of the Department of Medicine at the Aga Khan University Hospital in Karachi, Pakistan. The study included all patients who had been diagnosed with HCC between February 2015 and February 2019.

Results: In total, 380 patients with HCC were included in this study. The mean serum albumin level was 2.79 g/dL (SD ± 0.655) and 318 (83.7%) had serum albumin levels of ≤ 3.5 g/dL. No statistically significant association was identified between albumin levels and parameters of tumor aggressiveness (tumor size, number of tumor nodules, portal vein thrombosis [PVT], and alpha-fetoprotein [AFP] levels) in our patients.

Conclusion: We found no association between low albumin levels and parameters of HCC progression in our patients. This highlights the need for additional markers to determine the severity of HCC in underdeveloped populations.

Keywords: Serum albumin, Hepatocellular carcinoma, Developing country

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and one of the leading causes of morbidity and mortality in patients with chronic liver disease (CLD). Tumor characteristics and the presence of underlying CLD were predictive variables for HCC. Tumor characteristics included tumor size, number of tumor nodules, presence of portal vein thrombosis (PVT), and alpha-fetoprotein (AFP) levels. The liver's synthetic functions, along with increased bilirubin levels and demographic details of the patients (age and sex), are relevant prognostic indicators of disease progression.[1] A larger tumor typically has a worse prognosis than one that is smaller.[2]

Serum albumin is one of the several inflammatory markers used to predict the prognosis of HCC and other malignancies. The Glasgow prognostic score and the albumin-bilirubin grading system (ALBI) are widely studied and include serum albumin levels.[3,4] Some experimental data have shown that albumin affects tumor cell suppression and growth.[5] The ALBI grading system plays an established role in predicting the survival of HCC patients.[6] Albumin is also part of the Child-Pugh scoring system for the prognosis of CLD, a recognized classification system used for liver function assessment and postoperative morbidity and mortality in patients with CLD and HCC. Carr and Guerra studied the correlation of low serum albumin levels with the aggressiveness of HCC and concluded that there is a relationship between low serum albumin levels and the overall progression of the disease.[1]

Only a few studies have been conducted in Pakistan to evaluate the prognostic variables associated with HCC. A recent study that evaluated various staging methods found no association between albumin levels and the severity of tumor parameters. However, male sex, PVT, low serum albumin, large tumor size, and high AFP levels are unfavorable prognostic markers in patients with HCC.[7]

We wanted to determine whether there was any association between low serum albumin levels and aggressive tumor parameters, such as larger tumor size (≥ 5 cm), multiple tumor nodules, the presence of PVT, and high serum AFP levels (> 100 ng/dL) in our patients. We also sought to determine the distribution of serum albumin levels among our patients.

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Materials and Methods

Subjects

This study was a retrospective review of data collected at a single tertiary care center in the section of gastroenterology, Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan. All patients diagnosed with HCC between February 2015 and February 2019 were included in this study.

Sample Size and Selection

With a confidence range of 95% and an error margin of 5%, a sample size of 380 was determined for the population proportion of 45.6% with low albumin using a sample size calculation formula.[1] The study included all patients with HCC of either sex or age between 18 and 80 years. The study excluded all patients with peritoneal cancer, metastatic liver tumors, and any other gastrointestinal cancers. To minimize bias in the results, patients with additional conditions causing low serum albumin levels, such as malabsorption syndrome, nephrotic syndrome, connective tissue disorders, protein-losing enteropathies, and other renal abnormalities, were excluded from the study.

Patient Data

Patient data were extracted from the hospital's electronic database, including demographic data (age and sex), comorbid conditions such as diabetes mellitus and hypertension, and relevant investigations, including total bilirubin, serum albumin, serum AFP, hepatitis B and C serology, a computed tomography scan that included information on tumor nodules, the size of the tumor, and the presence of PVT. Serum albumin levels were defined by taking the lower limit of 3.5 g/dL as the cut-off value and readings less than or equal to 3.5 g/dL were considered low, measured by chemical pathological analysis of the patient's blood serum sample.

Tumor size, number of nodules, presence or absence of PVT, and AFP levels were among the HCC parameters. A CT scan of the liver was used to measure the tumor dimensions (a small tumor is less than 5 cm in diameter and a large tumor is greater than or equal to 5 cm), as well as the number of tumor nodules, which were determined as either single or multiple nodules. On a CT scan, PVT is identified as being present or not. Blood serum analysis was used to determine serum AFP levels (low AFP < 100 ng/mL and high AFP > 100 ng/mL).[1]

Statistical Analysis

Data were analyzed using SPSS software version 19. For categorical variables such as sex, low serum albumin levels, and HCC parameters, the frequencies and percentages were determined. The means and standard deviations were determined for numerical variables, such as age, serum albumin level, serum total bilirubin level, and AFP level. The effects of numerous independent factors were examined using the chi-squared test. Statistical significance was set at $P \leq 0.05$.

Results

A total of 380 patients with HCC were included in the study, 275 (72.4%) of whom were men. The mean age was 58.86 years with a standard deviation of ± 11.18. The most common etiology of CLD and HCC was hepatitis C, 256 (67.6%), followed by hepatitis B, 65 (17.1%), and 59 (15.5%), including hepatitis B and C co-infection, alcohol, and autoimmune liver disease, respectively. The mean serum albumin level was 2.79 g/dL with a standard deviation of ± 0.655, and 318 (83.7%) had serum albumin levels of ≤ 3.5 g/dL (Figure 1).

The distribution of tumor parameters is such that the tumor was mainly a single lesion in 213 (56.1%), of small size in 263 (69.2%), with 255 (67.1%) AFP levels ≤ 100 ng/dL, and PVT was seen in only 83 (21.8%) patients. The general characteristics of patients are shown in Table 1.

There was no significant relationship at the 5% significance level between serum albumin and tumor parameters (size, number, AFP levels, and PVT) (Table 2).

Discussion

One of the main reasons why individuals with CLD experience higher morbidity and mortality worldwide is HCC. Liver function status, tumor stage, and patient performance status are three key determinants of overall survival in patients with HCC.[8] HCC is usually associated with underlying cirrhosis; however, a variable number of patients present with advanced fibrosis. In such cases, liver dysfunction is related to the tumor itself.[9]

The mainstays for the diagnosis of HCC are radiological investigations such as CT or MRI. In a few cases, small size or atypical characteristics require histological evidence before starting management.[10] There are numerous staging systems, and BCLC, which incorporates the Child-Pugh score, tumor characteristics, and performance status, is one of the more popular ones.[11]

Low serum albumin level in patients with HCC is multifactorial, that is, caused by CLD-related liver dysfunction, malnutrition that is common in both CLD and cancer patients, and persistent cancer-related inflammation.[12] The proliferation of tumor cells has been shown to be inhibited by albumin, although additional

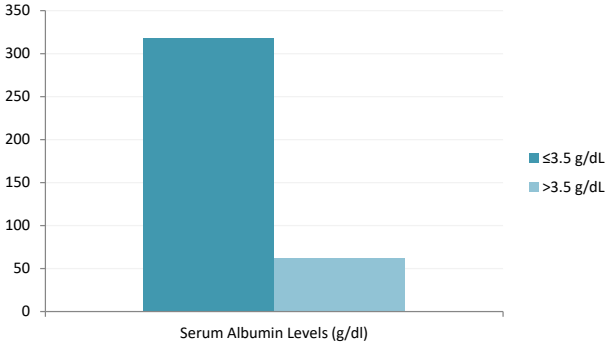

Figure 1. Distribution of serum albumin levels

Table 1. Baseline characteristics of the patients

Parameters		Frequency/Mean (SD) (n = 380)	Percent
Age		58.86 (11.188)	-
Sex	Male	275	72.4
	Female	105	27.6
Co-morbidity	None	185	48.7
	DM	78	20.5
	HTN	22	5.8
	Multiple	95	25
Hepatitis	B	65	17.1
	C	257	67.6
	Others	58	15.2
Mean serum albumin levels (g/dL)		2.79 (0.65)	-
Mean AFP levels (ng/dL)		2939.2 (7946.6)	-
Mean TB levels (mg/dL)		4.80 (7.25)	-

DM, diabetes mellitus; HTN, hypertension; AFP, alpha-fetoprotein; TB, total bilirubin; Multiple, diabetes mellitus, hypertension, hypothyroidism; Others, hepatitis B and C, alcohol, autoimmune liver disease.

Table 2. Serum albumin levels association with tumor parameters

Tumor parameters		Serum Albumin levels		Total	*P* value
		≤3.5g/dL	>3.5g/dL		
Size	<5 cm	219 (83.3%)	44 (16.7%)	263 (100%)	0.74
	≥5 cm	99 (84.6%)	18 (15.4%)	117 (100%)	
Number	Single	173 (81.2%)	40 (18.8%)	213 (100%)	0.14
	Multiple	145 (86.8%)	22 (13.2%)	167 (100%)	
AFP levels	≤100 ng/dL	217 (85.1%)	38 (14.9%)	255 (100%)	0.28
	>100 ng/dL	101 (80.8%)	24 (19.2%)	125 (100%)	
PVT	Absent	244 (82.2%)	53 (17.8%)	297 (100%)	0.12
	Present	74 (89.2%)	9 (10.8%)	83 (100%)	

AFP, Alpha fetoprotein; PVT, Portal vein thrombosis.

research is needed to confirm these findings.[13]

In the study by Carr and Guerra, 1189 (45.6%) of 4139 patients had low serum albumin levels (< 3.5 g/dL), which is associated with higher AFP levels and other tumor markers.[1] We found that 318 (83.7%) of the 380 patients in our study had low serum albumin levels, which is a notably high rate. Another study found an inverse relationship between high serum albumin levels and tumor parameters in patients with CLD.[14] However, our investigation did not find any association between serum albumin levels and tumor-related parameters.

Strengths and Limitations

The primary weakness of this study was the lack of a control group (healthy population). A smaller sample size that might not be representative of the total population is another restriction. Further prospective studies are required to validate the findings of this retrospective study. The strength of this study is that it raises an important question concerning the role of serum albumin as a predictive marker in HCC. This brings more attention to the requirement for more accurate markers among populations of underdeveloped countries with high rates of poverty.

Conclusion

Our study showed that serum albumin levels are not a reliable indicator of the severity of HCC in our population, despite the fact that numerous studies have established serum albumin levels as a predictor of HCC aggressiveness. When using hypoalbuminemia as a gauge of illness severity in underdeveloped nations where malnutrition is prevalent, it is imperative to consider other causes of the condition. Further prospective studies involving a healthy population serving as a control group and a larger cohort are required to validate these findings.

Authors' Contribution

Conceptualization: Om Parkash, Mahrukh Ali.
Data curation: Mahrukh Ali, Om Parkash.
Formal analysis: Mahrukh Ali.
Investigation: Mahrukh Ali.
Methodology: Om Parkash.
Project administration: Om Parkash, Mahrukh Ali.
Resources: Om Parkash.
Software: Mahrukh Ali, Om Parkash.
Supervision: Om Parkash.
Validation: Om Parkash, Mahrukh Ali.
Visualization: Mahrukh Ali.
Writing–original draft: Mahrukh Ali.
Writing–review & editing: Om Parkash, Mahrukh Ali.

Competing Interests

The authors declare no conflict of interest related to this work.

Data Availaibilty Statement

Data will be available upon request.

Ethical Approval

The study conformed to the ethical guidelines of the Declaration of Helsinki and was started after taking approval from the Ethical Review Committee of Aga Khan University Hospital Karachi (code: 2019-0961-2640).

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None to declare.

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