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Albumin and its association with lung cancer: An Indian perspective

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Abstract

Studies have been carried out world over, to evaluate the role of albumin in lung cancer. However, limited studies which have addressed association of albumin with patient factors such as type of lung cancer, gender, performance status, stage, hemoglobin levels, and neutrophil lymphocyte ratio. In our study, we aimed to evaluate the association of albumin with these factors. Amongst the 100 lung cancer cases, 69 were adenocarcinoma, 16 squamous cell, 13 small cell and 2 adenosquamous and, value of albumin below 3.4gm/dl was taken as hypoalbuminemia. Hypoalbuminemia was seen in 84% of small cell, 65% of adenocarcinoma, performance score (PS) of 1 - 47%, PS2- 61%, PS3- 75%, 65% of females, 61% of males, 70% of cases with symptoms less than 3 months duration, 41% of more than 3 months duration, 76% of stage IV, 13% of stage III, 68% of the males with anemia, 35% males with normal hemoglobin, 86% of females with anemia, and 14% with normal Hb. Lower albumin values co-relate with advanced disease and is considered as an adverse prognostic factor. However, this association is not absolute, as a significant number of patients without adverse features also have hypoalbuminemia. There are probably multiple roles of albumin in a cancer patient along with multiple factors effecting albumin levels whether treating hypoalbuminemia with albumin improve overall survival also need to be elucidated by further studies.

Keywords: albumin; lung cancer; prognostic factor.

Introduction

Several important prognostic factors have been identified in the literature, some generic to all cancers and some specific for different cancer types. One of the key factors determining cancer survival is malnutrition [1]. Malnutrition in cancer patients has been attributed to several factors involving the tumor, the host response to the tumor, and anticancer therapies [2, 3]. There are various methods of assessing nutritional status in cancer, each with its own advantages and disadvantages and the most commonly used tool is measurement of serum albumin [4].

Serum albumin provides a simple method of estimating visceral protein function [1]. In an adult the normal range of serum albumin is defined as 3.5-5.0 g/ dL and levels <3.4 g/dL is called hypoalbuminemia. The inverse correlation between body weight index and albumin synthesis in cancer patients supports the possibility of a compensatory enhanced albumin synthesis in these metabolically affected patients [2]. As part of the systemic inflammatory response to the tumor, pro-inflammatory cytokines and growth factors are released and have a profound catabolic effect on host metabolism [1]. Interleukin-6, produced by the tumor or surrounding cells, stimulates liver production of acute-phase reaction proteins (such as C-reactive protein (CRP) and fibrinogen) in both the fasted and fed states. This increases the demand for certain amino acids, which if limited in the diet, may be obtained from breakdown of skeletal muscle. The lower serum albumin concentration may be due to the production of cytokines such as IL-6, which modulate the production of albumin by hepatocytes [5]. Alternatively, tumor necros is factor may increase the permeability of the microvasculature, thus allowing an increased transcapillary passage of

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albumin. Presence of micrometastatic tumor cells in liver may induce the Kupffer cells to produce a variety of cytokines (IL-Ib, IL-6, TNF), which may modulate albumin synthesis by hepatocytes [5]. There is mild or no hypoalbuminemia in early stages of cancer but as the disease progresses albumin levels drop significantly and serve as good indicators of prognosis of cancer [5].

Serum albumin is used to assess the nutritional status, severity of disease, disease progression and prognosis and many reports have related serum albumin level to in-hospital mortality (6), length of stay [7], and nosocomial infection [8]. Serum albumin has also been described as an independent prognosticator of survival in various cancers [9] like lung [1], gastric [10], colorectal [11] and breast [12]. Low serum albumin has also been shown to be an independent indicator for prognosis in cancer patients with unknown primaries [13].

A significant number of ecological and observational studies suggest that low serum albumin is associated with higher mortality and research has demonstrated that serum albumin levels (either considered alone or in combination with other parameters) provide useful prognostic information. For example, some studies have used an inflammation based score, which is derived from the acute phase proteins CRP and albumin and is termed the Glasgow Prognostic Score (GPS). The GPS has been defined as follows: patients with both an elevated CRP (>10 mg/l) and hypoalbuminemia (<3.5 g/dL) are allocated a score of 2; patients in whom only one of these biochemical abnormalities is present are allocated a score of 1; patients in whom neither of these abnormalities is present are allocated a score of 0. With CRP > 10 mg/L and serum albumin levels >=3.5 g/dL the HR was 2 (CI = 1.47-2.70 and $p < 0.001$) [14].

Several studies have been carried out for assessing association of albumin in non small cell lung cancer (NSCLC), such as by Win et al. [15]. Factors significantly ($p < 0.05$) associated with poor overall survival were age at assessment, diabetes, serum albumin, shuttle walk distance, and predicted postoperative transfer factor. The value of an inflammation based prognostic score (GPS) was compared with PS in a longitudinal study of patients with inoperable NSCLC. At diagnosis, stratified for treatment, only the GPS hazard ratio (HR) 2.32, 95% confidence interval (CI) 1.52-3.54, $P < 0.001$) was a significant predictor of survival. In contrast, in another study by Forrest et al, neither the GPS nor PS measured at 3-6 months follow-up were significant predictors of residual survival [16]. Another study by Maeda et al [17] analyzed prognostic factors in patients with advanced NSCLC who had been enrolled in clinical trials conducted by the Okayama Lung Cancer Study Group. PS, clinical stage, liver metastasis or serum albumin level was an independent prognostic factor by Cox's analysis.

A group of consecutive patients with NSCLC were studied by Muers et al [18] and the prediction of their physicians as to how long they would survive (in months) was compared with their actual survival. A prognostic index was also developed using features recorded at the patients' initial presentation. Using Cox's regression model, the sex of the patient, the activity score, the presence of malaise, hoarseness and distant metastases at presentation, and lymphocyte count, serum albumin, sodium and ALP levels were all identified as useful prognostic factors. Another study by Hespanhol et al [19] assessed the influence on survival of 21 clinical, anatomical, hematological and biochemical factors in 411 patients with advanced NSCLC. The main determinants of survival were found to be performance status, weight loss and serum albumin. A study by Espinosa et al. [20] was done with an objective to find factors related to response, the duration of response and overall survival in patients with advanced NSCLC and included albumin levels. They concluded that albumin level identified a group of patients with advanced NSCLC who are more likely to respond to cisplatin-containing chemotherapy.

Similar studies have also been carried out in small cell lung cancer (SCLC). Tas et al [21] conducted a study to investigate the distribution of metastatic lesions and their influence on survival, as well as other prognostic factors on the outcome of patients with extensive small cell lung cancer (SCLC). Response to treatment was the most important prognostic factor; and albumin levels was amongst the other relevant.

Material and methods

This is an observational study conducted at Krishna Institute of Medical Sciences, Secunderabad, a tertiary care center, over duration of 24 months (2020 to 2021) and the first 100 cases of lung cancer were studied after taking approval from the Ethics Committee of the Institute.

Results

The data from the 100 patients was collected and tabulated with respect to the parameters of the study. The parameters were histopathological types of lung cancer, gender, ECOG performance score, duration of symptoms, stage, anemia and neutrophil lymphocyte ratio (NLR).

(A) Albumin and different histopathological types of lung cancer: Of the 69 cases were of adenocarcinoma, 40 cases (65%) had hypoalbuminemia, of 16 cases of squamous cell 9 (56%) had hypoalbuminemia, of 13 cases of small cell 11 (84%) had hypoalbuminemia and both the cases of adenosquamous lung cancer (100%) had hypoalbuminemia (Table 1).

(B) Gender: Of 77 males in the study 47 (61%) and out of 23 females 15 had hypoalbuminemia (65%) (Table1).

(C) ECOG performance score: Of the 19 cases with performance score (PS) 1, 9 (47%), and out of the 57 cases of PS 2, 35 (61%), and of the 24 cases of PS 3, 18 (75%) has hypoalbuminemia (Table 1).

(D) Duration of symptoms: Of the 73 patients, with less than 3 months of symptoms, 51 (70%) and of 27 patients, who presented after more than 3 months, 11(41%) had hypoalbuminemia (Table 1).

(E) Stage: Of the 23 patients of Stage III, 3 patients (13%), of the 77 patients of stage IV, 59(76%) had hypoalbuminemia (Table 1).

(F) Albumin and anemia: 60 males had anemia (Hb less than 13 g/dl) and of these 41 (68%), of the 17 males with Hb more than 13 g/dl, 6 (35%) had hypoalbuminemia. Amongst the females, of the 16 with anemia (Hb less than 12 g/dl), 14 (86%) and of the 7 females with Hb more than 12 g/dl, one (14%) had hypoalbuminemia (Table 1).

(G) Neutrophil lymphocyte ratio: Of the 33 cases with NLR less than 3, 3 (9%) and of the 67 cases with NLR more than 3, 59(88%) had hypoalbuminemia (Table 1).

Table 1: Details of association of albumin with other factors in lung cancer.

Sl. No.	*Category*	*Total Patients*	*Albumin <3.4g/dl*	*% withalbumin <3.4g/dl*	*Albumin >andequal to3.4g/d*	*Percentage : albumin > and equal to3.4g/dl*
1.	Types of cancer	100	62		38	
	Adenocarcinoma	69	40	65	29	35
	Squamous cell	16	9	56	7	44
	Small cell	13	11	84	2	16
	Adenosquamous	2	2	100	-	-
2.	Gender					
	Male	77	47	61	30	39
	Female	23	15	65	8	35
3.	Albumin and ECOG PS					
	PS 0	-	-	-	-	-
	PS 1	19	9	47	10	53
	PS 2	57	35	61	22	39
	PS 3	24	18	75	6	25
4.	Duration of symptoms atpresentation					
	< 3 Months	73	51	70	22	30
	>3 months	27	11	41	16	59
5.	Albumin and stage					
	Stage III	23	3	13	20	87
	Stage IV	77	59	76	18	24
6..	Albumin and hemoglobin					
	Males Hb <13g/dl	60	41	68	19	32
	Males Hb >13g/dl	17	6	35	11	65
	Females Hb<12g/dl	16	14	86	2	14
	Females Hb>12g/dl	7	1	14	6	86
7.	Albumin and NLR					
	< than & equal to 3	33	3	9	30	91
	>3	67	59	88	8	12

Discussion

The findings of our study are in concordance to those documented by other studies, which have studied these parameters, in the world population. There are no studies presently which have documented these findings of albumin with reference to the various parameters in context to the Indian population of lung cancer patients. In our study of 100 lung cancer cases, higher prevalence of hypoalbuminemia was seen in small cell lung cancer, compared to adenocarcinoma, probably because of more aggressive nature of squamous cell carcinoma. The females, compared to the males had more hypoalbuminemia and this could be because of the greater prevalence of malnutrition in the female Indian population. The incidence of hypoalbuminemia increased with the decrease in the performance status, and patients with symptoms of less than 3 months had relatively higher incidence of hypoalbuminemia, both can be explained by the of aggressiveness of the disease and higher disease burden. Low hemoglobin and albumin are considered adverse prognostic factors and, in our study, both males and females who had low Hb, had lower albumin levels. This could be because of the poor nutritional status of females compared to males in middle- and lower-class Indian society. Cases with higher NLR values had significantly lower levels of albumin and this reflects the association between NLR which is a marker of inflammation and an adverse prognostic factor with hypoalbuminemia. Serum albumin level is not only a window into the patient's nutritional status but also a useful factor for predicting patient prognosis. The potential advantage of serum albumin level as a pretreatment prognostic factor in cancer patients is that it is inexpensive, reproducible and powerful.

Limitations

The present study is limited by the number of cases, and though it is inadequate to provide conclusive evidence concerning the association of albumin with these multiple parameters in Indian population. It does however document the findings, which may be later used to further study these parameters. Also, the tertiary center data does not precisely reflect the disease profile of the community. Using albumin itself as a prognostic marker, or for response evaluation, also, has its limitations as the interpretation of serum albumin is often difficult because of multiple factors that effect the serum levels, such as nutritional factors, hydration state and last but not the least, disease process. Furthermore, serum albumin has a relatively long half-life, thus, assessing changes in its value over a short period of time is itself challenging.

This being an observational study and as the number of cases studied was only 100, which is one of the limitations of our study, it is not possible to draw a firm conclusion concerning the role of albumin and the use of this information as a predictive and prognostic marker in lung cancer. However, there are studies which have also found a similar relation, though individual parameters were studied and not as comprehensively as our study, infact there are very limited studies which have documented the relation of NLR with albumin in lung cancer. Association of pretreatment serum albumin levels has been found to serve as a useful prognostic tool tin cancer and this association of albumin with various facets of lung cancer needs further evaluation.

Conclusion

In our study, the presence of the adverse factors were associated with relatively lower albumin levels, however, this relation is not sacrosanct as in all the factors studied, there were a significant number of cases that despite having adverse factors, did not have a low albumin level and similarly, few patients without adverse factors had low albumin levels. There are probably multiple other factors that are playing a role between albumin and adverse prognosis that need to be elucidated. Further studies are needed to throw more light on these associations, and accordingly, serum albumin level could be used in clinical trials to better define the baseline risk in cancer patients. A critical gap for demonstrating causality, however, is the absence of clinical trials demonstrating that raising albumin levels by means of intravenous infusion or by hyper alimentation decreases the excess risk of mortality in cancer.

Conflicts of interest

Authors declare no conflicts of interest.

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