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## Research Article

# Can Prealbumin, Albumin and CRP Levels be used to Predict Prognosis in Patients with Gastric Cancer

### Abstract

**Background:** The impact of systemic inflammatory response on carcinogenesis and tumor progression has recently gained much attention. Biochemical markers such as albumin, pre-albumin and C-reactive protein (CRP) are currently used to predict prognosis in several cancer types, and the usefulness of these biomarkers in gastric cancer has become an emerging topic of research. The present study aims to assess the correlation between tumor stage and the levels of pre-albumin, albumin and CRP in patients who underwent surgery for gastric cancer.

**Methods:** Albumin, pre-albumin and CRP levels of the patients who underwent surgery for gastric cancer in our division, were prospectively recorded and retrospectively evaluated. Age, gender, duration of hospital stay, TNM stage, and preoperative albumin, pre-albumin and CRP levels were recorded. Albumin levels lower than 3.5 mg/dL and pre-albumin levels lower than 20 mg/dL were considered to be below the normal range. CRP levels higher than 5 mg/L were considered to be elevated. Patients with another focus of inflammation were excluded from the study.

**Results:** A total number of 41 patients, 32 (78%) men and 9 (22%) women, were included in the study. Albumin levels were significantly associated with the age ( $p=0.010$ ). There was no significant correlation between disease stage, gender, presence of metastatic lymph nodes and albumin levels ( $p>0.05$ ). There was a significant correlation between the TNM stage and pre-albumin levels ( $P=0.014$ ). No significant correlation was demonstrated between pre-albumin levels and the other parameters ( $P>0.05$ ). The independent variables were not found to be significantly different between the groups with normal and elevated CRP levels ( $p>0.05$ ).

**Conclusions:** The present study showed that the patients with lymph node metastasis and advanced stage gastric cancer more frequently have decreased levels of albumin and pre-albumin, and elevated levels of CRP. Decreased pre-albumin level was found to be associated with the TNM stage. The albumin levels were found to be decreasing by age. Although we failed to demonstrate a statistically correlation with albumin and CRP, preoperative albumin, pre-albumin and CRP levels may be useful to predict prognosis of patients with gastric cancer.

## Introduction

In the presence of a cancer, malnutrition and systemic inflammatory response result in a lower survival rate, reduced treatment response and a higher rate of complications associated with therapy [1]. Currently, surgery is the best treatment option with a proven efficacy in gastric cancer. In particular, the efficacy of therapy increases after surgery in the presence of a tumor diagnosed in early stages. Tumor node metastases (TNM) staging still represents the main tool for the estimation of disease prognosis.

However, validity of TNM staging is limited by the individual variability of gastric cancer. Therefore, there is an urgent need to establish the optimum methods to predict disease prognosis after surgery [2]. The impact of systemic inflammatory response on carcinogenesis and tumor progression has recently gained much attention. Inflammation is one of the most significant indicators of cancer. Chronic inflammation increases the risk of cancer development. Cancer cells may increase the production of inflammatory proteins and induce tumor growth as well as an inflammatory response in the tissues surrounding the tumor [3,4].

Therefore, the proteins associated with inflammatory process can be predictors of the severity or aggressiveness of certain cancer types. Moreover, such biomarkers can help to establish the risk of metastasis or recurrence of the disease. Serum amyloid A, C-reactive protein (CRP) and  $\alpha$ 1-acid glycoprotein may be listed among the inflammatory markers that are associated with malignant conditions [5].

Although individual prognostic Systemic inflammatory response and the effects of cytokines associated with inflammation increase serum CRP levels which, in turn, enhance cancer progression [6]. values of albumin, pre-albumin and CRP have been investigated, different scoring systems based on various combinations of these markers or incorporating other parameters such as lymphocyte and white blood cell counts, have been recently developed; examples of which include the Glasgow prognostic score (GPS), prognostic index (PI) and prognostic nutritional index (PNI) [2,7-13]. Biochemical markers such as albumin, pre-albumin and C-reactive protein (CRP) are currently used to predict prognosis in several cancer types, and the usefulness of these biomarkers in gastric cancer has become an emerging topic of research. In the present study, we aimed to assess

the correlation between tumor stage and the levels of pre-albumin, albumin and CRP in patients who underwent surgery for gastric cancer.

## Methods

Albumin, pre-albumin and CRP levels of the patients who underwent surgery for gastric cancer in our division, were prospectively recorded and retrospectively evaluated. Age, gender, duration of hospital stay, TNM stage, and preoperative albumin, pre-albumin and CRP levels were recorded. Albumin levels lower than 3.5 mg/dL and pre-albumin levels lower than 20 mg/dL were considered to be below the normal range. CRP levels higher than 5 mg/L were considered to be elevated. Patients with another focus of inflammation were excluded from the study. Malignant tumors were staged according to the American Joint Committee on Cancer (AJCC) TNM classification (7th version, 2010). Except Stage IV cases, all cases underwent D2-lymph node resection (LND). Albumin, CRP and pre-albumin levels; TNM stage, metastatic lymph node positivity, number of metastatic lymph nodes, age, gender and duration of hospital stay were compared separately.

## Statistical analysis

IBM SPSS Statics version 22 software package (IBM SPSS, Inc., USA) was used for the statistical analysis. Variables that were not suitable for normal distribution were examined with Mann-Whitney U test. For the comparison of categorical variables between groups, Pearson Chi-Square test, and Fisher's exact test were used. Values of  $p < 0.05$  were considered significant.

## Results

A total number of 41 patients, 32 (78%) men and 9 (22%) women, were included in the study. The mean age was 67.3 (43-88) years. The mean duration of hospital stay was 12.8 (4-46) days. Except two cases with stage IV disease, all cases underwent D2-LND. Among 41 cases that underwent D2-LND, 31 (75.6%) had metastatic lymph nodes. Preoperative albumin levels were below the expected range in 13 (33.3%) of 39 patients with albumin measurements available. Mean age of the patients with normal and decreased albumin levels was  $63.62 \pm 11.87$  and  $74.15 \pm 12.33$  years, respectively; albumin levels were significantly associated with the age ( $p = 0.010$ ). When these 13 cases were evaluated in terms of disease stage; 10 (76.9%) had Stage III, 2 (15.38%) had Stage II and one case (7.69%) had Stage I disease. There was no significant correlation between disease stage, gender, presence of metastatic lymph nodes and albumin levels ( $p > 0.05$ ) (Table 1).

Preoperative pre-albumin levels were decreased in 7 (70%) of 10 cases with pre-albumin measurements available. Among the cases with decreased pre-albumin levels, one (14.2%) had Stage II, 5 (71.4%) had stage III and one case had Stage IV disease. There was a significant correlation between the TNM stage and pre-albumin levels ( $P = 0.014$ ). No significant correlation was demonstrated between pre-albumin levels and the other parameters ( $P > 0.05$ ) (Table 2). CRP levels were elevated in 12 (60%) of 20 cases with CRP measurements available. Among these 12 cases, 4 (33.3%) had Stage II, 7 (58.3%) had Stage III and one (8.3%) had Stage IV disease. Gender, stage, presence of metastatic lymph nodes, age, duration of hospital stay, number of

metastatic lymph nodes and the mean distribution of total number of lymph nodes were not found to be significantly different between the groups with normal and elevated CRP levels ( $p > 0.05$ ) (Table 3).

## Discussion

There is increasing evidence supporting the significant role of systemic inflammatory response in carcinogenesis and tumor progression [14]. Moreover, several studies demonstrated that systemic inflammatory response is associated with poor prognosis in various cancer types [7,9,14,15]. There is also strong evidence of the correlation between malignancy and tumor stage, proliferative activity of the tumor cells and the systemic inflammatory response associated with the tumor [16]. CRP is an acute phase protein that is known to be an independent risk factor for several cancer types including gastric cancer [15]. There is sufficient evidence showing that CRP can be used as an important parameter to predict prognosis, particularly in cases of colorectal cancer [17,18]. Decreased pre-albumin level is known to be an independent risk factor in cancer patients and its use is recommended in terminal cancer patients [19]. Similarly, hypo-albuminemia is a typical index of malnutrition and has been associated with poor prognosis in patients with advanced cancers [20].

These parameters have been separately or simultaneously investigated in several previous studies aiming to demonstrate their effects on cancer prognosis. In their review, Gao and Huang recommended the use of albumin and CRP in prognosis estimation, but they still underlined the need for further research [8]. Pan et al., performed a survival analysis based on low albumin and high CRP levels. They found that these parameters were associated with the survival rates in 1, 3 and 5 years, in addition to the mean survival and disease free survival. Moreover, increasing TNM stages were found to be associated with shorter survival time in that study [2]. In their study involving patients with advanced stages of gastric cancer, Esfani et al., reported a significant correlation of decrease prealbumin and increased CRP levels with the presence of metastatic disease, while no such correlation was found with albumin levels. In that study, the sensitivity and specificity of decreased pre-albumin levels for predicting metastases in inoperable patients were found to be 77.1% and 52.2%, respectively [7]. Moreover, the authors argued that the pre-albumin/CRP ratio could be a more useful predictor of metastasis. The present study similarly demonstrated an association between increasing disease stage and decreased pre-albumin levels. However, such a correlation was not found with CRP levels. Albumin levels were also not found to be related to the disease stage.

Since the half-life of pre-albumin in blood circulation is as short as 2 days, it is a much more sensitive marker of nutritional status than albumin [7]. Ho et al., suggested that a decreased pre-albumin level is an independent risk factor in cancer patients and recommended its use for the patients with terminal cancers [19]. On the other hand, pre-albumin is currently used to evaluate treatment outcome and nutritional status in colon [21], esophagus [22], ovarian [23] and lung [24] cancers. Another study suggested that pre-albumin levels can be used to predict the early recurrence of colorectal cancer. In that study, albumin was found to be more sensitive than pre-albumin in predicting the recurrence of colorectal cancer [25].

**Table 1:** Independent variables according to albumine levels.

		Albumin				Total (n=39)		p
		Normal (n=26)		Low (n=13)		n	%	
		n	%	n	%			
Gender	Female	5	19,2	4	30,8	9	23,1	0,447
	Male	21	80,8	9	69,2	30	76,9	
TNM stage	0	1	3,8	0	0	1	2,6	0,564
	1	1	3,8	1	7,7	2	5,1	
	2	9	34,6	2	15,4	11	28,2	
	3	13	50	10	76,9	23	59	
	4	2	7,7	0	0	2	5,1	
Metastatic lymph node positivity	No	5	19,2	4	30,8	9	23,1	0,447
	Yes	21	80,8	9	69,2	30	76,9	
Total		26	66,7	13	33,3	39	100	
		Ort.±SS	Min.-Max.	Ort.±SS	Min.-Max.	Ort.±SS	Min.-Max.	p
Age		63,62±11,87	43-88	74,15±12,33	49-87	67,13±12,89	43-88	<b>0,010</b>
Duration of hospital stay		12,62±9,6	4-46	13,92±7,34	7-29	13,05±8,84	4-46	0,338
Number of metastatic lymph nodes		11,86±12,31	1-45	13,56±15,04	3-52	12,37±12,94	1-52	0,563
Total number of lymph nodes		38,12±17,51	3-77	34,38±23,2	4-96	36,87±19,36	3-96	0,219

Fisher's Exact test, Ki-kare trend analizi, Mann Whitney U.

**Table 2:** Independent variables according to prealbumine levels.

		Prealbumin				Total (n=10)		p
		Normal (n=3)		Low (n=7)		n	%	
		n	%	n	%			
Gender	Female	1	33,3	2	28,6	3	30	1,000
	Male	2	66,7	5	71,4	7	70	
TNM stage	0	1	33,3	0	0	1	10	<b>0,014</b>
	1	1	33,3	0	0	1	10	
	2	1	33,3	1	14,3	2	20	
	3	0	0	5	71,4	5	50	
	4	0	0	1	14,3	1	10	
Metastatic lymph node positivity	No	2	66,7	1	14,3	3	30	0,183
	Yes	1	33,3	6	85,7	7	70	
Total		3	30	7	70	10	100	
		Ort.±SS	Min.-Max.	Ort.±SS	Min.-Max.	Ort.±SS	Min.-Max.	
Age		57±9	48-66	76±12,41	50-88	70,3±14,31	48-88	0,067
Duration of hospital stay		20±22,52	7-46	15,29±9,96	7-37	16,7±13,57	7-46	0,667
Number of metastatic lymph nodes		1±	1-1	11,17±3,71	6-16	9,71±5,12	1-16	0,286
Total number of lymph nodes		29,33±26,01	3-55	26,86±14,19	8-50	27,6±16,91	3-55	0,833

Fisher's Exact test, Ki-kare trend analizi, Mann Whitney U.

CRP is a marker of systemic inflammatory response and increased CRP levels represent in independent risk factor for the prognosis of gastro-esophageal cancers [1]. Tang et al., reported that elevated CRP levels are associated with increasing disease stages [26]. That study demonstrated that CRP is produced at a larger amount as the disease progresses. Similarly, Baba et al. [6], showed that CRP levels per se are a prognostic factor in cases of Stage IV gastric cancer. In another study investigating the roles of inflammatory proteins in gastric cancer, Wang et al., found that elevated CRP levels were only associated with metastatic disease and, contrary to the above referred studies, elevated CRP levels were not related to Stage I, Stage II and Stage III disease [5]. Moreover, increased CRP levels were associated with male gender in that study, but no such association was established with mean age; a finding that is contradictory to ours [26]. In the present study, CRP levels were elevated in Stage II and Stage III cases but the difference was not statistically significant. We believe that our failure to demonstrate

a significant correlation can be due to the limited number of cases. In their study investigating the factors affecting mean survival of patients with gastric cancer, Liu et al., reported a significant correlation of decreased albumin and increased CRP levels with shorter survival. Moreover, they also underlined the value of CRP/albumin ratio as an independent prognostic marker, particularly in cases with Stage I and Stage III disease [14]. The authors also argued that this ratio might be related to the nutritional status; but they could not demonstrate its correlation with weight loss and body mass index. The authors asserted that an increased CRP/albumin ratio requires closer follow-up and more aggressive treatment especially in cases with an early stage cancer. Administration of anti-inflammatory therapy and nutritional support was also recommended for cases with increased CRP/albumin ratio [14].

Chen et al., proposed two possible causes of decreased albumin levels in patients with gastric cancer. The first cause was associated

**Table 3:** Independent variables according to elevated CRP levels.

		CRP				Total		
		Normal (n=8)		High (n=12)				
		n	%	n	%	n	%	
Gender	Female	2	25	2	16,7	4	20	1,000
	Male	6	75	10	83,3	16	80	
TNM stage	0	1	12,5	0	0	1	5	0,064
	1	1	12,5	0	0	1	5	
	2	3	37,5	4	33,3	7	35	
	3	3	37,5	7	58,3	10	50	
	4	0	0	1	8,3	1	5	
Metastatic lymph node positivity	No	3	37,5	3	25	6	30	0,642
	Yes	5	62,5	9	75	14	70	
Total		8	40,0	12	60,0	20	100	
		Ort.±SS	Min.-Max.	Ort.±SS	Min.-Max.	Ort.±SS	Min.-Max.	
Age		61,63±16,43	43-82	68,67±15,26	49-88	65,85±15,71	43-88	0,208
Duration of hospital stay		16±13,73	7-46	15,92±9,92	7-37	15,95±11,25	7-46	0,734
Number of metastatic lymph nodes		11,4±11,55	2-31	7,44±7,2	1-22	8,86±8,76	1-31	0,606
Total number of lymph nodes		29,75±15,37	3-50	34,17±17,81	4-59	32,4±16,6	3-59	0,521

*Fisher's Exact test, Ki-kare trend analizi, Mann Whitney U.*

with the chronic depletive nature of gastric cancer, which results in catabolization of albumin as the cancer progresses; and the second cause was explained by impaired absorption of nutrients from the gastrointestinal tract, which leads to hypo-albuminemia [27]. Some studies showed a correlation between hypo-albuminemia and poor prognosis in gastric cancer patients [20]. In the study of Jiang et al., both albumin and CRP levels were found to be associated with mortality [15]. In the present study, we have observed that the older age group with a mean age of 74.15 years had significantly lower albumin levels. In addition to the above mentioned causes, we believe that this finding can be explained by decreased food intake in this age group, as gastric cancer is typically a disease of the elderly [28]. Supporting this argument, our patient group also represented a relatively aged population with a mean age of 67.3 years.

Although albumin, pre-albumin and CRP have separately been effective in estimating disease prognosis, several new prognostic factors have also been introduced in the recent years. These new prognostic factors include pre-albumin/CRP ratio [7], CRP/albumin ratio [14], Glasgow prognostic score based on CRP and albumin levels, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, PI based on CRP-white blood cell count and PNI based on albumin-lymphocyte values [2,8]. However, none of these are yet used in clinical practice for gastric cancer or any other cancer type. Until standardization is achieved, these parameters should be used separately or in combination. There are certain limitations of the present study. First, this study was performed as a retrospective study. Second, the patient group was operated by the one surgeon and the third, particularly the CRP and pre-albumin measurements were not available for all patients. The fourth and last limitation is the short duration of follow-up period, which restricted us from reporting the survival data. The present study showed that the patients with lymph node metastasis and advanced stage gastric cancer more frequently have decreased levels of albumin and pre-albumin, and elevated levels of CRP. However, only decreased prealbumin level was found to be associated with the TNM stage. Lack of a significant correlation with

hypo-albuminemia and elevated CRP levels may be explained by the limited number of cases. Moreover, albumin levels were found to be decreasing by age. Although we failed to demonstrate a statistically significant correlation with albumin and CRP, preoperative albumin, pre-albumin and CRP levels may be useful to predict prognosis of patients with gastric cancer.

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