

# The effect of CEA/Albumin ratio in gastric cancer patient on prognostic factors



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## The effect of CEA/Albumin ratio in gastric cancer patient on prognostic factors

**AIM:** Gastric cancer is an important disease worldwide with high mortality and morbidity rates. Novel targeted treatment approaches and recent improvements in immunotherapy have significantly improved survival. New indicators that can help determine the prognosis of stomach cancer have been of interest to researchers. We evaluated and recorded the patients' final preoperative CEA/albumin ratios and investigated the effect of this ratio on lymph node involvement, pathological tumor stage, and overall survival.

**MATERIAL AND METHOD:** We retrospectively evaluated data from electronic files of patients who were operated for stomach cancer in our center between January 2012 and December 2017. The study included 195 patients who were followed up regularly and whose complete medical data were available.

**RESULTS:** The effect of CEA/Albumin ratio on the number of Metastatic Lymph Nodes was analyzed using Linear Regression and was found to be statistically significant ( $p = 0.001$ ). One unit increase in CEA/Albumin ratio increases the number of Metastatic Lymph Nodes by 0.223 (Confidence Interval: 0.097-0.380) units, and this variable alone explains 5.7% of the change in the number of Metastatic Lymph Nodes.

**CONCLUSION:** Neoadjuvant treatment decisions can be made by estimating the T and N stages by using CEA/albumin ratio in cases where conventional radiological methods are insufficient.

**KEY WORDS:** Albumin, Carcinoembryonic antigen, Gastric cancer, Lymph node, Prognosis

## Introduction

Gastric cancer is an important disease worldwide with high mortality and morbidity rates <sup>1</sup>. Approximately 900,000 new cases are reported every year worldwide <sup>2</sup>. Novel targeted treatment approaches and recent improvements in immunotherapy have significantly improved

survival. Currently, the TNM staging system, which evaluates tumor size, lymph node involvement, and distant metastasis, is the most commonly used method to predict prognosis. However, since this method is limited to pathological staging, new indicators that can help determine the prognosis of stomach cancer have been of interest to researchers. Multiple recent studies have reported promising results for predicting the prognosis of stomach cancer <sup>3-5</sup>.

Albumin, the major component of serum total protein, is synthesized in the liver. Albumin play a role in the regulation of blood colloid osmotic pressure and the transport of metabolites in the blood and is a significant indicator of nutritional status <sup>6</sup>. Many studies on serum albumin levels have shown that low albumin levels are associated with poor prognosis in stomach cancer <sup>7</sup>. Activation of the fibrinolytic system and triggering of the inflammatory process plays a role in tumori-

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## ABBREVIATIONS

CEA: Carcinoembryonic antigen  
 LVI: Lymphovascular Invasion  
 PNI: Perineural Invasion  
 TNF: Tumor Necrosis Factor  
 CRP: C-Reactive Protein

genesis and progression. Albumin is a marker of the inflammatory process that is fundamental to tumorigenesis and progression<sup>8-10</sup>.

Carcinoembryonic antigen (CEA) is a protein that is secreted during fetal development, after which its levels decline. In later stages of life, this molecule can be secreted by primitive tissues like tumors, and blood CEA levels may rise again. There are no clinical studies supporting its use for screening purposes. In clinical practice, CEA is used to monitor recurrence and progression. There are studies that have correlated preoperative CEA levels and prognosis.

This study aims to examine the prognostic predictive value of two different biochemical markers in terms of their correlation with each other.

## Material and Method

We retrospectively evaluated data from electronic files of patients who were operated for stomach cancer in our center between January 2012 and December 2017. The study was granted ethical approval by the ethics committee of our hospital. The study included 195 patients who were followed up regularly and whose complete medical data were available. The inclusion criteria were as follows: having undergone gastrectomy and lymph node dissection due to gastric cancer, not having received preoperative enteral or parenteral nutrition or neoadjuvant treatment, not having distant metastasis, not having a history of other additional cancers or chronic inflammatory diseases, and having normal liver and kidney functions. Patients' age, gender, biochemical parameters, tumor markers, types of operations, TNM stages, additional organ resection, and LVI and PNI statuses were recorded. We evaluated and recorded the patients' final preoperative CEA/albumin ratios and investigated the effect of this ratio on lymph node involvement, pathological tumor stage, and overall survival.

## STATISTICAL ANALYSIS

The SPSS 11.5 software was used in the analysis of the data. For descriptive analysis, quantitative variables were presented as mean  $\pm$  standard deviation and median

(minimum-maximum) and qualitative variables were presented as number of patients (percentage). Linear Regression analysis was used to determine the risk factors affecting the quantitative dependent variable and Logistic Regression analysis was performed to determine the risk factors affecting the qualitative dependent variable. Survival analysis was performed using the Kaplan-Meier method for qualitative and quantitative variables and the log-rank test was used to determine significant differences between the groups. A p value of  $<0.05$  was considered statistically significant.

## Results

195 patients underwent gastrectomy and lymph node dissection for stomach cancer. The mean age of the subjects was determined as  $62.83 \pm 13.67$  years. Of the cases, 82 (44.3%) underwent open total, 91 (49.2%) underwent open subtotal, and 12 (6.5%) underwent laparoscopic subtotal gastrectomies. There was no significant correlation between survival and operation type ( $p > 0.05$ ). Of the patients, 121 were male and 66 were female. Patient characteristics are presented in Table 1. The effect of CEA/Albumin ratio on the number of Metastatic Lymph Nodes was analyzed using Linear Regression and was found to be statistically significant ( $p = 0.001$ ). One unit increase in CEA/Albumin ratio increases the number of Metastatic Lymph Nodes by 0.223 (Confidence Interval: 0.097-0.380) units, and this variable alone explains 5.7% of the change in the number of Metastatic Lymph Nodes.

TABLE I - Patient characteristics

Variables		
Age	Mean $\pm$ SD	62.83 $\pm$ 13.67
Gender, n (%)	Male	121 (64.7)
	Female	66 (35.3)
CEA/Albumin Ratio	Mean $\pm$ SD	3.24 $\pm$ 7.94
Total Lymph Number	Mean $\pm$ SD	21.38 $\pm$ 10.83
Metastatic Lymph Number	Mean $\pm$ SD	6.45 $\pm$ 7.95
Survival Time	Mean $\pm$ SD	22.67 $\pm$ 16.96
Type of Operation	Open Total	82 (44.3)
	Open Subtotal	91 (49.2)
	Lap. Subtotal	12 (6.5)
Additional Organ Resection	Yes	11 (5.9)
	No	174 (94.1)
N Stage	Negative	61 (32.6)
	Positive	126 (67.4)
T Stage	T1-T2	50 (27.9)
	T3-T4	129 (72.1)
	Yes	98 (52.5)
LVI	No	89 (47.5)
	Yes	84 (45)
PNI	No	103 (55)
	Yes	84 (45)
Survival	Exitus	73 (39.0)
	Survived	114 (61.0)

TABLE II - Factors affecting survival

Variables		Survival			p value
		3-year (%)	5-year (%)	Survival time Mean ± SE Median ± SE	
Overall survival		37.2	29.5	32.90 ± 2.17 24.00 ± 2.86	-
CEA/Albumin Ratio	0.86	42.4	35.9	37.32 ± 3.09 30.00 ± 4.67	0.037
	>0.86	31.3	23.2	27.77 ± 2.76 18.00 ± 3.80	
N Stage	Negative	65.9	62.2	49.86 ± 3.49 -	<0.001
	Positive	22.7	12.5	23.45 ± 2.09 16.00 ± 2.19	
T Stage	T1-T2	56.6	52.5	45.50 ± 3.88 -	<0.001
	T3-T4	28.9	20.0	27.27 ± 2.39 17.00 ± 2.35	
Metastatic Lymph Node	No	65.9	62.2	49.86 ± 3.49 -	<0.001
	Yes	22.7	12.5	23.45 ± 2.09 16.00 ± 2.19	
LVI	No	50.8	39.9	39.95 ± 3.02 38.00 ± 5.68	<0.001
	Yes	24.2	19.8	25.55 ± 2.71 16.00 ± 2.68	
PNI	No	50.2	43.1	42.42 ± 3.01 38.00 ± 8.38	<0.001
	Yes	21.1	13.4	21.41 ± 2.39 13.00 ± 2.45	

SE: Standard Error

The effect of CEA/Albumin ratio on N and T Stages was evaluated using Logistic Regression and was found to be statistically significant ( $p = 0.005$  and  $p = 0.034$ , respectively). One unit increase in CEA/Albumin ratio increases the risk of positive N Stage by 1.295 (Confidence Interval: 1.081-1.550) units and a T Stage of T3-T4 by 1.170 (Confidence Interval: 1,012-1,354) units. The CEA/Albumin ratio was not found to significantly affect additional organ resection ( $p = 0.649$ ). The effect of CEA/Albumin ratio on PNI was evaluated using Logistic Regression and was found to be statistically significant ( $p = 0.031$ ). One unit increase in CEA/Albumin ratio increases the risk of having PNI by 1.082 (Confidence Interval: 1.007-1.162) units. The effect of CEA/Albumin ratio on LVI was not statistically significant ( $p = 0.069$ ).

Considering overall survival, of the 195 patients, 106 (72.6%) survived, while 40 (27.4%) died. The mean survival was  $22.67 \pm 6.82$  months during the average follow-up period of 22 months. Table 2 presents the results of the variables that were considered to affect survival, the relevant 3 and 5-year survival probabilities, the mean  $\pm$  standard error (SE) and median  $\pm$  SE values, and the p values that indicate statistical significance. The survival curve according to the CEA/Albumin cut-off value of 0.86 ( $\leq 0.86$ : low-risk and  $> 0.86$  high-risk) is presented in Fig. 1.

### Discussion

Stomach cancer is still one of the most common cancers and is the third-leading cause of cancer-related deaths (11). Despite advances in diagnosis and treatment with advancing technology, the 5-year overall survival rate of stomach cancer is around 20-25%<sup>12</sup>. Currently, the TNM staging system, which evaluates tumor size, lymph node involvement, and distant metastasis, is the most commonly used method to predict stomach cancer prognosis. However, since this method is limited to tumor pathologies, it is insufficient in predicting prognosis.

To date, many studies have investigated the relationship between zinc and diabetes. Particularly the presence of lymph node metastasis<sup>13</sup>, tumor invasion depth<sup>14,15</sup>, and tumor size<sup>16,17</sup> have been found as independent prognostic factors. Additionally, Chou et al. have found perineural invasion (PNI) to be a prognostic factor<sup>18</sup>. Tanaka et al. reported that lymphovascular invasion (LVI), as well as perineural invasion, were significant prognostic factors for tumor recurrence<sup>19</sup>. In our study, we found the T stage, N stage, PNI, and LVI to be factors that affect survival ( $p < 0.001$ ). When pathology results are examined, it should be kept in mind that

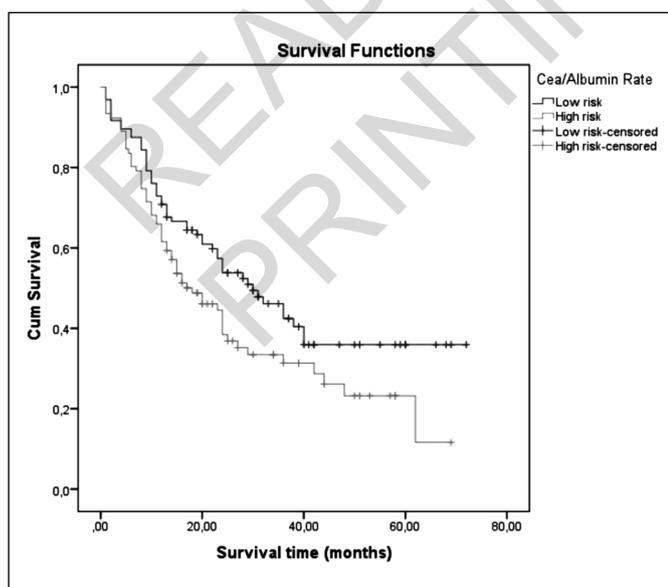


Fig. 1: Overall survival curve for CEA/Albumin ratio.

increased tumor invasion depth and metastatic lymph node number and LVI and PNI are poor prognostic factors and these patients should be followed up more carefully.

Carcinoembryonic antigen (CEA) was first defined by Gold and Freedman in 1965<sup>20</sup>. The sialofucosylated glycoforms of CEA, which act as selectin ligands, serve as indicators of colon cancer metastasis<sup>8-10</sup>. CEA is synthesized in many cancers and plays an important role in the detection of tumor metastasis<sup>10</sup>. A systematic review demonstrated that increased serum CEA levels were associated with survival in stomach cancer<sup>21</sup>. Although some studies report the effect of pre-treatment CEA levels on the prognosis of gastric cancer to be controversial<sup>22,23</sup>, numerous recent studies have reported a significant effect on mortality and prognosis. In their meta-analysis of 187 studies, Hideaki Shimada et al. found that elevated CEA levels were associated with poor prognosis<sup>21</sup>. Likewise, the meta-analysis of 14651 patients by Deng et al. found that elevated serum CEA levels increased mortality approximately 2-fold<sup>24</sup>. In our study, we did not find any effect of CEA on survival. This may be related to the small sample size and the short follow-up time.

As is known, inflammation plays an important role in tumor development, malignant transformation, and many stages of cancer development such as invasion and metastasis<sup>25</sup>. From this point of view, several inflammation-related biomarkers have been investigated to predict stomach cancer, including the Glasgow Prognostic Score, the neutrophil-lymphocyte ratio, and the platelet-lymphocyte ratio<sup>3,4,26</sup>. In our study, we found that hypoalbuminemia was correlated with poor survival ( $p = 0.001$ ). Albumin, one of the most prominent serum proteins, is synthesized in the liver and takes part in material transport and the regulation of plasma osmotic pressure<sup>27</sup>. Albumin does not only indicate nutritional status but also plays a role in demonstrating the level of inflammation and tumor development stages<sup>28</sup>. Compared to the early stages, advanced gastric cancer patients are at risk of malnutrition and cachexia<sup>29</sup>. In addition, the cytokine-induced tumor microenvironment (TNF- $\alpha$ , interleukin-6, interleukin-1) can reduce albumin synthesis in the liver and decrease serum albumin levels by allowing the passage of albumin from the serum to the interstitial space by increasing vascular permeability<sup>30</sup>. Eating difficulties and digestive system dysfunctions caused by stomach cancer can cause malnutrition and decreased serum albumin<sup>31,32</sup>. Albumin acts as an antioxidant against tumor carcinogenesis and contributes to the stabilization of DNA replication and cell growth<sup>33</sup>. In addition, low serum albumin levels cause the deterioration of calcium and steroid hormone homeostasis, increased anatomical barrier permeability, and the disturbance of anticancer drug distribution and activity<sup>34</sup>. Numerous studies have shown that reduced serum albumin levels are associated with poor prognosis<sup>28,35,36</sup>. In their retrospective analysis, Wang et al. found that C-

reactive protein (CRP), CEA, albumin, and lymphocyte levels were independent risk factors for the prognosis of stomach cancer<sup>37</sup>. In our study, we found the factors affecting survival to be T stage, metastatic lymph node number, hypoalbuminemia, and the presence of perineural invasion and lymphovascular invasion. Albumin was the indicator of inflammatory processes in our study, and we observed that hypoalbuminemia negatively affected survival. We believe that it is important to examine albumin values in the preoperative period and that postoperative prognosis can be improved with nutritional support in patients with poor nutritional status.

We found that the CEA/albumin ratio had an effect only on LVI among factors affecting prognosis. Considering the effect of CEA/albumin ratio on tumor size, lymph node metastasis, and PNI positivity, we believe that it may be an effective predictor of gastric cancer prognosis. In addition, neoadjuvant treatment decisions can be made by estimating the T and N stages by using CEA/albumin ratio in cases where conventional radiological methods are insufficient. We think that diagnostic laparoscopy may play an important role particularly in the management of patients with a high CEA/Albumin ratio where abdominal tomography is not sufficient. This will allow a rapid neoadjuvant treatment decision and directing patients to the right treatment option without wasting time.

Our study has several limiting factors. One of the major limitations is its retrospective design. Since most of our patients were lost to follow-up, their adjuvant treatments could not be recorded, and nutritional status was determined by evaluating only preoperative albumin levels. The biomarkers we used in our study should be considered with the calibration differences of the biochemistry devices changing with the developing technology.

Despite the developments in the diagnosis and treatment over the years, the overall survival outcomes of stomach cancer are not satisfactory. Nevertheless, advances in chemotherapy and immunotherapy are promising. Further studies are needed to develop affordable and reliable tests to predict stomach cancer prognosis and to determine the stage preoperatively.

## Riassunto

Il cancro gastrico è una patologia con alti tassi di mortalità e morbilità in tutto il mondo. Nuovi approcci terapeutici mirati e recenti miglioramenti nell'immunoterapia hanno notevolmente migliorato la sopravvivenza. Sono stati di interesse per i ricercatori nuovi indicatori che possono aiutare a determinare la prognosi del cancro allo stomaco. Abbiamo valutato e registrato i rapporti CEA/albumina preoperatori dei pazienti e studiato l'effetto di questo rapporto sul coinvolgimento dei linfonodi, sullo stadio patologico del tumore e sulla sopravvivenza globale.

Si è trattato di uno studio di valutazione retrospettiva dei dati provenienti da cartelle elettroniche di pazienti operati per cancro allo stomaco nel nostro centro tra gennaio 2012 e dicembre 2017. Lo studio ha incluso 195 pazienti che sono stati seguiti regolarmente e di cui erano disponibili i dati medici completi.

Risultati: l'effetto del rapporto CEA/albumina sul numero di linfonodi metastatici è stato analizzato utilizzando la regressione lineare ed è risultato statisticamente significativo ( $p = 0,001$ ). Un aumento di un'unità nel rapporto CEA/albumina aumenta il numero di linfonodi metastatici di 0,223 unità (intervallo di confidenza: 0,097-0,380) e questa variabile da sola spiega il 5,7% della variazione del numero di linfonodi metastatici.

Conclusione: le decisioni sul trattamento neoadiuvante possono essere prese stimando gli stadi T e N utilizzando il rapporto CEA/albumina nei casi in cui i metodi radiologici convenzionali sono insufficienti.

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