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Effect of preoperative C-reactive protein/albumin ratio on postoperative survial in gastric adenocarcinomas

Gastrik adenokarsinomlarda ameliyat öncesi C-reaktif protein/albümin oranının ameliyat sonrası sağkalıma etkisi

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ABSTRACT

Aim: Since survival time is still low in end-stage gastric cancers, additional treatment and prognostic factors are being investigated. This study aimed to evaluate the significance of the preoperatively measured C-reactive protein (CRP)/ Albumin ratio in gastric adenocarcinomas and its effect on postoperative survival.

Materials and Methods: A total of 258 patients who underwent elective gastric adenocarcinoma surgery were investigated retrospectively. Disease-free and overall survival were evaluated according to the last CT, MRI, and PET/CT scans performed during their follow-up. Demographic data, operation reports, pathology reports, and imaging results of the patients were collected. The preoperative values of CRP and albumin were recorded, and the CRP/ Albumin ratio was calculated. After exclusion criteria, 208 patients were included in the study.

Results: There was a significant relationship between the preoperatively measured CRP/Albumin ratio and postoperative survival time. The predictive power of the CRP/Albumin ratio on the exit was 4.7%. Together with the other parameters affecting survival, the predictive power of the CRP/albumin ratio on the exit increased to 42.5%.

Conclusion: A high CRP/Albumin ratio measured preoperatively was associated with low postoperative survival in patients with gastric adenocarcinomas who underwent curative surgery. Considering that the elevation of CRP may not be kept down due to tumoral tissue, fixing the albumin level by healing the nutritional status of the patients in the preoperative period is the most important way to manage this rate.

Keywords: CRP/ albumin ratio, gastric adenocarcinoma, survival.

ÖZ

Amaç: *Son evre mide kanserlerinde sağ kalım süresi hala düşük olduğundan, ek tedavi ve prognostik faktörler araştırılmaktadır. Bu çalışmada, mide adenokarsinomlarında ameliyat öncesi ölçülen C-reaktif protein (CRP)/Albümin oranının önemi ve ameliyat sonrası sağ kalım üzerindeki etkisinin değerlendirilmesi amaçlanmıştır.*

Gereç ve Yöntem*: Elektif mide adenokarsinom ameliyatı geçiren toplam 258 hasta retrospektif olarak incelendi. Hastalıksız, genel sağ kalım, takipleri sırasında yapılan son BT, MRI ve PET/BT taramalarına göre değerlendirildi.*

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Hastaların demografik verileri, ameliyat raporları, patoloji raporları ve görüntüleme sonuçları toplandı. Ameliyat öncesi CRP ve albümin değerleri kaydedildi ve CRP/Albümin oranı hesaplandı. Dışlama kriterlerinden sonra, toplam 208 hasta çalışmaya dahil edildi.

Bulgular: *Ameliyat öncesi ölçülen CRP/Albümin oranı ile ameliyat sonrası sağ kalım süresi arasında anlamlı bir ilişki vardı. CRP/Albümin oranının ölümü belirmedeki öngörü gücü %4,7 idi. CRP/Albümin oranının ölümü öngörü gücü, sağkalımı etkileyen diğer parametrelerle birlikte %42,5'e kadar yükseldi.*

Sonuç: *Ameliyat öncesi ölçülen yüksek CRP/Albümin oranı, küratif cerrahi geçiren gastrik adenokarsinomlu hastalarda postoperatif dönemde düşük sağkalımla ilişkiliydi. CRP yüksekliğinin tümör dokusu nedeniyle düşük tutulamayabileceği gerçeği göz önüne alındığında, ameliyat öncesi dönemde hastaların beslenme durumunun iyileşmesiyle albümin düzeyinin sabitlenmesi bu oranı yönetmenin en önemli yoludur.*

Anahtar Sözcükler: *CRP/albümin oranı, gastrik adenokarsinom, sağkalım.*

INTRODUCTION

Gastric cancer is the third leading cause of cancer-related death diagnosed cancer types. According to GLOBOCAN 2020 data, the number of newly diagnosed cancers worldwide in 2020 is 19.3 million, and cancer-related deaths are 10 million. Gastric cancer includes 5.6% of patients diagnosed with new cancer and 7.7% of patients who died of cancer (1). Surgery is the only curative treatment for gastric cancer (2). Surgery can be performed after neoadjuvant therapy or before adjuvant therapy, depending on several factors such as tumor localization, metastatic lymph node, and size of the tumor. Despite all this, the survival time is still low in end-stage gastric cancers, and additional management methods are required to be carried out. For this reason, many prognostic values that may predict survival in gastric cancers are being investigated.

The 5-year survival rates for resected gastric adenocarcinoma stages I, II, and III in the United States are approximately 75%, 50%, and 25%, respectively. Adjuvant chemotherapy alone has not proven effective, at least in studies from Europe and the United States (3). A high neutrophil/lymphocyte ratio (NLR) is associated with a worse prognosis (4). R0 resection must be done for a better survival ratio. However, there is a recurrence of gastric cancer even after R0 resection in many cases, reflecting the current limits of this parameter (5, 6). The C-reactive protein (CRP) /Albumin ratio is a newly defined marker of inflammation and is associated with lower survival time in different diseases, such as sepsis in patients with burn injuries (7) and pancreatic and hepatocellular cancers (8). Few studies also demonstrate the impact of CRP and albumin values in patients with gastric cancer (9, 10).

We aimed to calculate the preoperative CRP/Albumin ratio in the patients with gastric adenocancer applied to our clinic and to investigate the effect on postoperative survival. Additionally, we aimed to reveal the predictive power of the CRP/Albumin ratio so that it may be considered a prognostic value measured preoperatively.

MATERIALS and METHODS

The study was conducted in the Ege University Department of General Surgery, and the ethics committee approval (No: 22-10.1T/13) was obtained. A total of 258 patients who underwent elective gastric adenocarcinoma surgery between May 2013- December 2020 were investigated. Both laparoscopic and laparotomy cases were included in the study. Elective patients who did not have perioperative distant metastasis and underwent D2 lymph node dissection were included. Due to the effects on the overall survival period, patients who underwent urgent and semi-urgent surgeries because of bleeding or obstruction and the patients who required reoperation due to postoperative complications were excluded. A total of 50 patients were excluded. The study target included the patients who underwent total, subtotal, and distal gastrectomy + D2 lymph node dissection.

Disease-free and overall survival durations were calculated according to the last CT, MRI, and PET/CT scans. Two hundred-eight patients matching the inclusion criteria were counted. Past medical records, including demographic data (age, gender), operation reports(operation data and operation technique: distal, subtotal or total gastrectomy + D2 lymph node dissection), pathology reports (tumor location, tumor size, postoperative histological type, and subtype,

surgical margins, lymphovascular invasion, perineural invasion, venous invasion, number of the metastatic lymph nodes and number of the removed lymph nodes, tumors T, N, and M stage according to the AJCC 8th edition), postoperative imaging results (local recurrence and distance organ metastasis during the follow-up periods) and the exitus data were evaluated.

The preoperative values of CRP and albumin were recorded, and CRP/ Albumin ratio was calculated for each patient. Tumor stages are classified according to pTNM values in the 8th edition of AJCC and UICC classification. The relationship between CRP/albumin ratio, gender distribution, neoadjuvant treatment status, tumor location, tumor size, histological subtype, surgical margin positivity, lymphovascular invasion, perineural invasion, venous invasion, and pTNM stages was evaluated between the groups.

Statistical Analysis

Statistical analyses were calculated with SPSS v25.0. Mean ± standard deviation was used for numerical measurements, and percentages and numbers were used for qualitative measurements from descriptive statistics. The normality of the cross-group distribution was tested with the Shapiro-Wilk test. Normally distributed independent data by Student's T test, dependent data were evaluated by Paired T and ANOVA tests, and non-normally distributed data by Mann Whitney U and Kruskal Wallis tests according to the number of groups—survival analysis performed by the Kaplan-Meier test. The Cox Regression model determined factors affecting survival. ROC-curve analysis and the Yuoden index were used to evaluate the CRP/Albumin ratio as a predictive value. A logistic regression test evaluated the survival effect of the parameters. The confidence interval was determined as 95%, and a p-value of <0.05 was significant.

RESULTS

137 of 208 patients were male (65.86%), while 71 were female (34.14%). The mean age was 66.48 (± 10.36 standard deviation), and the median was 67 (min. 40- max. 93).

Two hundred-eight patients were divided into three groups according to the type of operation. Total gastrectomy was performed in 115 patients (55.29%), subtotal gastrectomy in 48 patients (23.07%), and distal gastrectomy in 45 patients (21.64%). In the compared data, only tumor location ($p<0.01$) was significantly correlated according to the operation type. At the same time, there was no statistically significant difference between the groups according to the operation type in other comparisons.

There was a statistically significant correlation between tumor size *($p<0.001$),* histological subtype *($p=0.001$),* surgical margin positivity *($p=0.01$),* lymphovascular invasion *($p<0.001$),* perineural invasion *($p<0.001$)* and venous invasion *($p<0.001$)* according to the pTNM stages.

Survival analysis

The mean survival time of those who underwent total gastrectomy, subtotal gastrectomy, and distal gastrectomy was found to be 48.21 months (41.04 – 55.37), 45.24 months (34.73 – 55.74), and 50.54 months (39.26 – 61-82), respectively (Figure-1).

There was a statistically significant difference between stages regarding survival times *($p<0,001$).* The mean survival of the patients with stage 1A was 87.71 months (79.4 – 95.9). It was 65.2 months for stage 1B (43.8-86.7), 66.9 months for stage 2A (55.77-78.1), 65.9 months for stage 2B (49.6 – 82.3), 51.1 months for stage 3A (37.0 – 65.3), 34.5 months for stage 3B (17, 6 – 51.4), 34.08 months for stage 3C (26.04 – 41.7) **(**Figure-2**).**

There was an inverse correlation between the CRP/Albumin ratio and survival, and a 1 unit increase in the cut-off value of the CRP/ Albumin ratio reduced survival 1.68 times (1.19 – 2.38) (Figure-3). Neoadjuvant therapy increased survival 2.69 times (0.55 – 13.06); lymphovascular invasion 0.63 times (0.41 – 0.98), perineural invasion 0.47 times (0.27 – 0.83), and distant organ metastasis 0.49 times (0.30 – 0.79) decreased survival.

The age parameter affected the survival 1.03 times (1.01 – 1.05) according to the stages, while the CRP/Albumin ratio affected the survival 1.73 times (1.12 – 2.66) (Figure-4). Considering the factors affecting survival in terms of stages, it was determined that neoadjuvant treatment status, surgical margin, lymphovascular invasion, perineural invasion, venous invasion, and local recurrence did not affect survival. However, distant organ metastasis decreased survival by 0.6 times (0,36 – 0,98) (Table-1).

Predictive analysis of CRP/Albumin ratio

Using the CRP/Albumin ratio as a predictive test was statistically significant(*$p=0.009$)*.

Considering the CRP/Albumin ratio as a predictive test, the true positivity of this parameter was determined as 68%. When true negativity, true positivity, false negativity, and false positivity were taken together, an average of 59.1% of results were statistically correct. It was determined that a 1 unit increase in the CRP/Albumin ratio could increase the death rate 21.7 times *(p=0,007*).

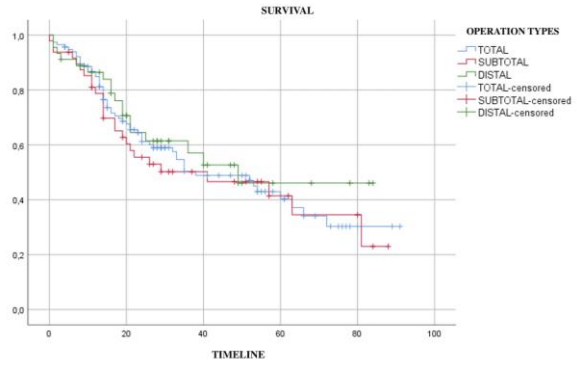

Figure-1. Overall Survival analysis regarding to operation types.

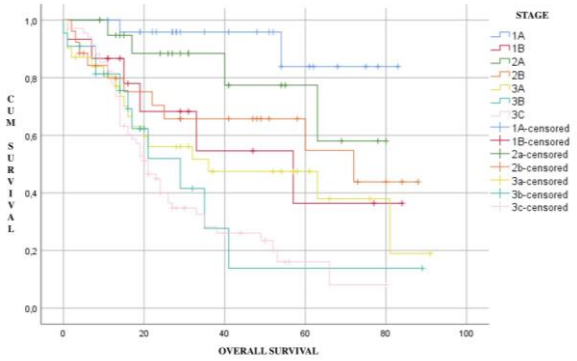

Figure-2. Overall Survival differences between pTNM stages.

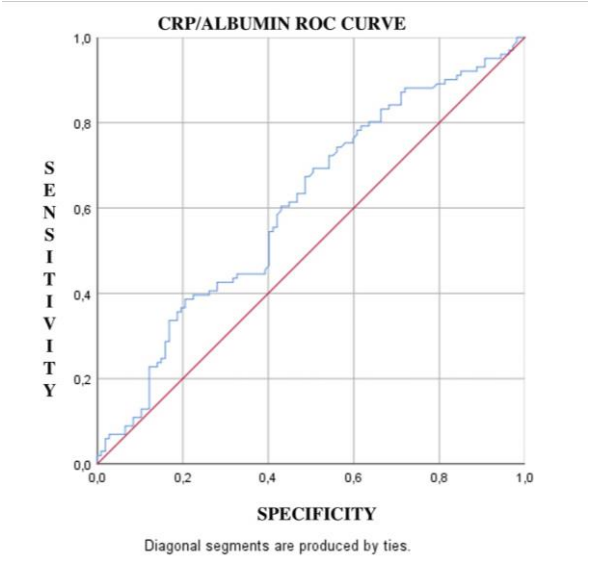

Figure-3. ROC curve of CRP/ Albumin ratio.

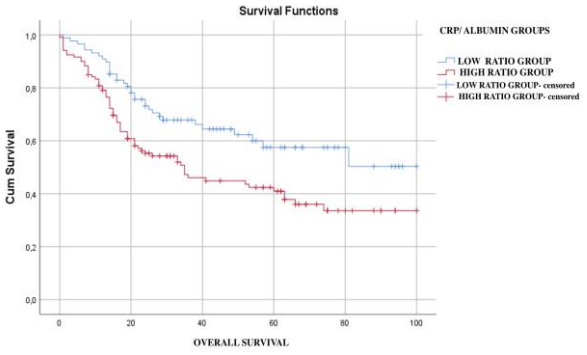

Figure-4. Overall survival regarding CRP/Albumin groups.

Table-1. Effect of the parameters included in the study on survival.

	p Value	Hazard ratio	95% CI	
			Lower Limit	Upper Limit
AGE	0.005*	1.032	1.01	1.054
CRP/ALBUMIN RATIO	0.003*	1.684	1.191	2.38
NEOADJUVANT THERAPY	0.22	2.69	0.554	13.068
SURGICAL MARGIN	0.002*	2.457	1.383	4.363
LYMPHOVASCULAR INVASION	0.044*	0.636	0.409	0.987
PERINEURAL INVASION	0.009*	0.477	0.273	0.834
VENOUS INVASION	0.905	0.967	0.554	1.687
LOCAL RECURRENCE	0.139	0.283	0.053	1.507
DISTANT METASTASIS	0.004*	0.494	0.305	0.798

The mean overall survival with a low CRP/Albumin ratio was 66.4 months, while it was 49.61 months in the patients with a high CRP/Albumin ratio. There was a statistically significant difference between the survival rates of these two groups *(p=0,005).*

Excluding the parameters of lymphovascular invasion, perineural invasion, and venous invasion from the analysis, which were determined to have no statistically significant contribution, the power of CRP/Albumin ratio, neoadjuvant treatment, surgical margin, tumor stage, and distant organ metastasis status together was found to determine the exitus with 42.5% probability. When the CRP/Albumin ratio was used alone to predict the exitus rate, a 1-unit CRP/Albumin ratio increased the exitus risk 21 times. The predictive power of the CRP/Albumin ratio on exitus was 4.7%.

DISCUSSION

The main goal of this study was to consider the preoperatively measured CRP/Albumin ratio as a predictive value in evaluating postoperative survival in patients with gastric adenocarcinoma. According to the cut-off value, the CRP/Albumin ratio had an effect on survival, and survival was lower in the patients with a higher CRP/Albumin ratio.

Age significantly impacts both overall survival and cancer-related survival [7, 8]. In younger patients, there is a higher prevalence of the diffuse histo-type, and tumors may be diagnosed at more advanced stages. However, when considering the tumor stage, young age alone does not independently affect prognosis. Gender does not have an independent prognostic value for cancer-related survival in most studies (7, 8). Additionally, geographic location and ethnicity are other patient-related prognostic factors for gastric cancer. Recent studies conducted have shown that Asian Americans have better outcomes compared to other ethnicities (9). In our study, age was found to affect survival 1.03 times. It was also revealed that the CRP/Albumin ratio affected the survival 1.73 times. With increasing age and comorbidities, the value of albumin decreases, so the correlation between increasing age and albumin can also be clarified.

The median tumor size value was 5 cm (4.81-5.87) in patients who underwent total gastrectomy, 4 cm (3.69-4.98) who underwent subtotal gastrectomy, and 3,5 cm (3,21-4,25) in the group of distal gastrectomy. As expected in the compared data, only the tumor location *(p<0.01)* was significantly correlated according to the operation type. Since the type of operation is determined according to the tumor location and size, such a statistical result was predicted. The other parameters were the results frequently obtained after the operation, and they did not affect the type of operation.

Several studies conducted the advantages of chemotherapy after D2 gastrectomy (4, 5). A study showed a 69% overall 5-year survival rate in locally advanced patients treated with D2 gastrectomy (6). Our study found that the advantage of neoadjuvant chemotherapy is that it increases survival by 2.69 times. Considering that tumor size, lymph node metastasis, and distant organ metastasis determine the pTNM stage of the disease, the statistical results obtained from our study were as expected. The reason why histological subtype and surgical margin positivity were associated with the stage of the disease is related to the unequal distribution of the 208 patients included in the study. Considering that 58% of the entire patient group included in our study consisted of stage 3 patients, it is natural to detect such a statistical relationship.

As in the 2016 study by Jin Qi et al. comparing total gastrectomy and distal gastrectomy in terms of survival (11) and as in the 1999 study by Bozzetti et al. in terms of survival(12), there was no significant difference between all 3 surgical procedures and the patient's survival. There was no significant relationship between the operation types and survival *(p=0,52).* In this respect, our results are substantially consistent with the literature.

Liu et al. reported that parameters of CRP and albumin might have predictive value in determining survival; however, they did not reveal a cut-off value (10-13). Besides, we obtained additional results by deciding that the predictive power of this rate alone was 4.7%. In all of the stages, CRP/Albumin ratio *(p=0.012),* neoadjuvant treatment status *(p=0.025),* pTNM stage *(p=0.022),* and distant organ metastasis were effective on survival. The predictive power was determined to increase to 42.5% when the parameters were used together.

In another study by Minjie Mao et al., consisting of 337 patients in 2017, there was a relationship

between the CRP/Albumin ratio and survival. Still, the neutrophil/lymphocyte ratio (NLR) parameter was used to increase this predictive power (14). Similarly, the effects of parameters, systemic immune-inflammatory index (SII), and Glasgow Prognostic Score (GPS) on preoperative survival in gastric adenocarcinomas have been investigated in the literature for predictive value purposes (10). However, they all have low predictive power and increase the predictive power when used together.

Considering that CRP elevation is related to the characteristics of the cancer (15), the most important way to change the CRP/Albumin ratio is to change the albumin value (16). Low albumin levels due to nutritional disorders are common in gastric cancers. So, increasing the value of albumin by good nutrition preoperatively may impact survival in the postoperative period.

CONCLUSION

This study evaluated the CRP/albumin ratio as a parameter that measured preoperatively in gastric adenocarcinomas and can guide us in predicting survival.

CRP/Albumin ratio alone was predictive in predicting survival *(p=0,006).* A 1-unit increase in the CRP/Albumin ratio increased the risk of death 21 times. The predictive power of the CRP/Albumin ratio alone on the exitus was 4.7%. When other parameters affecting survival (neoadjuvant treatment, surgical margin, pTNM stage, and distant organ metastasis status) were evaluated with the predictive effect of CRP/Albumin, the predictive power on the exitus increased to 42.5%.

Considering the effect of the CRP/Albumin ratio on survival in gastric cancers, it is essential to correct patients' low albumin values in the preoperative period and thus improve their nutritional status.

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References

1. H. Sung *et al.*, “Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries,” *CA Cancer J Clin*, vol. 71, no. 3, pp. 209–249, May 2021, doi: 10.3322/CAAC.21660.
2. B. J. Dicken, D. L. Bigam, C. Cass, J. R. Mackey, A. A. Joy, and S. M. Hamilton, “Gastric Adenocarcinoma: Review and Considerations for Future Directions,” *Ann Surg*, vol. 241, no. 1, p. 27, Jan. 2005, doi: 10.1097/01.SLA.0000149300.28588.23.
3. I. H. Kim, “Current status of adjuvant chemotherapy for gastric cancer,” *World J Gastrointest Oncol*, vol. 11, no. 9, p. 679, Sep. 2019, doi: 10.4251/WJGO.V11.I9.679.
4. H. Shimada *et al.*, “High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer,” *Gastric Cancer*, vol. 13, no. 3, pp. 170–176, Aug. 2010, doi: 10.1007/S10120-010-0554-3.
5. M. W. Kattan, M. S. Karpeh, M. Mazumdar, and M. F. Brennan, “Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma,” *J Clin Oncol*, vol. 21, no. 19, pp. 3647–3650, Oct. 2003, doi: 10.1200/JCO.2003.01.240.
6. V. E. Strong *et al.*, “Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram,” *Ann Surg*, vol. 251, no. 4, pp. 640–646, Apr. 2010, doi: 10.1097/SLA.0B013E3181D3D29B.
7. Y. Yu, W. Wu, Y. Dong, and J. Li, “C-Reactive Protein-to-Albumin Ratio Predicts Sepsis and Prognosis in Patients with Severe Burn Injury,” *Mediators Inflamm*, vol. 2021, 2021, doi: 10.1155/2021/6621101.
8. Y. J. Fu, K. Z. Li, J. H. Bai, and Z. Q. Liang, “C-reactive protein/albumin ratio is a prognostic indicator in Asians with pancreatic cancers: A meta-analysis,” *Medicine*, vol. 98, no. 48, Nov. 2019, doi: 10.1097/MD.0000000000018219.
9. Q. Yu *et al.*, “Clinical significance and prognostic value of C-reactive protein/albumin ratio in gastric cancer,” *Ann Surg Treat Res*, vol. 100, no. 6, pp. 338–346, Jun. 2021, doi: 10.4174/ASTR.2021.100.6.338.
10. X. Liu *et al.*, “Preoperative C-Reactive Protein/Albumin Ratio Predicts Prognosis of Patients after Curative Resection for Gastric Cancer,” *Transl Oncol*, vol. 8, no. 4, pp. 339–345, Aug. 2015, doi: 10.1016/J.TRANON.2015.06.006.

11. J. Qi, P. Zhang, Y. Wang, H. Chen, and Y. Li, “Does Total Gastrectomy Provide Better Outcomes than Distal Subtotal Gastrectomy for Distal Gastric Cancer? A Systematic Review and Meta-Analysis,” 2016, doi: 10.1371/journal.pone.0165179.
12. F. Bozzetti, E. Marubini, G. Bonfanti, R. Miceli, C. Piano, and L. Gennari, “Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group,” *Ann Surg*, vol. 230, no. 2, pp. 170–178, Aug. 1999, doi: 10.1097/00000658-199908000-00006.
13. H. Saito *et al.*, “Prognostic Significance of the Preoperative Ratio of C-Reactive Protein to Albumin and Neutrophil–Lymphocyte Ratio in Gastric Cancer Patients,” *World J Surg*, vol. 42, no. 6, pp. 1819–1825, Jun. 2018, doi: 10.1007/S00268-017-4400-1/TABLES/2.
14. M. Mao *et al.*, “C-reactive protein/albumin and neutrophil/lymphocyte ratios and their combination predict overall survival in patients with gastric cancer,” *Oncol Lett*, vol. 14, no. 6, pp. 7417–7424, Dec. 2017, doi: 10.3892/OL.2017.7179/HTML.
15. S. Lee, J. W. Choe, H. K. Kim, and J. Sung, “High-Sensitivity C-Reactive Protein and Cancer,” *J Epidemiol*, vol. 21, no. 3, pp. 161–168, May 2011, doi: 10.2188/JEA.JE20100128.
16. D. Gupta and C. G. Lis, “Pretreatment serum albumin as a predictor of cancer survival: A systematic review of the epidemiological literature,” *Nutr J*, vol. 9, no. 1, pp. 1–16, Dec. 2010, doi: 10.1186/1475-2891-9-69/TABLES/5.