RESEARCH ARTICLE

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Does the Albumin to Globulin Ratio Predict Short-term Complications in Gastric Cancer Patients?

ABSTRACT

Objective: Gastric cancer (GC) is a cancer with poor prognosis despite advances in diagnosis and treatment methods, and postoperative morbidity and mortality rates are high. The aim of this study was to evaluate the predictive and early prognostic effect of the pre-treatment albumin to globulin ratio (AGR) in patients with gastric adenocarcinoma (GAC).

Methods: The study included male and female patients who were operated on with the diagnosis of GAC in our general surgery clinic between January 2016 and November 2020. The demographic and postoperative histopathological findings, postoperative complications and in-hospital mortality findings of the patients were evaluated retrospectively from the hospital data.

Results: Evaluation was made of a total of 70 patients operated on with the diagnosis of GAC. In the ROC curve analysis applied to the AGR ratio, the optimum cut-off value was 1.54. A statistically significant difference was found between the high (≥1.54) and low (<1.54) AGR groups in terms of intensive care unit (ICU) length of stay, serious postoperative complications, anastomotic leakage, and in-hospital mortality ($p = 0.050$, $p = 0.016$, $p = 0.011$; $p = 0.005$). In univariate analysis with postoperative serious complications, statistically significant results were found with age> 65 years, high American Society of Anesthesiologist (ASA) score and low AGR ($p = 0.035$, $p <0.001$, $p = 0.016$), whereas in multivariate analysis, only high ASA score was found to be an independent risk factor ($p = 0.031$).

Conclusions: The results of this study demonstrated the relationship between low AGR and serious postoperative complications, anastomotic leakage and early mortality risk in GAC. The AGR ratio, which can be calculated from the albumin and globulin values used in routine clinical practice, can be used as a suitable prognostic factor in this patient group to enable the clinician to take the necessary preoperative precautions.

Keywords: Gastric adenocarcinoma, albumin / globulin ratio, postoperative complication

Albümin-Globulin Oranı Mide Kanseri Hastalarında Kısa Dönem Komplikasyonları Öngörür mü?

ÖZET

Amaç: Gastrik kanser (GK), tanı ve tedavi metodlarındaki gelişmelere rağmen kötü prognozlu bir kanser olup, postoperatif morbidite ve mortalite oranları yüksek seyretmektedir. Bu çalışmada tedavi öncesi bakılan albümin-globülin oranı (AGO)' nun gastrik adeno kanser (GAK) hastalarındaki prediktif ve erken dönem prognostik etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Ocak 2016 ile kasım 2020 arasında, genel cerrahi kliniğimizde GAK tanısı ile opere edilen kadın ve erkek hastalar çalışmaya dahil edildi. Hastaların demografik ve postoperatif histopatolojik bulguları, postoperatif komplikasyonları ve hastane içi mortalite bulguları hastane veri datasından retrospektif olarak değerlendirildi.

Bulgular: GAK tanısı ile ameliyat edilen toplam 70 hastanın değerlendirmesi yapıldı. AGO oranına uygulanan ROC eğri analizinde en uygun kesme değeri 1.54 idi. Yüksek (≥1.54) ve düşük (<1.54) AGO grupları arasında yoğun bakım ünitesi (YBÜ) kalış süresi, postoperatif ciddi komplikasyon, anastomoz kaçağı ve hastane içi mortalite gelişimi için istatisksel anlamlı fark tespit edildi ($p=0.050$, $p=0.016$, $p=0.011$; $p=0.005$). Postoperatif ciddi komplikasyon ile univarite analizde >65 yaş, yüksek American Society of Anesthesiologist (ASA) skoru ve düşük AGO ile istatsisksel anlamlı sonuç bulunurken ($p=0.035$, $p<0.001$, $p=0.016$), multivarite analizde ise sadece yüksek ASA skoru, bağımsız risk faktörü olarak bulundu ($p=0.031$).

Sonuç: AGO ile GAK' da postoperatif ciddi komplikasyon, anastomoz kaçağı ve erken mortalite riski arasındaki ilişki çalışmamızda ortaya konmuş , bu hasta grubunda rutin klinik pratikle ölçülebilen düşük maliyetli AGO oranı preoperatif dönemde klinisyeni gerekli önlemleri alması için uyaran uygun bir prognostik araç olarak kullanılabilir.

Anahtar Kelimeler: Gastrik adenokanser, albümin/globülin oranı, postoperatif komplikasyon

INTRODUCTION

Gastric cancer (GC) is a cancer with poor prognosis despite advances in diagnosis and treatment methods, and postoperative morbidity and mortality rates are high. Although gastric cancer (GC) incidence and mortality rates have decreased in recent years, it still ranks as the third most common cause of cancer-related death (1).

The most widely used current classification system for GC in preoperative staging and predicting prognosis is the tumor, node, metastasis (TNM) staging system defined by the American Joint Committee on Cancer (AJCC) (2). Even in patients with the same TNM staging, early morbidity and survival may differ after curative surgical resection and / or systemic treatment. This has attracted the attention of researchers, and various studies have been conducted to show that there may be different immune mechanisms that affect the development and spread of cancer. It has been discussed in various studies that each patient may have different immune system responses to the development of cancer and that the morbidity and prognosis will be different because the ratio of protective immune system cells secreted against cancer cells and the cytokines secreted are different in each patient (3-6).

Globulin, which constitutes two main components of serum proteins and contains albumin and inflammatory cytokines, which are generally indicators of nutritional status, plays an important role in cancer immunity and prognosis (7). Studies have been conducted on the albumin to globulin ratio (AGR), some of which have included only albumin to predict survival in various types of cancer and others which more recently have evaluated albumin and globulin together (8-10). There are only a few studies in the literature that have examined the relationship between AGR rate and GAC, in terms of severe postoperative complications, early mortality and TNM staging.

Serum markers are easy to measure, reproducible and inexpensive tests, which may be useful in predicting the morbidity and mortality rates of GAC patients during postoperative follow-up, and for closer follow-up of high-risk patients. The aim of this study was to evaluate the predictive and prognostic effect of pre-treatment AGR in GAC patients.

MATERIAL AND METHODS

Approval for the study was granted by the Clinical Research Ethic Committee (decision no:2021/21:545, dated:15.01.2021). Informed consent was not required due to the retrospective nature of the study.

The study included male and female patients who were operated on with the diagnosis of gastric adenocarcinoma (GAC) in our general surgery clinic between January 2016 and November 2020. Patients were excluded from the study if they had chronic liver disease or hematological disease, had undergone surgery for a diagnosis of gastric malignancy other than GAC, had a diagnosis of synchronous or metachronous malignancy, had recurrent disease, had received preoperative chemotherapy and / or radiotherapy, who were operated on under emergency conditions due to obstruction, bleeding or perforation, or if the data were not available.

For retrospective evaluation of the patients, data were retrieved from the hospital database related to age, gender, ASA score, T stage, lymph node, metastasis status, TNM stage, postoperative complications of Clavien-Dindo grade ≥3, anastomotic leaks, albumin, total protein, globulin (total protein-albumin) values, length of stay in hospital and in intensive care unit (ICU), and early mortality (within the first postoperative month). The AGR value was calculated using the formula: AGR = serum albumin / total protein-serum albumin).

Tumor staging was applied according to the AJCC 8th edition TNM staging system published in 2017 (2). Postoperative complications were defined as those that developed in the hospital or within 1 month after surgery. Complication staging was determined according to the Modified Clavien Dindo Classification and severe complications were accepted as those of grade 3 or higher (11). The relationships between AGR and severe postoperative complications, TNM staging and early mortality were analyzed.

Statistical Analysis: Data obtained in the study were analyzed statistically using IBM ® SPSS vn. 23.0 software. Numerical data were expressed as mean ± standard deviation (SD), median (inquartile range) values or as percentages. The normal distribution of the data was determined by histogram graphics and the Kolmogrov Smirnov Test. The optimal cut-off level of AGR was determined using ROC curve analysis. In the comparison of demographic and clinicopathological features and postoperative outcomes between patients with low and high AGR, the Chi -square test or Fisher Exact Test were applied to categorical variables and the Student's t-test or Mann Whitney U-test to numerical variables. Binary logistic regression analysis was used to determine the factors affecting serious postoperative complications. A value of $p<0.05$ was considered statistically significant.

RESULTS

Evaluation was made of a total of 70 patients operated on with the diagnosis of GAC. The patients comprised 48 (68.6%) males and 22 (31.4%) females with a mean age of 64.24 ± 1.50 years. As a result of ROC curve analysis, the optimal cut-off level of AGR for serious postoperative complications was determined as 1.54 (AUC: 0.648 95% CI: 0.579-0.697 p = 0.001; 78% specificity and 72% sensitivity). According to the

optimal cut-off level of 1.54, there were 38 (54.2%) patients in the low AGR (<1.54) group and 32 (45.8%) patients in the high AGR (≥1.54) group. There was no significant difference between the groups in terms of age, gender, TNM stage and operation type. In the low AGR group, patients were determined to have significantly more comorbid diseases compared to the patients in the high AGR group (p = 0.021). The comparisons of demographic and clinicopathological features between the groups of low and high AGR are summarized in Table 1.

Table 1. Comparison of demographic and clinicopathological features between the groups of low and high AGR.

Variables	Total n=70	Low AGR (<1.54) n=38	High AGR (≥1.54) n=32	p value
Age (years)	64.24±13.50	65.84±12.03	62.34±15.03	0.283
Gender (male)	48(68.6)	28(73.7)	20(62.5)	0.315
ASA score				**0.021**
I	18(25.7)	7(18.4)	11(34.4)	
II	37(52.9)	18(47.4)	19(59.4)	
III	14(20)	12(31.6)	2(6.3)	
Operation				0.519
TG	37(52.9)	23(60.5)	14(43.8)	
SG	26(37.1)	12(31.6)	14(43.8)	
GE	2(2.9)	1(2.6)	1(3.1)	
LTG	1(1.4)	0(0)	1(3.1)	
LSG	4(5.7)	2(5.3)	2(6.3)	
TNM stage				0.320
1a	7(10)	2(5.3)	5(15.6)	
1b	11(15.7)	8(21.1)	3(9.4)	
2a	10(14.3)	3(7.9)	7(21.9)	
2b	14(20)	8(21.1)	6(18.8)	
3a	5(7.1)	4(10.5)	1(3.1)	
3b	15(21.4)	8(21.1)	7(21.9)	
3c	4(5.7)	2(5.3)	2(6.3)	
4	4(5.7)	3(7.9)	1(3.1)	
Albumin (g/dl)	38.72±5.19	37.06±4.34	40.70±5.49	**0.003**

Numerical values are given as mean±standard deviation or percentages. AGR: Albumin to Globulin Ratio, ASA: American Society of Anesthesiologists, TG: Total Gastrectomy, SG: Subtotal Gastrectomy, GE: Gastroenterostomy, LTG: Laparoscopic Total Gastrectomy, LSG: Laparoscopic Subtotal Gastrectomy, TNM:Tumor-Node-Metastasis.

Comparisons of postoperative outcomes between the groups of low and high AGR are summarized in Table 2. The length of hospital stay was similar between the groups, and length of ICU stay was significantly longer in patients with low AGR (p=0.050). Significantly more serious postoperative complications were determined in patients with low AGR (42.1% vs 15.6% p=0.016). No anastomotic leakage or in-hospital mortality were observed in patients with high AGR, and these complications were observed at a significant level in the low AGR group (p=0.011; p=0.005 respectively).

Table 2. Comparison of postoperative outcomes between the groups of low and high AGR.

Variables	Total n=70	Low AGR (<1.54) n=38	High AGR (≥1.54) n=32	p value
Hospital Stay (days)	9(7-12)	10(7-12)	9(7.25-11.75)	0.986
ICU Stay (days)	1(0-3)	1.5(0.75-4.25)	1(0-2)	**0.050**
CD ≥3 complications (n%)	21(30)	16(42.1)	5(15.6)	**0.016**
Anastomotic Leakage (n%)	5(7.1)	5(15.6)	0(0)	**0.011**
In-hospital mortality (n%)	6(8.6)	6(15.8)	0(0)	**0.005**

Numerical values are given as median(IQR) or percentage. AGR: Albumin to Globulin Ratio, ICU: Intensive Care Unit, CD: Clavien-Dindo.

In univariate analysis, advanced age (OR: 3.33 95% CI: 1.05-10.52 p=0.035), high ASA score (OR: 8.00 95% CI: 2.26-28.21 p<0.001) and low AGR (OR: 0.25 95% CI: 0.08-0.80 p=0.016) were found to be risk factors associated with serious postoperative complications (CD≥3). In multivariate analysis, high ASA score (OR: 0.22 95% CI: 0.56-0.87 p=0.031) was found to be an independent predictor of serious postoperative complications (Table 3).

Table 3. Univariate and Multivariate analysis of risk factors associated with serious postoperative complications.

Variable	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Age (>65 years)	3.33	1.05-10.52	**0.035**	-	-	-
High ASA score	8.00	2.26-28.21	**<0.001**	0.22	0.56-0.87	**0.031**
Low AGR (<1.54)	0.25	0.08-0.80	**0.016**	-	-	-

OR: Odds Ratio, CI: Confidence Interval, ASA: American Society of Anesthesiologists, AGR: Albumin to Globulin Ratio.

DISCUSSION

Although the rate of early diagnosis has increased due to widespread screening methods in the East Asian countries, GC is mostly diagnosed at the local advanced or late stage in western countries (1, 12). GC patients lose weight due to malnutrition in the advanced stage of the disease and their immune system is weakened. The close relationship between inflammation and cancer development has recently attracted the attention of researchers (5, 6).

Many recent studies have shown that the albumin protein synthesized by liver cells may be a prognostic marker for survival in various types of cancer (13-15). Serum albumin level is generally accepted to reflect the nutritional status of the body. Recent studies have also shown that the serum albumin level can also reflect the inflammatory state of the body (16). The main task of albumin is to maintain oncotic pressure in plasma and to carry various agents in serum. It has an antioxidant function against carcinogenesis with functions such as albumin, steroid hormone and calcium homeostasis, and the protection of DNA stabilization (17). The cause of hypoalbunemia in patients with GC is due to malnutrition, especially in advanced stages (18). More important than nutrition, proinflammatory cytokines (interleukin-6, interleukin-1 and tumor necrosis factor-alpha) secreted due to inflammation suppress albumin synthesis in the liver and increase vascular permeability, which causes albumin to pass into the interstitial space and consequently a decreased serum albumin level (19).

Serum globulin level has complex components such as acute phase proteins, immunoglobulins and interleukins and is closely related to the immune and inflammatory status of the body. It has been shown that high serum globulin levels caused by the accumulation of acute phase proteins and immunoglobulins generally reflect a persistent inflammatory response (20). Chronic inflammation markers play an important role in the metastasis, development, progression, and proliferation of tumor cells (21). High serum globulin has been reported to be associated with poor outcomes in prostate (22) and ovarian (23) cancers. However, many studies have found no relationship for the prognosis of gastric cancer (17, 24).

Serum albumin and globulin are the two main components of total protein in serum. While inflammation and changes in nutritional status in cancer patients cause different changes in albumin and globulin levels, both proteins are easily affected by dehydration and edema. AGR, however, takes serum albumin and globulin levels into account simultaneously, and can more precisely reflect the nutritional and inflammatory states of the body. Today, there are many studies in literature that have been conducted to predict survival for AGR in various cancer diseases. Guo et al stated that low AGR is associated with poor survival in digestive cancers (9). In a metanalysis of 15,356 patients with various types of cancer, Lv et al reported that low AGR before treatment was associated with poor survival (8).

There are also many studies of AGR predicting survival in GC patients. Low AGR was reported to be associated with poor survival in GC patients who underwent curative treatment (stage 1-3) by Liu et al (25), and in metastatic GC patients by Bozkaya et al. (7). In contrast, Xiao at al. (17) found that albumin was more valuable than AGR for the prediction of survival in a study in which, unlike other studies, albumin and AGR were compared with survival in GC patients.

Studies of albumin and AGR in GC patients are mostly related to survival, and there are few studies which have examined the relationships of albumin and AGR with the risk of postoperative complications. Ai et al. (10) stated that the rate of decrease in albumin values on the first day after surgery in GC patients may be a predictive factor for the risk of postoperative complications. In the current study, a statistically significant relationship

was found between low AGR and length of stay in ICU, serious postoperative complications, anastomotic leakage, and in-hospital mortality. In univariate analysis with serious postoperative complications, advanced age, high ASA score and low AGR were found to be statistically significant, while in multivariate analysis only a high ASA score was found to be an independent risk factor. This study is one of the few studies in literature to have evaluated the predictive value of AGR for the risk of serious postoperative complications, anastomotic leakage and early mortality.

Limitations

This study had some limitations, primarily that it was a single-center retrospective study with a small sample size of 70 patients. Second, due to insufficient data, it was not possible to evaluate medical conditions that could affect the patient's immune system. Third, there was no standard cut-off value for AGR. Until now, no combined method has been used to determine the AGR cut-off value, and various methods have been used to determine the best cut-off value. Different statistical methods can give different cut-off values and therefore a more accurate and predictive measurement can be made by determining a definitive cut-off value with a standardized statistical method.

Conclusion

The results of this study demonstrated the relationship between AGR and serious postoperative complications, anastomotic leakage and the risk of early mortality in gastric cancer patients. The AGR rate can be measured in routine clinical practice at no extra cost and can be used as an appropriate prognostic factor enabling the clinician to take the necessary preoperative precautions. Nevertheless, there is a need for further, multicenter, prospective randomized studies with larger samples to confirm these results.

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