EJMI

DOI: 10.14744/ejmi.2021.51056
EJMI 2022;6(1):106–110

Research Article

Can Albumin Bilirubin Ratio Predict Survival in Metastatic Gastric Cancer?

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Abstract

Objectives: This study evaluated the prognostic significance of the new index designed with albumin and bilirubin ratio (ABR) in patients with metastatic gastric cancer (GC).

Methods: The data of patients with metastatic gastric cancer followed in the medical oncology clinic between February 2012, and May 2020 were retrospectively reviewed. ABR was defined by dividing the albumin level by the bilirubin level.

Results: Overall survival (OS) of all patients was reported as 12.9 months (95% CI, 10.9-14.9). The effect of ABR on survival time was not found statistically significant (p=0.462; p>0.05).

Conclusion: This study evaluated the prognostic significance of the new index designed with ABR in patients with metastatic gastric cancer (GC), but no statistically significant result was obtained. Simple, accessible, and inexpensive tests showing recurrence, treatment response, and prognosis of GC are needed. Studies should be conducted with a more significant number of patient populations to determine the role of ABR in GC.

Keywords: Albumin bilirubin ratio, gastric cancer, glasgow prognostic score, overall survival

Cite This Article: *Ekinci F, Erdogan AP. Can Albumin Bilirubin Ratio Predict Survival in Metastatic Gastric Cancer? EJMI 2022;6(1):106–110.*

The incidence of GC, which is the 5th most common cancer in the world and the third most fatal cancer, has decreased relatively compared to the past in recent years.[1] Since it is not a practical and cost-effective screening method, it is usually diagnosed in advanced stages and incidentally.[2] Surgery is the only curative treatment option in early-stage cases. However, since there are no specific signs and symptoms in the early stages, the rate of radical resection is also low in parallel with the low diagnosis rate. In the advanced stage, chemotherapy is pivotal. It cannot be said that dramatic results have yet been achieved with molecularly targeted therapies such as immunotherapy and trastuzumab.[3,4]

Biomarkers are objectively measured and evaluated parameters during the normal biological and pathogenic process or as an indicator of the pharmacological response to a therapeutic intervention. GC, which is biologically and genetically heterogeneous, is not yet sufficiently understood at the molecular level. Therefore, a reliable marker that can be used effectively has not yet been found, except for the carcinoembryonic antigen (CEA) and the carbohydrate antigen 19-9 (CA19-9) both at the diagnostic stage and during follow-up.[3-5] Unfortunately, as with many other types of cancer, it is a heterogeneous disease in which each GC patient exhibits a different genetic and molecular profile. Undoubtedly, such a marker could have an essential role in early diagnosis, selecting appropriate treatment strategies, effective monitoring, reducing disease-related deaths, and predicting survival in gastric cancer, which has a very aggressive course.[5]

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Submitted Date: Noveber 08, 2021 **Accepted Date:** December 10, 2021 **Available Online Date:** February 28, 2022

Inflammation can play a role in cancer development by stimulating angiogenesis in tumor cells. The most prominent feature of cancer-related inflammation is the presence of mediators such as inflammatory cells, chemokines, and cytokines in tumor tissues. As a result of the hematopoietic response caused by active cytokines produced by tumor cells, an increase can be observed in many indicators such as leukocytes, neutrophils, and platelets in peripheral blood.[6,7] In addition to these, C-reactive protein (CRP), albumin and bilirubin levels are the most accepted inflammatory response indicators in cancer patients. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (TLR), Glasgow Prognostic Score (GPS: C-reactive protein/albumin), Platelet/hemoglobin ratio (PHR) are the main factors used in disease recurrence, prognosis, and response to treatment in both GC and many other cancer types.[7,8] The primary purpose of all studies is to obtain disease-specific, inexpensive, and practical formulation. This study evaluated the prognostic significance of the new index designed with albumin and bilirubin ratio (ABR) in metastatic GC patients.

Methods

The data of patients with metastatic GC followed in the medical oncology clinic between February 2012 and May 2020 were retrospectively reviewed. Patients diagnosed with gastric cancer histopathologically and staged according to TNM criteria were included. The patients' age, gender, location of metastases, operation status, laboratory results, 1 and 2 step treatment status were questioned and recorded with the electronic medical record system. The ABR was defined by dividing the albumin level by the bilirubin level.

The study complied with good clinical practice and the declaration of Helsinki and was approved by the local ethics committee.

Statistical Analysis

OS was determined using the date of diagnosis and date of death or the date of last clinical follow-up for patients who did not die. While evaluating the findings obtained in the study, SPSS (Statistical Package for Social Sciences) for Windows 16.0 program was used for statistical analysis. Descriptive statistics were prepared to include frequency (n), mean, standard deviation, minimum, median, and maximum values. Comparisons were made between groups in calculations made with Kaplan–Meier. The results were evaluated at the 95% confidence interval and the significance at the $p<0.05$ level.

The effect of the ABR on the survival of the patients included in the study data was evaluated in the Cox regression model. In the survival analysis, the model was created by taking the follow-up time, ex status, and relevant laboratory results' rates. The follow-up period was evaluated as months.

Results

Patient Characteristics

The total number of patients included in our study was 152, and their mean age was 61.40±11.71 (All patient characteristics are shown in Table 1). 43 (28.3%) of the patients were female, and 109 (71.7%) were male. Gastrectomy was performed in 45 patients (29.6%) because they were

Table 1. Frequency distribution of patient characteristics

	Frequency (n)	Percent (%)
Age (years) (Mean±SD)	61.40±11.71	
Gender		
Female	43	28.3
Male	109	71.7
Operation		
Yes	45	29.6
No	107	70.4
Liver metastasis		
Yes	66	43.4
No	86	56.5
Lung metastasis		
Yes	28	18.4
No	124	81.6
Bone metastasis		
Yes	27	17.8
No	125	82.2
LN metastasis		
Yes	145	95.4
No	7	4.6
Other metastasis		
Yes	129	84.9
No	24	15.1
Brain metastasis		
Yes	2	1.3
No	149	98.7
First-line treatment		
Yes	129	84.9
No	23	15.1
Second-line treatment		
Yes	67	44.0
No	85	56.0
Exitus status		
No	9	5.9
Yes	143	94.1

admitted to the operable stage. However, the remaining 107 patients (70.4%) were evaluated as de novo metastatic. When the metastasis status of the patients was examined, it was reported that 66 (43.4%) had liver, 28 (18.4%) had lung, 27 (17.8%) had a bone, 145 (95.4%) had distant lymph nodes, and 129 (84.9%) had spread to other regions. When the treatment status was examined, 129 (84.9%) patients were able to receive primary care, and 67 (44.0%) patients received secondary care. 23 (15.1%) patients could not receive any treatment.

Survival Analysis

The final analysis noted that 143 (94.1%) of the 152 patients included in the study died, and 9 (5.9%) were still alive. OS of all patients was reported as 12.9 months (95% CI, 10.9-14.9). The effect of ABR on survival time was not found statistically significant (p=0.462; p>0.05) (Table 2, Fig. 1).

Discussion

Since a link was first established between cancer and inflammation in the 19th century, an increasing number of studies have revealed that inflammatory markers also play an important role in tumor progression and metastasis.[9] The mechanism by which these markers have a negative effect on survival remains unclear. However, it is thought that it may be associated with a complex system that includes cellular signaling and genetic instabilities and results in tumor growth, tissue remodeling, angiogenesis, and dysregulation of innate/adaptive immune responses.[10] The most important distinguishing feature of albumin, one of the routinely used inflammation markers, is that it can show the effects of both nutritional status and systemic inflammation. This may indicate that the use of albumin alone or in formulations may be a better indicator than other inflammatory markers. Hypoalbuminemia can often be considered a good index for malnutrition and cachexia in patients with advanced cancer. Studies have shown that hypoalbuminemia is associated with poor survival in gastric cancer.[9]

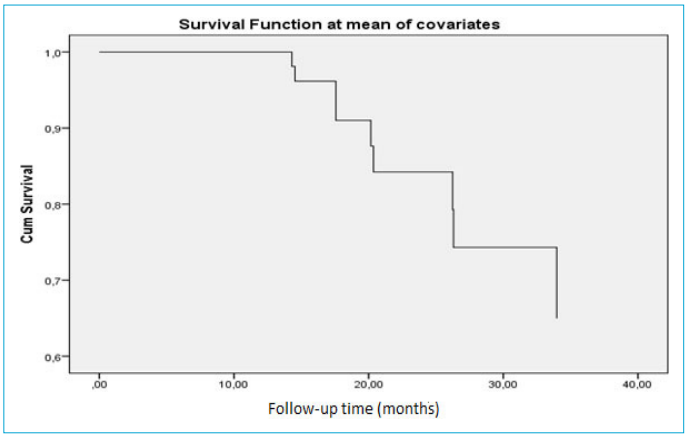

Figure 1. The effect of albumin/bilirubin ratio on survival time.

GPS, which is calculated using albumin and CRP levels in combination, is very popular in GC. GPS has been included as an inflammatory and nutritional-based reliable and independent marker that predicts survival.[9,11] Modified systemic inflammatory score (mSIS), a new scoring including lymphocyte and monocyte instead of CPR and albumin, has been replaced as a unique, valuable and straightforward prognostic factor for postoperative survival in preoperative GC patients. Here, the fact that CRP is not widely used in all clinics is seen as the main reason for researchers to search for another score.[9,10,12]

The combination of albumin and bilirubin was first designed in 2015 to eliminate the confusion created by the subjective parameters of Child-Pugh (CP) scoring in predicting prognosis in patients with hepatocellular cancer (HCC).[13] In the analysis, it was seen that similar results were obtained with the CP scoring of this combination. In other recent studies conducted after this study, the relationship between ALBI scoring and survival was also tested, and its reliability was proven.[14,15]

After these positive data of ALBI scoring, especially in HCC patients, it was used to show disease-free survival and disease-specific survival in patients diagnosed with GC who underwent radical gastrectomy in 2017. The difference between the groups in terms of disease-free survival was significant (p=0.004).[16] Again, in a more recent study conducted in 2020 on GC patients, this time, the ALBI score was evaluated in two different categories with similar formulations but low and high. According to the results obtained from this study, postoperative complication rates were higher in the

Table 2. The Effect of Albumin/Bilirubin Ratio on Survival in Metastatic Gastric Cancer

	β	SH	Wald	SD	p	Exp (β)	%95 Confidence Interval	
							Lover limit	Upper limit
Albumin/ Bilirubin	-0.073	0.099	0.541	1	0.462	0.930	0.765	1.129

A negative value of beta means less risk. The Exp (β) value shows the Hazard Function and the level found important for the model is 93.0% more risky than the reference category. The effect of albumin/bilirubin ratio on survival was not statistically significant (p=0.462).

high ALBI group than in the low ALBI group (p=0.005). At the same time, it was observed that there was worse overall survival in local advanced-stage patients with a high ALBI score (p<0.001). However, it should be emphasized that stage 4 patients were not included in this study.[17]

Like other GIS tumors, GC is closely related to nutritional causes. In patients who are both operated on and inoperable and malnourished due to the mass effect, there is an increase in susceptibility to infections, blood clotting disorders, susceptibility to the fragility in vascular walls, and delay in wound healing.[18] This is also a cause of secondary immunodeficiency. As a result, T-cell-mediated immune response, cytokine production, and lymphocytes' ability to respond appropriately to cytokines are also affected. As a result of immunodeficiency, which is getting weaker, the progression of the tumor also accelerates.[19] The best indicator of these results in peripheral blood can be considered as albumin level.[17,18] The liver is the main region for the synthesis and metabolism of nutrients. At the same time, an abnormal liver function affects the nutritional status of the body. Again, liver function is closely related to chemotherapy tolerance. Elevated bilirubin has also taken its place in routine use in terms of showing prognosis or treatment response in both CP scoring and ALBI scoring. Similarly, bilirubin also acts as an immunomodulator through inhibition of T cell activity.[20] However, ALBI scoring is calculated with logarithmic formula, and patients are evaluated in 3 different categorizations. These reasons make the routine use of the formula complicated.[13] Therefore, the ABR formula was developed considering that it would be more helpful. However, in the survival analysis of our patients diagnosed with metastatic GC, it was observed that ABR did not reach statistical significance as an indicator of survival (p=0.462). However, to achieve more definitive results, studies should be conducted with more patient populations.

Conclusion

The primary purpose of all studies is to obtain disease-specific, inexpensive, and practical formulation. In this study, the prognostic significance of the new index, which was designed by proportioning albumin and bilirubin in metastatic GC patients, was evaluated, but no statistically significant result was obtained. Simple, accessible, and inexpensive tests showing recurrence, treatment response, and prognosis of GC are needed. Studies should be conducted with more significant patient populations to determine the role of ABR in GC.

Acknowledgments

We are grateful to Prof. Dr. Gamze Göksel for their support in conducting the study and accessing the archive data.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Manisa Celal Bayar University Faculty of Medicine (dated 22.03.2021 and numbered E-85252386-050.04.04-49119) and was conducted in accordance with the principles of the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflicts of interest relevant to this article.

Authorship Contributions: Concept – F.E.; Design – F.E.; Supervision – F.E.; Materials – A.P.E.; Data collection &/or processing – F.E.; Analysis and/or interpretation – A.P.E.; Literature search – A.P.E.; Writing – F.E.; Critical review – A.P.E.

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