Comprehensive Analysis of Prognostic Factors in Advanced Gastric Cancer Patients Treated with Chemotherapy

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ABSTRACT

Objective: To evaluate the strongest prognostic factors in advanced gastric cancer.

Study Design: Observational study.

Place and Duration of Study: Department of Medical Oncology, Tekirdag Namik Kemal University, Tekirdag, Turkey, between March 2012 and April 2022.

Methodology: Adult patients with metastatic cancer who had completed at least two months of chemotherapy, without any other comorbidity were included. Using Kaplan-Meier methodology and Cox regression methods, potential prognostic factors were analysed for overall survival. Two different models were created for multivariate analysis by using statistically significant factors in univariate analysis.

Results: The median overall survival in 216 patients was 7.8 months. The univariate analysis showed that body-mass index, performance status, liver metastasis, albumin, gamma-glutamyl transferase, carcinoembryonic antigen, carbohydrate antigen (CA 19-9), neutrophil-lymphocyte ratio (NLR), systemic immune-inflammation index, albumin-to-alkaline phosphatase ratio, sodium-globulin ratio (SGR) prognostic nutritional index (PNI), albumin-bilirubin ratio, and albumin-globulin ratio were associated with survival. In Model 1, which included only laboratory indices, multivariate analyses revealed that NLR (p=0.001), SGR (p=0.025), and PNI (p=0.032) were prognostic for overall survival. In Model 2, established with all parameters, NLR (p=0.003), albumin (p=0.003), performance status (p<0.001), and CA 19-9 (p<0.001) were found to be independent prognostic factors.

Conclusion: Pretreatment NLR, SGR, PNI, albumin, performance status, and CA 19-9 are strong prognostic factors in patients with advanced gastric cancer. These prognostic factors, which are easily accessible in clinical practice, may be utilised as useful tools for clinicians.

Key Words: *Gastric cancer, Prognosis, Overall survival, Chemotherapy, Metastasis, Prognostic biomarkers.*

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INTRODUCTION

Gastric cancer (GC) is one of the most common types of cancer and the leading cause of cancer-related deaths. It has a high prevalence, especially in Central Asian countries. In recent years, the prevalence of gastric cancer has been increasing, especially in young people.[1] In the early-stage, the five-year survival rate is approximately 70% with curative treatment.[2] However, most patients are diagnosed at an inoperable stage as the symptoms emerge late in the course of the disease. Despite the advances in treatment options, the 5-year survival rate remains below 25% and median survival is less than 12 months in advanced GC.[3,4]

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Due to its high prevalence and mortality, there is a great need for analyses to be conducted with advanced gastric cancer patients and research that can guide further studies. It is important to determine prognostic factors in order to improve survival, guide proper treatment strategies, and allow an efficient follow-up. GC has a considerably heterogeneous nature; therefore, even patients in the same stage may vary in their response to treatment and survival duration.[5] Due to this heterogeneous nature of gastric cancer, it also leads to the identification of many prognostic factors for gastric cancer. Previous studies have investigated various factors such as clinicopathological characteristics, inflammatory markers, hemogram parameters, and serum electrolytes.[6,7] However, despite promising developments, the majority of these studies focused on operable gastric cancers and currently there is no consensus on the most appropriate marker for clinical practice.

In this study, the aim was to determine strong prognostic factors by means of a comprehensive prognostic factor analysis in advanced GC patients receiving chemotherapy and to

determine the most appropriate prognostic factors that may guide oncologists in clinical practice.

METHODOLOGY

Data of advanced gastric cancer patients treated at the Department of Medical Oncology, Tekirdag Namik Kemal University, between March 2012 and April 2022 were analysed retrospectively. The Local Ethics Committee approved this study. The patients eligible for inclusion were proven gastric cancer patients aged >18 years having completed at least two months of first-line chemotherapy (platin, taxane, fluorouracil) after the diagnosis; metastasis in other organs confirmed by imaging, absence of concomitant chronic kidney disease, no other current or prior history of malignancy, and absence of active infectious disease, immunosuppressive medication or nutritional support. Patients with oesophageal junction tumour and a known human epidermal growth factor (HER2) receptor pathology were excluded from this study.

Demographic information, clinicopathological characteristics, and serum laboratory parameters measured before the first chemotherapy were obtained from the electronic medical record system. Prognostic nutritional index (PNI), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), the De Ritis ratio (aspartate transaminase (AST)-to-alanine transaminase (ALT) ratio), albumin-to-alkaline phosphatase (ALP) ratio (AAPR), sodium-to-globulin ratio(SGR), albumin-to-bilirubin ratio (ABR), and albumin-to--globulin ratio (AGR) were measured and recorded from laboratory data. Globulin value was calculated using the formula "total protein-serum albumin" and PNI value was calculated using the formula "10 x serum albumin (g/dL)+0.005 x lymphocyte count (per mm^3)".

SPSS statistical software version 24 (SPSS Inc., Chicago, IL) was used to perform statistical analyses. Categorical variables were presented as numbers and percentages, and continuous measurements as mean and standard deviation. Optimal cut-off values for SII, SGR, AAPR, PNI and carbohydrate antigen (CA 19-9) were determined by the receiver operating characteristic (ROC) curve. Median cut-off values were used for the other laboratory parameters. These cut-offs were used to differentiate two groups as low and high. Kaplan-Meier and Cox regression methods were used for overall survival (OS) analysis. The Forward: LR method was used for multivariate analyses. Hazard ratios (HR) were presented with the corresponding 95% confidence intervals (CI). OS was taken into account from the date of death or the last available follow-up. Statistical significance was accepted as $p < 0.05$.

RESULTS

A total of 874 patients were examined. Recurrent disease was identified in 108 patients, 387 patients had early-stage disease, and laboratory data before the first treatment could not be found for 126 patients. Eleven patients had concomitant conditions (such as renal impairment, rheumatologic disease, *etc*.) that could affect laboratory results, and death was attributed to non-cancer causes in 26 patients. After having excluded these patients, the study was completed with 216 patients. The median age was 67 (28–91) years. One hundred and eighty-eight (87%) of the entire patients population died due to cancer-associated reasons. The median OS (mOS) in all patients was 7.8 months (95% CI 6.3-9.3).

According to the ROC-AUC analysis, the ideal cut-off value were 880.84 (AUC: 0.615, 95% CI 0.50-0.73, p=0.05) for SII, 48.81 (AUC: 0.675, 95% CI 0.57-0.78, p=0.003) for SGR, 0.037 (AUC: 0.632, 95% CI 0.52-0.74, p=0.024) for AAPR, 9.82 (AUC: 0.652, 95.5 CI 0.55-0.76, p=0.010) for ABR, 37.11 (AUC: 0.639, 95% CI 0.53-0.75, p=0.018) for PNI, and 34 (AUC: 0.633, 95% CI 0.53-0.74, p=0.023) for CA 19-9. For the OS analysis, median values were considered and the cut-off value was 2.9 for globulin, 138 for sodium, 23 for AST, 17 for ALT, 34 for GGT (gamma-glutamyl transferase), 101 for ALP, 0.46 for total bilirubin, 4 for CEA (carcinoembryonic antigen), 3.06 for NLR, 191.3 for PLR, 1.39 for De-Ritis, and 1.3 for AGR.

Of the patients, 65 (30.1%) were female, and 162 (75%) were over 60 years of age. The most common site of the metastasis was liver (n=122, 56.5%), while 124 (57.4%) patients received only one line of chemotherapy. Table I shows the general features and laboratory data for patients.

In the univariate analysis, gender, age, histological type, peritoneal metastasis, haemoglobin, globulin, sodium, AST, ALT, De Ritis, total bilirubin, ALP, and PLR were not associated with survival. BMI (p=0.030), ECOG PS (p<0.001), liver metastasis (p=0.003), albumin (p=0.003), GGT (p=0.010), CEA (p=0.017), CA 19-9 (p<0.001), NLR (p<0.001), SII (p=0.007), AAPR (p=0.005), SGR (p=0.001), PNI (p=0.001), ABR (p=0.033), and AGR (p=0.007) were found to be significantly predictors for OS in the univariate analysis (Table II).

Using the significant parameters found in the univariate analysis, two different multivariate models were established to accurately assess the predictive factors of OS. Prognostic indices (NLR, SII, AAPR, SGR, PNI, ABR, and AGR) were evaluated in Model 1. In this model, NLR (p=0.001), SGR (HR=0.71, 95% CI 0.52-0.96, p=0.025), and PNI (HR=0.72, 95% CI 0.53-0.97, p=0.032) showed independent predictive properties for OS.

All predictors in the univariate analysis (BMI, ECOG PS, liver metastasis, albumin, GGT, CEA, CA 19-9, NLR, SII, AAPR, SGR, PNI, ABR, and AGR) were evaluated together in Model 2. In this model, NLR (HR=1.61, 95% CI 1.18-2.21, p=0.003), albumin (HR=0.63, 95% CI 0.46-0.86, p=0.003), CA 19-9 (HR=2.04, 95% CI 1.51-2.77, p<0.001), and ECOG PS (HR=3.40, 95% CI 2.20-5.26, p<0.001) exhibited independent predictive properties for OS. Other factors were not found to be independent prognostic in multivariate analysis.

Survival curves were fitted by means of the Kaplan-Meier analysis of prognostic factors identified as independent prognostics in both models. The corresponding mOS values according to

NLR, SGR, PNI, albumin, ECOG PS, and CA 19-9 were 10.0 (95% CI 8.7–11.4) *vs.* 5.9 (95% CI 4.5–7.4) (p<0.001), 10.4 (95% CI 7.7–13.1) *vs.* 6.1 (95% CI 4.4–7.8) (p<0.001), 10.4 (95% CI 9.0–11.8) *vs.* 6.0 (95% CI 4.9–7.2) (p=0.001), 10.0 (95% CI 8.8–11.2) *vs.* 6.0 (95% CI 4.4–7.6) (p=0.003), 9.4 (95% CI 7.9–11.0) *vs.* 3.8 (95% CI 3.0–4.6) (p<0.001), and 10.1 (95% CI 7.0–13.2) *vs.* 6.1 months (95% CI 4.4–7.7, p<0.001), respectively (Figure 1).

Table I: Demographic, clinicopathological characteristics, and blood parameters of the patients.

Clinicopathological characteristics	N	%
Age		
<60	54	25
≥60	162	75
BMI		
< 25	132	62
≥25	84	38
Gender		
Male	151	69.9
Female	65	30.1
ECOG PS		
0-1	29	13.4
≥2	187	86.6
Histological type		
Well, Moderately	71	32.9
Poorly, Mucinous	145	67.1
Peritoneal metastasis		
Yes	74	34.3
No	142	65.7
Liver metastasis		
Yes	122	56.5
No	94	43.5
Lung metastasis		
Yes	11	5.1
No	205	94.9
Chemotherapy lines		
1	124	57.4
≥2	92	42.6
Blood parameters	**Low* (N/%)**	**High* (N/%)**
Albumin	82 (38)	134 (62)
Globulin	114 (52.8)	102 (47.2)
Sodium	129 (59.7)	87 (40.3)
AST	95 (44)	121 (56)
ALT	96 (44.4)	120 (55.6)
GGT	94 (43.5)	122 (56.5)
ALP (IU/L)	94 (43.5)	122 (56.5)
Total biluribine (mg/dl)	95 (44)	121 (56)
Hemoglobin (g/dl)	107 (49.5)	109 (50.5)
CEA (ng/ml)	98 (45.4)	118 (54.6)
CA 19-9 (U/ml)	112 (51.9)	104 (48.1)
NLR	108 (50)	108 (50)
PLR	107 (49.5)	109 (50.5)
SII	88 (40.7)	128 (59.3)
De Ritis	105 (48.6)	111 (51.4)
AAPR	119 (55.1)	97 (44.9)
SGR	112 (51.9)	104 (48.1)
PNI	114 (52.8)	102 (47.2)
ABR	111 (51.4)	105 (48.6)
AGR	110 (50.9)	106 (49.1)

**Low and high values were calculated according to optimal cut-offs.*

DISCUSSION

The present study investigated prognostic factors on overall survival in advanced GC patients receiving chemotherapy. Laboratory parameters recorded at the time of diagnosis and indices created thereof were included in the analyses. The study identified BMI, ECOG PS, liver metastasis, albumin, GGT, CEA, CA 19-9, NLR, SII, AAPR, SGR, PNI, ABR, and AGR as prognostic factors. According to the multivariate models created for this study, NLR, SGR, PNI, albumin, ECOG PS, and CA 19-9 were found to have strong prognostic values for survival.

Table II: Univariate analyses of overall survival (OS).

Variables	Category	Univariate analysis HR (95% CI)	p
Clinicopathologic characters			
Gender	Male / Female	1.09(0.80-1.51)	0.580
Age	<60 / ≥60	1.28(0.90-1.82)	0.164
Histologic type	A/B*	1.36(0.99-1.86)	0.059
ECOG PS	0-1 / ≥2	3.54(2.33-5.39)	<0.001
BMI	<25 / ≥25	0.71(0.53-0.97)	0.030
Peritoneal metastasis	No / Yes	1.01(0.74-1.36)	0.964
Lung metastasis	No / Yes	0.93(0.48-1.81)	0.839
Liver metastasis	No / Yes	1.56(1.16-2.10)	0.003
Chemotherapy lines	1/ ≥ 2	0.76(0.56-1.02)	0.062
Laboratory parameters			
Hemoglobin (g/dl)	<10 / ≥10	0.91(0.68-1.21)	0.504
Albumin (g/dl)	<3.5 / ≥3.5	0.64(0.48-0.86)	0.003
Globulin (g/dl)	<2.9 / ≥2.9	1.31(0.98-1.74)	0.067
Sodium (mmol/L)	<138 / ≥138	0.77(0.58-1.04)	0.092
AST (IU/L)	<23 / ≥23	1.31(0.98-1.76)	0.071
ALT (IU/L)	<17 / ≥17	1.03(0.77-1.38)	0.838
Total biluribine (mg/dl)	<0.46 / ≥0.46	1.13(0.84-1.53)	0.422
GGT (IU/L)	<34 / ≥34	1.49(1.10-2.00)	0.010
ALP (IU/L)	<101 / ≥101	1.29(0.95-1.74)	0.099
CEA (ng/ml)	<4 / ≥4	1.43(1.07-1.91)	0.017
CA 19-9 (U/ml)	<34 / ≥34	1.86(1.38-2.50)	<0.001
Indexes			
NLR	<3.06 / ≥3.06	1.86(1.38-2.49)	<0.001
PLR	<191.3 / ≥191.3	1.27(0.95-1.69)	0.105
SII	<880.8 / ≥880.8	1.51(1.12-2.03)	0.007
De Ritis	<1.39 / ≥1.39	1.27(0.95-1.69)	0.107
AAPR	<0.037 / ≥0.037	0.66(0.49-0.88)	0.005
SGR	<48.81 / ≥48.81	0.60(0.47-0.80)	0.001
PNI	<37.11 / ≥37.11	0.61(0.46-0.82)	0.001
ABR	<9.82 / ≥9.82	0.73 (0.55-0.97)	0.033
AGR	<1.3 / ≥1.3	0.67(0.50-0.89)	0.007

*Significant values are indicated in bold. *A, Well, Moderately; B, Poorly, Mucinous; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio; AAPR, Albumin-ALP ratio; SGR, Sodium-globulin ratio; PNI, Prognostic nutritional index; ABR, Albumin-bilirubin ratio; AGR, Albumin-globulin ratio.*

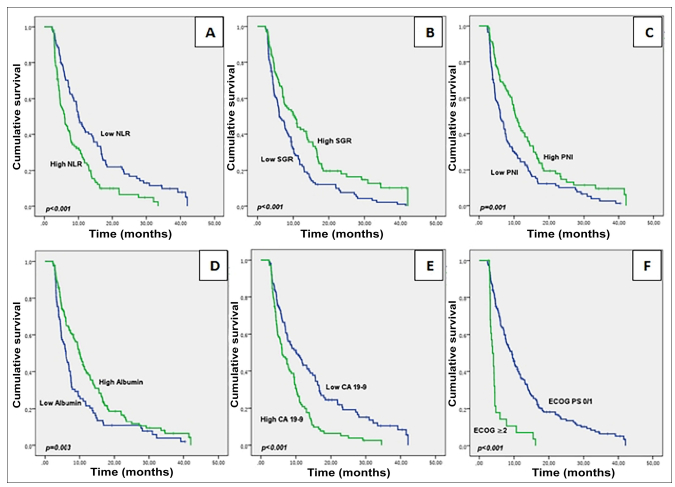

Figure 1: Kaplan Meier survival curves for Overall Survival according to NLR (A), SGR (B), PNI (C), albumin (D), CA 19-9 (E), and ECOG PS (F). NLR, Neutrophil-lymphocyte ratio; SGR, Sodium globulin ratio; PNI, Prognostic nutritional index.

The close relationship between inflammation and cancer is well--known. Uncontrolled inflammation weakens immune responses, thereby causing cancer progression.[8] Recently, an increasing number of studies have focused on the prognostic properties of inflammatory markers in different types of cancer. SII, PLR, and NLR indices, which are derived from hemogram parameters, are considered important indicators of inflammation and immune system functioning.[9,10] Numerous studies have reported that

these indices are of prognostic value in non-metastatic gastric cancer.[11] However, there is only a limited number of studies on metastatic GC. Among these, previous studies by Murakami *et al*. and Zhang *et al*. showed the prognostic value of NLR;[12,13] and Chen *et al*. reported SII as a prognostic factor.[14] In the study by Hirahara *et al*. SII for inflammatory gastric cancers and NLR for non-inflammatory gastric cancers were found to be prognostic factors.[11] The present study showed that SII and NLR were prognostic factors, while PLR was not. In addition, NLR was found to be an independent prognostic factor. There is no consensus in the literature for the most accurate and useful hemogram index. Well-designed studies that can reveal the underlying mechanism are needed to determine the most beneficial factor.

GC is recognised as a common cause of cachexia, which is a result of weight loss and decreased nutrition.[15] Albumin and globulin are sensitive serum proteins whose levels can change due to both inflammation and nutrition-related reasons. Furthermore, gastric cancer is a systemic disease closely related to changes in serum electrolytes.[16,17] The close association of gastric cancer with nausea-vomiting and cachexia further increases the risk of electrolyte disturbances. As a result of all these factors, previous studies have investigated a number of different prognostic factors in patients with advanced GC. Crumley *et al*. reported low albumin levels as a predictor of poor prognosis,[18] Eo *et al*. showed that PNI was associated with survival.[19] Ekinci *et al*. reported that ABR was not prognostic for metastatic GC.[20] Zhang *et al*. analysed SGR in patients with advanced GC and found that low SGR was associated with poor survival.[6] Bozkaya *et al*. reported AGR as a prognostic factor in advanced GC.[21] In a study that included patients with resectable GC, Wang *et al*. determined that AAPR had prognostic value.[22] The present study identified albumin levels, ABR, PNI, SGR, AGR, and AAPR as prognostic factors. Furthermore, albumin, SGR and PNI showed independent prognostic properties in the multivariate analysis. The fact that AGR, AAPR, and ABR did not maintain their predictive feature in the multivariate analysis may be related to the higher proportion of patients with liver metastases in this study compared to previous studies. Because it is known that the liver plays a major role in the production of the parameters included in these indexes.

Performance status is an important prognostic factor in GC, as is the case in many types of cancer.[23] CA 19-9 was reported as a prognostic factor for advanced GC.[24,25] Similarly, ECOG PS and CA 19-9 were found as independent prognostic factors in this study.

This study is not without limitations. Firstly, the study has a single-centre and retrospective design. Secondly, although the patient selection criteria were chosen carefully, there are various circumstances that could influence laboratory markers. One of the strengths of this study is that multiple factors were investigated together in the same patient population, which were reported to be prognostic in the literature or have been analysed for the first time in this study to the best of authors' knowledge.

CONCLUSION

Pretreatment NLR, SGR, PNI, albumin, ECOG PS, and CA 19-9 have been identified as strong prognostic factors in advanced gastric cancer patients receiving chemotherapy. In routine clinical practice, these survival predictors can be used as easily accessible, simple and appropriate prognostic factors to guide the clinician in taking necessary actions. However, multi-centre prospective randomised studies with larger patient populations are warranted to be able to generalise these results.

ETHICAL APPROVAL:

The Local Ethics Committee of the Tekirdag Namik Kemal University, Tekirdag, Turkey approved this study.

PATIENTS' CONSENT:

Since it was designed as a retrospective study, the data were obtained from the electronic medical record system after approval of the Ethics Committee.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

EC: Conceptualisation, data curation, investigation, methodology writing-review, and editing.
YI: Conceptualisation, methodology, visualisation, writing-review, and editing.
OA: Data curation and methodology.
ESS: Writing, investigation, and methodology.
All the authors have approved the final version of the manuscript to be published.

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