

The prognostic role of neutrophil/lymphocyte ratio and monocyte/lymphocyte ratio in advanced stage gastric cancer patients receiving chemotherapy: a single center experience

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Abstract

Objective: Several studies revealed that peripheral blood Neutrophil/Lymphocyte ratio (NLR) and Monocyte/Lymphocyte Ratio (MLR) were prognostic in various cancer types. However, there are no excessive information about the prognostic significance of NLR and MLR in patients with advanced gastric cancer. As a result, we examined whether NLR and/or MLR could be used as a prognostic marker to predict survival outcomes in patients with advanced gastric cancer receiving palliative chemotherapy.

Methods: We retrospectively analyzed 119 patients with gastric cancer receiving chemotherapy. We evaluated the relationship between potential prognostic factors and overall survival (OS) times using the Kaplan-Meier method and Cox regression survival modelling.

Results: The median overall survival of the patients was 6.9 (2.1-41.6) months. In univariate analysis, NLR ($p < 0.001$), ECOG performance status ($p < 0.001$), presence of liver metastases ($p < 0.001$) and presence of peritoneal metastases ($p < 0.001$) were found to be associated with survival. The multivariate survival model showed the high NLR (HR=1.59, 95% CI 1.6-2.40, $p = 0.026$), the patients with ECOG performance score 2-3 (HR=2.91, 95% CI 1.60-5.27, $p < 0.001$), the presence of liver metastasis (HR=2.10, 95% CI 1.35-3.21, $p = 0.001$) and the presence of peritoneal metastases (HR=2.68, 95% CI 1.72-4.17, $p < 0.001$) as independent predictors of survival.

Conclusion: Pretreatment high NLR, ECOG performance status, and presence of liver or peritoneal metastases are powerful prognostic factors in advanced gastric cancer patients. These prognostic factors, which are easily accessible in clinical practice, can be used as helpful tools for clinicians in the management of the disease.

Keywords: Gastric Cancer, Chemotherapy, Survival, Neutrophil-Lymphocyte Ratio, Monocyte-Lymphocyte Ratio

INTRODUCTION

Gastric cancer is one of the most common cancers worldwide (1). Although the incidence of gastric cancer has decreased with the recognition of risk factors such as *Helicobacter pylori*, environmental factors or dietary influences, the annual absolute number of new cases are increasing due to the aging of the world population (2,3). Mortality has been declining in recent years, thanks to advances in gastric cancer management, including improved surgical techniques, early detection tools, and perioperative chemotherapy; however, it is still an important cause of cancer-related deaths (4). Currently, the prognosis of the gastric cancer is primarily based on the TNM staging classification (6). It is thus essential to identify readily available biomarkers that predict the prognosis and help clinicians to implement better treatment strategies. Recently, emerging data has revealed that systemic inflammatory response markers could be used as independent prognostic biomarkers in various tumor types (7,8). Of these markers, the neutrophil/lymphocyte ratio and the monocyte/lymphocyte ratio have been

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identified as promising prognostic markers (9). Studies have shown that inflammatory markers such as NLR and/or MLO are highly reproducible, cost-effective, and widely available (10). In literature, there are studies showing that survival can be predicted by NLR and MLR in early stage or operable, locally advanced gastric cancer patients (11,12,13). In this study, we aimed to investigate the relationship between NLR and MLR before chemotherapy and survival in patients with advanced gastric cancer.

METHODS

In this study, patients who were treated with the diagnosis of pathologically proven gastric cancer between January 2016 and December 2019; were retrospectively analyzed. Patients aged 18 years and older who received at least 2 months of chemotherapy (platinum, taxane, fluorouracil) as for the first-line therapy and who were radiologically considered metastatic were included in the study. Patients with active infection, using immunosuppressive drugs, under nutritional support or those with missing data were excluded from the study.

Data

Patients' demographic data, clinicopathological characteristics and peripheral blood hemogram neutrophil, lymphocyte and monocyte values before chemotherapy were recorded from the hospital electronic record system. NLR was calculated by the neutrophil count divided by the lymphocyte count; MLR was calculated by dividing the number of monocytes by the number of lymphocytes.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences version 26.0; SPSS Inc.Chicago, Illinois, USA) package program was used for statistics. Overall survival (OS) was defined as the time from diagnosis of the disease to the date of death, while for survivors, the time from diagnosis to last follow-up was considered. Optimal cut-off value for NLR was determined by Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC). The median value was used as the cut-off for MLO. With these cut-off values, patients were divided into two groups as "low NLR/ high NLR" and "low MLR/ high MLR" separately for NLR and MLR (Figure 1). Survival analysis was performed using the Kaplan-Meier method and Log-Rank test was used for group comparison. Multivariate analysis of factors affecting survival was created with the Cox proportional-hazards model. "Forward: LR" method was used for multivariate analysis. Statistical significance was accepted as $p < 0.05$.

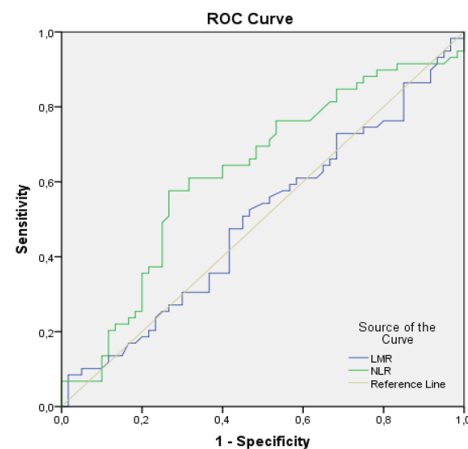


Figure 1. Roc-Curve analysis of NLR for survival

RESULTS

A total of 119 patients were included in our study. The median age of the patients was 68 (37-91). 116 (97.5%) patients died due to cancer-related reasons. The median overall survival of the patients was 6.9 (2.1-41.6) months. General characteristics and laboratory data of the patient population are summarized in Table 1.

Table 1. Demographic, clinical and biochemical characteristics of the patients

| Clinicopathologic Characteristics | n | % |
|-----------------------------------|-----|-------|
| Age | | |
| ≤60 | 32 | 26.9 |
| >60 | 87 | 73.1 |
| BMI | | |
| < 25 | 86 | 72.3 |
| ≥ 25 | 33 | 27.7 |
| Sex | | |
| Male | 82 | 69.9 |
| Female | 37 | 30.1 |
| ECOG PS | | |
| 0-1 | 101 | 84.9 |
| ≥2 | 18 | 15.1 |
| Peritoneal Metastasis | | |
| Yes | 39 | 32.78 |
| No | 80 | 67.22 |
| Liver Metastasis | | |
| Yes | 73 | 61.34 |
| No | 46 | 38.66 |
| NLR | | |
| <3.22 | 69 | 57.98 |
| ≥3.22 | 50 | 42.02 |
| MLR | | |
| ≤2.79 | 60 | 50.42 |
| >2.79 | 59 | 49.58 |

BMI, Body Mass Index; ECOG PS, Eastern Cooperative Oncology Group Performance Score; MLR, Monocyte-Lymphocyte Ratio; NLR, Neutrophil-Lymphocyte Ratio

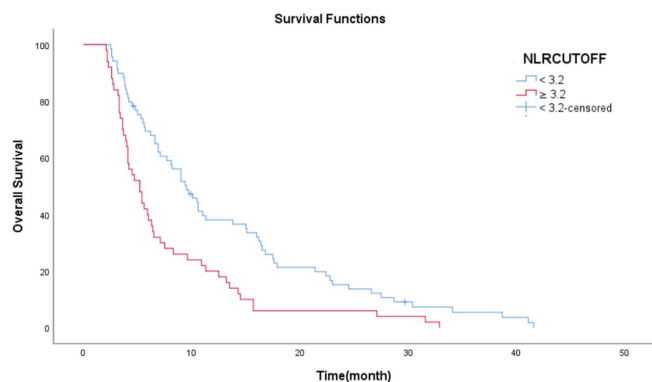


Figure 2. Survival analysis of high NLR versus low NLR

Cut-off values for NLR and MLR

According to the relationship between neutrophil-lymphocyte ratio and survival time, the ideal threshold value that divides patients into two groups was calculated as 3.22 with Roc-Curve (n=119 AUC: 0.625, 0.52-0.73 at 95% confidence interval, P=0.019) (Figure 2). The specificity

(specificity) of this value was 73.3% and the sensitivity (sensitivity) was 69.9%. The ideal cut-off for MLR could not be determined. The median value was accepted for cut-off.

Univariate and Multivariate Survival Analysis

In univariate analysis, high NLR (p<0.001) as well as ECOG performance score (p<0.001), presence of liver metastases (p<0.001), and presence of peritoneal metastases (p<0.001) were significantly associated with overall survival. There was no relationship between age, gender, body mass index, MLR and survival (Table 2).

A multivariate survival model was created with the parameters found to be significant in the univariate analysis (Table 3). According to this model, high NLR (HR=1.59, 95% CI 1.6-2.40, p= 0.026), ECOG performance score (HR=2.91, 95% CI 1.60-5.27, p<0.001), presence of liver metastases (HR=2.10) 95% CI 1.35-3.21, p=0.001) and presence of peritoneal metastases (HR=2.68, 95% CI 1.72-4.17, p<0.001) were determined as independent predictors of survival.

Table 2. Kaplan-Meier analysis of patients' clinical and laboratory parameters

| | n | OS(months) | p value |
|------------------------------|-----|------------|---------|
| Age | | | |
| ≤60 | 32 | 6.4 | 0.452 |
| >60 | 87 | 7.1 | |
| BMI | | | |
| < 25 | 86 | 6.9 | 0.787 |
| ≥ 25 | 33 | 6.6 | |
| Sex | | | |
| Male | 82 | 7.1 | 0.266 |
| Female | 37 | 5.6 | |
| ECOG PS | | | |
| 0-1 | 101 | 0.266 | <0.001 |
| ≥2 | 18 | 0.266 | |
| Peritoneal Metastasis | | | |
| Yes | 39 | 4.8 | <0.001 |
| No | 80 | 8.3 | |
| Liver Metastasis | | | |
| Yes | 73 | 9.7 | <0.001 |
| No | 46 | 6.0 | |
| NLR | | | |
| <3.22 | 69 | 9.5 | <0.001 |
| ≥3.22 | 50 | 5.2 | |
| MLR | | | |
| ≤2.79 | 60 | 6.9 | 0.469 |
| >2.79 | 59 | 6.6 | |

*Since the age variable provides the assumption of normality, the p value was determined according to the independent sample student's t-test, and the p value of the other variables was defined by the chi-square test.

NLR: Neutrophil/lymphocyte ratio, MLR, Monocyte-lymphocyte ratio, OS: Overall survival time, BMI: Body-Mass Index

Table 3. Multivariate cox regression model predicting overall survival

| Variable | HR | (95% CI) | p value |
|--|-------|-------------|---------|
| High NLR (vs. Low NLR) | 1.592 | 1.057-2.398 | 0.026 |
| ECOG PS. 2-3 (vs ECOG PS 0-1) | 2.906 | 1.603-5.267 | <0.001 |
| Presence of liver metastases | 2.080 | 1.346-3.212 | 0.001 |
| Presence of peritoneal metastases | 2.679 | 1.722-4.169 | <0.001 |

HR: Hazard Ratio, NLR: Neutrophil/Lymphocyte Ratio, ECOG PS: ECOG Performance Score

DISCUSSION

In this study, we investigated the prognostic significance of NLR and MLR along with the clinical and laboratory data of 119 patients with advanced gastric cancer. Patients with the high peripheral blood sample NLR before chemotherapy had worse overall survival compared to those with low NLR, whereas high or low MLR did not affect overall survival. Both univariate analysis and multivariate analysis showed that NLR, ECOG performance score, presence of liver metastases or peritoneal metastases can be used as a prognostic marker. In recent years, knowledge of the inflammatory microenvironment of cancer has grown rapidly, and there is increasing interest in the relationship between inflammation and cancer (14). Various indicators investigating this relationship between cancer and inflammation have been researched and developed (15). Albumin-bilirubin index, Nutritional risk score (NRS-2002), NLR, Platelet-Lymphocyte Ratio (PLO), monocyte-lymphocyte ratio (MLR), Gamma-

interferon/Interleukin-4 ratio are among the reported and investigated markers (16-18). There are many studies showing a relationship between NLR and gastric cancer prognosis, however, these studies focused on postoperative survival in patients with early or operable gastric cancer rather than metastatic gastric cancer patients (19-21). In addition, the relationship between NLR and therapeutic response in gastric cancer is important for predicting chemotherapeutic response and prognosis in gastric cancer patients (22). In a study that included advanced gastric cancer patients divided into two groups as high/low by median NLR pre-chemotherapy, Cho, In Rae et al. showed that patients with higher NLR before chemotherapy had shorter survival and disease-free survival (23). In a study of 537 patients with advanced gastric cancer receiving chemotherapy, Zhou, Danyang et al. reported that high NLR and MLR were associated with poor PFS and OS (24). In our study, in accordance with the literature, patients with high NLR before treatment were found to be disadvantaged in terms of survival, but no significant relationship was found between LMO and overall survival.

In a study by Zhao, Guanghui et al. in metastatic gastric cancer patients, high baseline NLR, high platelet-lymphocyte ratio, being older, and having liver or peritoneal metastases were shown to be predictors of overall survival (25). In another study by Chau, Ian et al., investigating the overall survival of 1080 patients with locally advanced or advanced gastric cancer, the presence of peritoneal metastases, the presence of liver metastases before treatment, and worse ECOG performance scores were reported as independent predictors of shorter overall survival (26,27). In the present study, the presence of liver or peritoneal metastases before treatment was associated with shorter survival. In addition, patients with worse performance status were found to be poor prognostic factors consistent with the literature.

The main limitation of this study is that it was a single center and retrospective design. Furthermore, current findings need to be validated in a larger patient population and by performing subgroup analysis with different treatment settings and regimens.

CONCLUSION

As a result, the treatment method in patients with advanced gastric cancer is planned by considering multiple clinical and biochemical factors, including prognosis estimation. Pretreatment high NLR is associated with worse survival in this group of patients; and it is suggested that these biomarkers, with their simplicity and usability, are useful in predicting the prognosis of advanced gastric cancer.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical approval was obtained from Tekirdağ Namık Kemal University Clinical Research Ethical Committee with date 31.05.2022 and number 2022.91.05.18, and Helsinki Declaration rules were followed to conduct this study.

Authorial Contributions

Concept: KK, Design: KK, EŞŞ, Supervising: KK, EŞŞ, Financing and equipment: KK, EŞŞ, Data collection and entry: EŞŞ, Analysis and interpretation: KK, EŞŞ, Literature search: KK

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