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ORIGINAL ARTICLE

# The prognostic value of the change in neutrophil-to-lymphocyte ratio during first-line palliative chemotherapy in patients with metastatic gastric cancer: A retrospective study

Oktay Bozkurt, Sedat Tarik Firat, Ender Dogan, Ramazan Cosar, Mevlude Inanc, Metin Ozkan

Department of Medical Oncology, Erciyes University Faculty of Medicine, Kayseri, Turkey

## Summary

***Purpose:*** *Metastatic gastric cancer (mGC) is linked with worse prognosis, and tools are needed for predicting disease course and chemotherapy response. The value of the change in the neutrophil-to-lymphocyte ratio (NLR) during first-line palliative chemotherapy on the outcomes in patients with mGC is not fully explained. This study aimed to investigate the importance of changes in NLR in predicting disease course and chemotherapy response in mGC.*

***Methods:*** *We retrospectively reviewed 194 patients diagnosed with mGC between August 2005 and November 2016. The NLR was assessed before and after chemotherapy to evaluate its relationship with survival. According to threshold values determined by receiver operating characteristics (ROC) analysis, the NLR was divided into two groups with <2.6 and ≥2.6.*

***Results:*** *Elevated prechemotherapy NLR was significantly correlated with worse overall survival (OS) on univariate analysis (p=0.01). On multivariate analysis, elevated prechemotherapy NLR (HR 1.43, p=0.036) was an independent prognostic element for worse OS, but not for progression-free survival (PFS). Constantly elevated NLR or an increase in NLR after chemotherapy was correlated with poor OS, PFS and chemotherapy response. In the multivariate analysis, constantly elevated NLR was identified to be independent predictor of reduced OS and PFS.*

***Conclusion:*** *NLR change during chemotherapy is a better index than prechemotherapy NLR for predicting survival in patients with mCG.*

***Key words:*** *neutrophils, gastric cancer, marker, prognosis, chemotherapy*

## Introduction

Gastric cancer is the fifth most frequent malignant tumor and one of the common cause of cancer-related death worldwide [1]. Gastric cancer is often diagnosed at an advanced stage [2,3] and has a dismal prognosis, particularly in patients with metastatic disease (mGC) [1,4]. In the palliative treatment of mGC, the dual chemotherapy regimen consisting of platinum and fluoropyrimide with or without a third drug constitutes the cornerstone of treatment and the response rates obtained with this combination therapy are 40-45%. Unfortunately, these response rates in HER2-expressing tumors provide a moderate increase in PFS and OS, which rarely exceed 7 and 12 months, respectively [5]. A randomized phase 3 study showed a significant survival benefit with the addition of transtuzumab (a monoclonal antibody against HER2) to combination chemotherapy with cisplatin and fluoropyrimidine in tumors overexpressing or having amplified HER2 [6]. Drugs targeting different molecules have also been explored, mostly with frustrating results [7,8]. Therefore, the identification of patients who

*Corresponding author:* Oktay Bozkurt, MD. Erciyes University, School of Medicine, M.K. Dedeman Oncology Hospital, Department of Medical Oncology, 38039 Kayseri, Turkey.
Tel: +90 352 2076666/27035, Fax: +90 352 4378659, Email:bozkurt.oktay8@gmail.com
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are likely to benefit from palliative chemotherapy reduces both the cost and side effects associated with an ineffective treatment, as well as improved survival outcomes.

Recently, there has been an argument supporting the role of inflammation in malignant tumor growth and progression [9]. Emerging researches have demonstrated that inflammatory markers such as NLR play substantial roles in the prediction of survival in different malignant neoplasms, including breast, colorectal, ovarian, renal, gastric and bladder cancer [10-15]. The researches focused mainly on pre-treatment systemic inflammatory markers, while the dynamic change of inflammatory markers after treatment was not considered. The post-treatment systemic inflammatory markers change might be a valuable tool to assess prognosis after treatment, because chemotherapy may change the inflammatory response. However, despite changes in systemic inflammatory markers might dynamically reflect the modification of balance between host inflammatory response and immune response against cancer after treatment, their value is not fully understood [16]. The aim of this study was to explore the prognostic impact of the change in NLR over the course of first-line palliative chemotherapy on outcomes in patients with mGC.

## Methods

### Study population

We evaluated 194 patients who received first-line palliative chemotherapy with target agent or not according to HER2 receptor status from August 2005 to November 2016. This study was approved by Erciyes University Medical School ethics committee.

The inclusion criteria were: (a) patients with gastric cancer proven by histopathology, (b) patients who administered first-line chemotherapy, and (c) patients with complete clinical archives including demographic data, pathologic tumor information, therapeutic methods and laboratory data. The exclusion criteria were: (a) patients with clinical confirmation of acute infection, systemic inflammation or other autoimmune disturbances, (b) patients prior taking steroid therapy, (c) patients suffering from hematologic disorders, and (d) patients diagnosed with second malignant tumor arising from different regions.

### Chemotherapy protocol, tumor response and laboratory data

Palliative chemotherapy was administered to all patients after the diagnosis of mGC. Platinum-based chemotherapy (n=168, 85.4%) was administered most often, and DCF (docetaxel, cisplatin and 5-fluorouracil) was the protocol most used. The chemotherapy regimen was chosen from the treating physician. Prechemotherapy blood tests, including complete blood count (CBC) were taken 2 to 24 h before applying chemotherapy. CBCs and blood chemistry (BC) tests were also taken every 8±4 weeks after the start of chemotherapy.

All patients underwent prechemotherapy staging screening with computed tomography of the abdomen and thorax to verify the extent of tumor. Additional imaging methods, such as magnetic resonance imaging, bone scan and positron emission tomography were performed taking into account the patients' symptoms or deemed necessary by the attending physician. Baseline CT scanning of the abdomen and thorax was performed 1-3 weeks before the beginning of chemotherapy, and follow-up imaging tests were implemented every 8±4 weeks after the start of chemotherapy. The Response Evaluation Criteria for Solid Tumors (RECIST) were used to evaluate the radiological response. Disease control rates (DCR) were characterized as the sum of partial response (PR), complete response (CR) and stable disease, while objective response rates (ORR) were characterized as CR or PR. Postchemotherapy blood tests, such as CBC and BC, were performed at the same time as follow-up screenings. No granulocyte colony-stimulating factor was administered during the 2 weeks before blood testing and response evaluation. The NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. ROC curves was used to assess the ideal cutpoint for NLR to predict survival outcomes.

### Statistics

For statistical analyses of the study data, SPSS22 software was used (IBM, United States). The ideal cutpoint for NLR was detected by ROC analysis. OS and PFS were calculated from the date of starting first-line chemotherapy until the date of death or disease progression, respectively. Univariate analyses for OS and PFS were performed using the Kaplan-Meier method with log-rank test. The Cox proportional hazards model was used for the multivariate analyses. The relationship between clinicopathological features and prechemotherapy NLR was calculated with the chi-square test and Wilcoxon test as appropriate. Two-sided tests of statistical significance were used, with $p<0.05$ considered statistically significant.

## Results

The median patient age was 59 years (range: 30-81), and the 194 patients included 129 men (66.5%) and 65 women (33.5%). The most frequent site of metastasis was the liver (43.8%) in 46 patients, followed by the peritoneum (29.4%) in 57 patients, and lymph node (8,8%) in 17 patients. According ROC curve analysis, the NLR was divided into two groups: <2.6 and ≥2.6 (the sensitivity was 60.5% and the specificity 47.1.9%). Baseline characteristics of patients with mGC by prechemotherapy NLR is shown in Table 1.

**Table 1.** Baseline characteristics of patients with mGC by prechemotherapy NLR

| *Characteristics* | *NLR <2.6 n (%)* | *NLR≥2.6 n (%)* | *p value* |
|---|---|---|---|
| Age, years | | | 0.060 |
| ≥65 | 19 (23.8) | 42 (36.8) | |
| <65 | 61 (76.3) | 72 (63.2) | |
| Sex | | | 0.218 |
| Female | 31 (38.8) | 34 (29.8) | |
| Male | 49 (61.3) | 80 (70.2) | |
| ECOG performance status | | | 0.189 |
| 0 | 47 (58.8) | 55 (48.2) | |
| ≥1 | 33 (41.3) | 59 (51.8) | |
| Hemoglobin[a] | | | 0.169 |
| Normal | 33 (41.3) | 35 (30.7) | |
| Anemia | 47 (58.8) | 79 (69.3) | |
| Albumin (g/dL) | | | 0.283 |
| ≥4 | 23 (28.7) | 27 (23.7) | |
| <4 | 53 (66.3) | 85 (74.6) | |
| Absent | 4 (5) | 2 (1.8) | |
| Weight loss | | | 0.892 |
| Yes | 54 (67.5) | 78 (68.4) | |
| No | 26 (32.5) | 36 (31.6) | |
| Peritoneal carcinomatosis | | | 0.429 |
| Yes | 26 (32.5) | 31 (27.2) | |
| No | 54 (67.5) | 83 (72.8) | |
| First-line chemotherapy | | | ≤0.001 |
| First-line chemotherapy | 58 (72.5) | 109 (95.6) | |
| Non-platinum based regimen | 22 (27.5) | 5 (4.4) | |

[a]Lower limits of reference range: men, 13.0 g/dL; women, 11.5 g/dL, EGOG: Eastern Cooperative Oncology Group

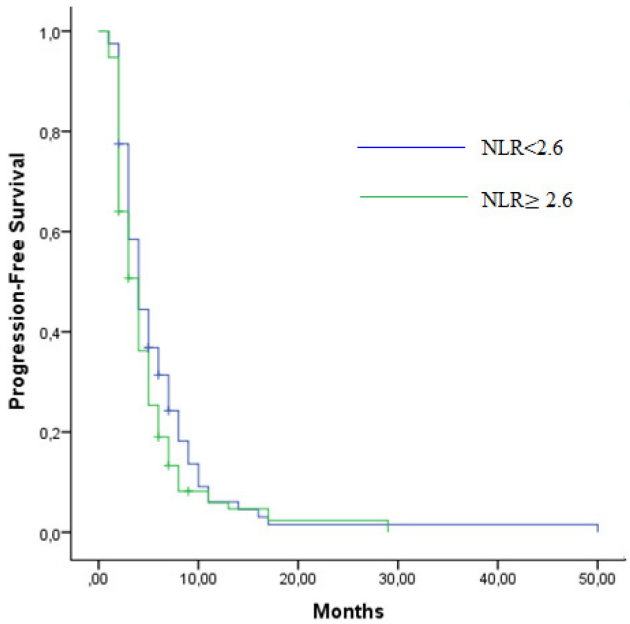


**Figure 1.** Kaplan-Meier curves for PFS according to the prechemotherapy NLR (p=0.10).

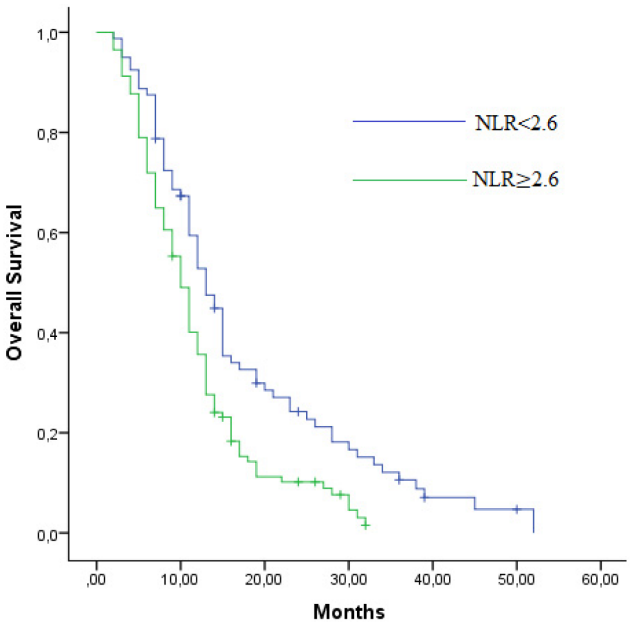


**Figure 2.** Kaplan-Meier curves for OS according to the prechemotherapy NLR (p=0.01).

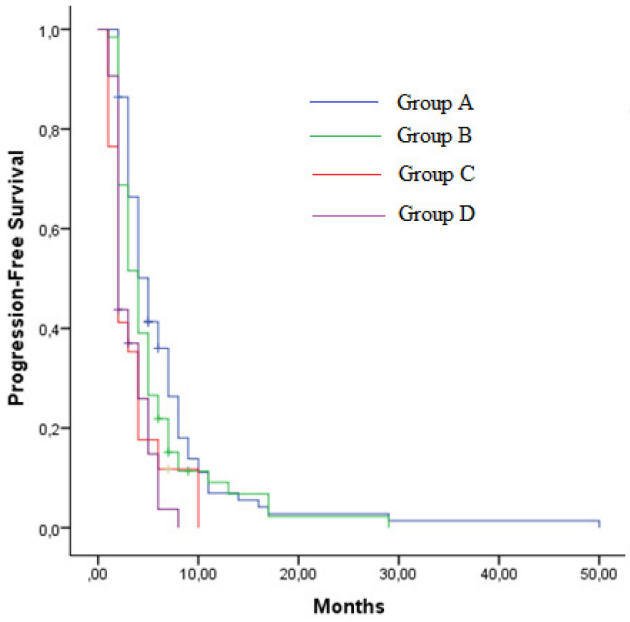


**Figure 3.** Kaplan-Meier curves for PFS according to the change patterns of NLR (p<0.001).

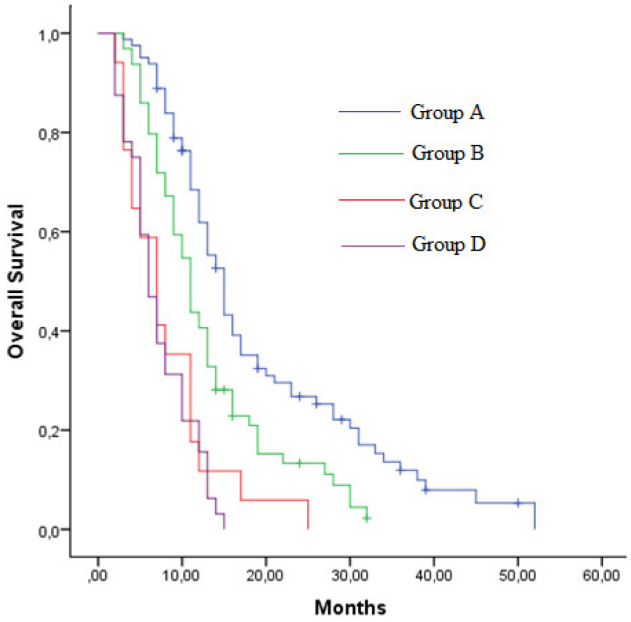


**Figure 4.** Kaplan-Meier curves for OS according to the change patterns of NLR (p<0.001).

**Table 2.** Univariate and multivariate analyses for OS in mGC according to prechemotherapy NLR

| *Variables* | *Univariate* | *Multivariate* | |
|---|---|---|---|
| | *p value* | *HR, 95% CI* | *p value* |
| Age, years | 0.037 | | 0.063 |
| ≤65 | | 1 | |
| >65 | | 0.729 (0.523-1,017) | |
| Sex | 0.126 | | 0.212 |
| Female | | 1 | |
| Male | | 0.790 (0.545-1.144) | |
| Peritoneal carcinomatosis | 0.011 | | 0.015 |
| No | | 1 | |
| Yes | | 1.525 (1.087-2.141) | |
| ECOG performance status | 0.066 | | 0.122 |
| 0 | | 1 | |
| ≥1 | | 0.777 (0.564-1.070) | |
| Hemoglobin[a] | 0.014 | | 0.438 |
| Normal | | 1 | |
| Anemia | | 1.153 (0.804-1.653) | |
| Albumin, g/dL | 0.617 | | 0.454 |
| ≥4 | | 1 | |
| <4 | | 0.872 (0.609-1.248) | |
| Weight loss | 0.918 | | 0.723 |
| Yes | | 1 | |
| No | | 1.062 (0.760-1.486) | |
| Prechemotherapy NLR | 0.001 | | 0.036 |
| Low | | 1 | |
| High | | 1.436 (1.024-2.015) | |

[a]Lower limits of reference range: men, 13.0 g/dL; women, 11.5 g/dL, EGOG: Eastern Cooperative Oncology Group

The importance of clinicopathological variables and prechemotherapy NLR on OS are shown in Table 2. Univariate analyses of OS indicated that detecting peritoneal carcinomatosis (p=0.011), an age of 65 years or older (p=0.037), anemia (p=0.014), and high prechemotherapy NLR (p =0.001) were significantly associated with worse survival. The results of multivariate analysis for OS showed that presence of peritoneal carcinomatosis (HR, 1.52, p=0.044), high prechemotherapy NLR (HR 1.43, p=0.036) were significant independent prognostic factors.

Median PFS was 4 months (95% CI 3.36-4.64) in patients with high NLR, and 4 months (95% CI 3.21-4.78) in patients with low NLR (p=0.10) (Figure 1). Median OS was 10 months (95% CI 8.78-11.2) in patients with high NLR, and 13 months (95% CI 10.7-15.3) in patients with low NLR (p=0.01) (Figure 2).

**Table 3.** Correlation of change patterns in NLR with chemotherapy response

| *Groups* | *ORR (n%)* | *p value* | *DCR (n %)* | *p value* |
|---|---|---|---|---|
| Group A | 30 (37.0) | 0.011 | 51 (63.0) | 0.004 |
| Group B | 19 (29.7) | | 34 (53.1) | |
| Group C | 2 (11.8) | | 6 (35.3) | |
| Group D | 3(9.4) | | 9 (28.1) | |

ORR: objective response rate; DCR: disease control rate; Group A: prechemotherapy low-to-postchemotherapy low; Group B: prechemotherapy high-to-postchemotherapy low; Group C: prechemotherapy low-to-postchemotherapy high; Group D: prechemotherapy high-to-postchemotherapy high.

**Table 4.** Multivariate analysis for PFS and OS in mGC according to the change pattern of NLR

| *Variables* | *PFS* | | *OS* | |
|---|---|---|---|---|
| | *HR, 95% CI* | *p value* | *HR, 95% CI* | *p value* |
| Age, years | | 0.030 | | 0.411 |
| 65< | 1 | | 1 | |
| 65 ≥ | 1.45 (1.03-2.02) | | 1.15 (0.81-1.63) | |
| Sex | | 0.644 | | 0.222 |
| Female | 1 | | 1 | |
| Male | 1.09 (0.75-1.58) | | 0.78 (0.52-1.16) | |
| Peritoneal carcinomatosis | | 0.732 | | 0.101 |
| Yes | 1 | | 1 | |
| No | 0.94 (0.66-1.33) | | 0.74 (0.52-1.05) | |
| ECOG performance status | | 0.569 | | 0.059 |
| 0–1 | 1 | | 1 | |
| ≥2 | 0.91 (0.66-1.25) | | 0.73 (0.53-1.01) | |
| Hemoglobin[a] | | 0.154 | | 0.811 |
| Normal | 1 | | 1 | |
| Anemia | 1.30 (0.90-1.88) | | 1.04 (0.72-1.52) | |
| Albumin, g/dL | | 0.504 | | 0.392 |
| ≥4 | 1 | | 1 | |
| <4 | 0.88 (0.61-1.26) | | 0.85 (0.58-1.23) | |
| Weight loss | | 0.388 | | 0.780 |
| Yes | 1 | | 1 | |
| No | 1.15 (0.83-1.61) | | 1.05 (0.74-1.48) | |
| NLR change pattern | | | | |
| Group A | 1 | | 1 | |
| Group B | 1.18 (0.80-1.72) | 0,394 | 1.57 (1.05-2.35) | 0.028 |
| Group C | 1.82 (1.00-3.31) | 0.047 | 3.18 (1.76-5.73) | <0.001 |
| Group D | 1.98 (1.25-3.16) | 0.004 | 3.75 (2.28-6.14) | p<0.001 |

[a]Lower limits of reference range: men, 13.0 g/dL; women, 11.5 g/dL; EGOG: Eastern Cooperative Oncology Group; Group A: prechemotherapy low-to-postchemotherapy low; Group B: prechemotherapy high-to-postchemotherapy low; Group C: prechemotherapy low-to-postchemotherapy high; Group D: prechemotherapy high-to-postchemotherapy high.

Changes in NLR were divided into prechemotherapy low to postchemotherapy low (group A), prechemotherapy high to postchemotherapy low (group B), prechemotherapy low to postchemotherapy high (group C), prechemotherapy high to postchemotherapy high groups (group D). Median PFS was 5 (95% CI 4.13-5.86) ,4 (95% CI 3.19-4.80), 2 (95% CI 1.33-2.66) and 2 (95% CI 1.63-2.36) months for group A, group B, group C and group D patients, respectively (p<0.001) (Figure 3). Median OS was 15 (95% CI 13.1-16.8), 11 (95% CI 9.44-12.5), 7 (95% CI 4.34-9.65) and 6 (95% CI 4.41-7.58) months for group A, group B, group C and group D patients, respectively (p<0.001) (Figure 4).The ORR (group A, group B, group C and group D were 37%, 29.7%, 11.8 % and 9.4 %, respectively; p=0.006) and DCR (group A, group B, group C and group D were 63%, 53.1%, 35.3% and 28.1%, respectively; p=0.004). These results were significantly diverse, depending on the NLR change pattern (Table 3). In multivariate analysis, groups B, C and D were significantly correlated with worse survival (HR 1.57, p=0.02; HR 3.18, p<0.001 and HR 3.75, p<0.001, respectively) compared to group A. Additionally, group C, D and age 65 years or older were significantly correlated with worse PFS (HR 1.82, p=0.047; HR 1.98, p=0.004 and HR 1.45, p=0.03, respectively) (Table 4).

## Discussion

Gastric cancer is among the malignancies with aggressive behavior. Although current treatments are applied to these patients, survival is not at the desired level. There are no markers that can be used to predict the response to treatment, except for HER-2-expressing tumors. Therefore, the need for predictive and prognostic markers is increasing in patients with mGC.

There is growing evidence that inflammation plays a significant role in the development and progression of malignancies owing to the release of chemokines and cytokines, facilitating proliferation and angiogenesis and suppressing apoptosis [17]. In the tumor microenvironment, neutrophils can promote the progression of cancer by means of production of tumor necrosis factor, interleukin (IL) -6 and IL1. Additionally, neutrophils support seeding to remote organ areas by secretion of VEGF and proteases [18,19]. Lymphocytes perform a important effect in cancer-specific immune response by inducing inhibition of tumor cell proliferatin and migration and cytotoxic cell death. Studies have clarified why enhanced tumor infiltrating lymphocytes (TILs) are related to good prognosis in the tumor micro environment [20,21].

The majority of studies evaluating the relationship between NLR and cancer prognosis were performed in the preoperative phase and a very lower proportion dealt with the metastatic stage [22].

Kim et al reported that permanently high NLR or an increased NLR after chemotherapy was linked with worse survival and chemotherapy response, while lower NLR was correlated with good response and an affirmative prognosis in metastatic colorectal cancer patients [23]. Another study discovered that increased postchemotherapy NLR was correlated with inferior results, and patients who exhibited a change from low prechemotherapy NLR to increased postchemotherapy NLR experienced worse outcomes in mGC. In contrast, a reduction in NLR after chemotherapy was an independent predictor of good prognosis and chemotherapy response in the same study [24]. Kaiser et al indicated that baseline NLR, and the change in NLR from baseline to mid-neoadjuvant chemotherapy (NAC) are independent prognostic parameters for DFS and OS in patients with muscle-invasive bladder cancer (MIBC). Also, they found that a permanently low NLR from baseline to mid-NAC is significantly linked with superior DFS and OS in MIBC patients, compared to a permanently high NLR [25]. Rossi et al evaluated the pretreatment and follow-up NLR after chemotherapy and observed that the high-high group had the worst outcome, where as the low-low group had the best outcome in patients with advanced urothelial cancer [26]. A retrospective analysis identified pretreatment NLR and its dynamic alteration during chemotherapy may be considerable prognostic factor in patients receiving neoadjuvant chemotherapy in advanced ovarian cancer [27].

In the current research, findings of univariate analysis revealed that higher pretreatment NLR was related to worse OS, while multivariate analysis showed that higher pretreatment NLR was an independent prognostic determinant of survival. Constantly elevated NLR or an increase in NLR after chemotherapy was correlated with poor OS, PFS and chemotherapy response. In the multivariate analysis, persistently elevated NLR or a shift to increased NLR was identified to be independent predictor of reduced OS and PFS.

Several clinical studies indicate that chemotherapy often interacts positively with immune checkpoint blockers-based immunotherapy. For example, pembrolizumab has been shown to improve the efficacy of platin/pemetrexed-based chemotherapy in advanced nonsquamous NSCLC [28]. If these chemotherapeutic regimens were only immunosuppressive, their efficacy would not

have been improved by immune checkpoint blockers [29]. Reduction of tumor burden linked with chemotherapy may lead to an increase in the host immune response to cancer as a result of a change in the tumor microenvironment. In the current research, dynamic changes in NLR were statistically correlated with increased mortality rates in patients with mGC and had better statistical power than the prechemotherapy NLR. Therefore, we believe that the change in NLR during treatment may be more accurate in predicting the response to treatment than in the NLR considered before treatment in patients receiving chemotherapy.

This study bears a number of limitations. First limitation is that the sample was relatively small, retrospective, non-randomized and came from a single-center in Turkey, which might erroneously cause the generalization of the results. Second, there is no concurrence on the precise cut-off level for NLR, although previous researches have declared the level of NLR for the prognosis of gastric cancer [16,24,30]. In the current research, NLR cut-off level of 2.6 was chosen using ROC analysis using the method reported in other investigations [16,22,30]. Several previous researchers used a median value of NLR to detect the cut-off level [24,31]. This lack of concurrence on the cut-off level makes NLR is arduous to be used in daily clinical practice. Therefore, we recommend prospective validation of these consequences in clinical researches to evaluate the clinical benefit of NLR in mGC patients prior to routine use of this marker in clinical practice. Third, some possible situations that might affect the NLR value were not excluded in this study.

In conclusion, prechemotherapy NLR levels were correlated with survival outcomes in mGC. NLR change patterns were relate to PFS, OS and chemotherapy response. Constantly elevated NLR or increased postchemotherapy NLR were identified as independent predictors of worse OS and PFS after chemotherapy in mGC. Further large prospective studies should be performed to verify whether NLR change patterns have prognostic and predictive markers in patients with mGC.

## Conflict of interests

The authors declare no conflict of interests.

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