

Research Article

The Effect of Neutrophile Lymphocyte Ratio (NLR) on Disease Free Survival (DFS) and Overall Survival (OS) In Gastric Cancer and its Relation with Clinicopathological Features

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Abstract

Objectives: Neutrophile-lymphocyte ratio (NLR) is an inflammatory marker and has prognostic significance for many cancers. In this study, we evaluated the prognostic value of NLR ratio and its relation with clinicopathological features in gastric cancer.

Methods: A retrospective review of 110 patients who underwent stomach cancer surgery between 2012 and 2014 was performed electronically.

Results: The mean age was 63.7 ± 11.6 years. Seventy percent of the patients were male and 43% underwent total and 57% subtotal gastrectomies. According to TNM staging; 11% were in stage 1, 29% in stage 2 and 60% in stage 3. Metastatic/total lymph node ratio is below 0.3 in 59% of patients. Neutrophil/lymphocyte ratio was found to be greater than 2.5 in 50% of patients and greater than 3 in 33% of patients. The mean NLR value was 3.38 ± 2.7 (1.09-19.1).

Conclusion: In our study, while NLR was not detected as an effective factor on disease-free survival; stage, metastatic lymph node ratio, tumor size and localization were found as independent factors effective on overall survival. As a significant factor in multivariate analysis, NLR reflects the immune status of the organism, not the tumor aggressiveness or stage and it is an independent prognostic factor.

Keywords: Disease free survival (DFS), gastric cancer, neutrophile lymphocyte ratio (NLR), overall survival (OS)

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Despite the decline in its incidence in recent years, gastric cancer remains as a major health problem. According to the data of GLOBACAN 2012 by world health organization, gastric cancer is the 5th most common cancer in the world with about one million new cases per year. It is located in the third place after lung and liver cancers in cancer-related deaths.^[1] Despite improvements in surgery, chemotherapy, and molecular therapy, the outcome of gastric cancer is not encouraging. This is usually due to distant metastasis or local recurrence.^[2] The classical staging system (TNM) is the most important criterion used for predicting prognosis and

determining treatment. However, there is heterogeneity among patients and the prognosis of patients in the same stage might be different.^[3] The most important reason for this is that the TNM staging system focuses on the tumor itself and its biological behavior. However, not only tumor behavior but also the host-response factor is also effective in prognosis.^[4] Systemic inflammatory response in cancer development has been shown to be effective both in tumor-associated factors and in host-related factors.^[5] This occurrence reveals the need to investigate new parameters in determining the true prognosis. Establishment of these pa-

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rameters may contribute to survival, as the treatment protocols might be changed. Neutrophils constitute 62-65% and lymphocytes 30-35% of white blood cells and the normal Neutrophil/Lymphocyte Ratio (NLR) is approximately 2. NLR is obtained by dividing the absolute number of neutrophils by the absolute lymphocyte count. NLR has been proposed as an inflammation-based prognostic marker in some cancer types (breast cancer, renal cell carcinoma, hepatocellular carcinoma, colorectal carcinoma).^[6-8] And also NLR found as an independent risk factor in bladder cancer.^[24]

Although, in some studies, it is claimed that NLR plays a role as a poor prognostic factor in gastric cancer, but there are also other studies that do not support this occurrence.^[9] The purpose of our work is to investigate the effect of NLR as a prognostic factor on total and disease-free survival in gastric cancer patients.

Methods

One hundred and ten stage I-III patients with gastric cancer that had been treated with curative surgery (total/subtotal gastrectomy + D2 lymph node dissection) in between 2012 and 2014 and had undergone regular follow-up were included in the study. Palliative interventions, emergent cases, histologies other than epithelial tumors, the cases with additional organ resection, neoadjuvant treated cases, the cases transfused with blood products during perioperative period and who were unable to complete adjuvant treatments and who could not be followed-up regularly were excluded from the study. Patients were evaluated by medical oncology and radiotherapy specialists after the operation and received the necessary adjuvant treatments. Control examinations were performed once every 3 months for the first 2 years and every 6 months for the next 3 years. Other than the history and physical examination, complete blood count, biochemical assays, and tumor markers (CEA, CA 19-9) were studied at each control visit. Abdominal ultrasonography, computed tomography (CT) or upper GIS endoscopy was performed in accordance with the patients' complaints. Abdominal radiologic imaging was performed once a year in patients with no complaints or examination findings. Age, gender, blood group, type of operation, pathology reports, tumor size and localization, TNM stage and the ratio of pathological lymph nodes to total lymph nodes were recorded. Absolute neutrophil and lymphocyte counts measured from blood samples taken during the last 2 weeks before operation were recorded and neutrophil/lymphocyte ratios were obtained.

Statistical calculations were performed using SPSS for Windows V16.0 (SPSS Inc., Chicago, IL, U.S.A.). Kaplan Meier test was used for survival analyzes and curves. The log-rank test was used in univariate analysis by comparing the factors with the survival curves, and Cox regression analysis was used for significant factors in univariate analysis. The level

of significance was set at $p < 0.05$. Multivariate analysis and univariate analysis were used. The other variables were age, gender, blood group (ARH+, ARH-, BRH+, BRH-, ORH+, ORH-, ABRH+), type of operation, pathology reports, tumor size and localization, TNM stage, Wbc, hemoglobin, neutrophil, lymphocyte, platelets, mpv, rdw, CEA, CA19-9.

Results

The average follow-up period was found to be 42 months in 110 patients included in the study. The median age was 64. Seventy percent of the patients were male and 43% underwent total and 57% subtotal gastrectomies. The tumors were localized at cardia in 24%, corpus in 19% and distal stomach in 56%. Pathological diagnoses were reported as 75% adenocarcinoma, 19% signet cell carcinoma and 3% mucinous carcinoma. In 60% of the patients, the tumor size was found to be larger than 4 cm and according to TNM staging; 11% were in stage 1, 29% in stage 2 and 60% in stage 3. Metastatic/total lymph node ratio is below 0.3 in 59% of patients. Neutrophil/lymphocyte ratio was found to be greater than 2.5 in 50% of patients and greater than 3 in 33% of patients. The mean NLR value was 3.38 ± 2.7 (1.09-19.1). The general characteristics of the patients are shown in Table 1. Age, gender, tumor size, localization, surgical type, histo-

Table 1. General characteristics of the patients

	n	(%)
Age		
<50	49	45
≥50	61	55
Gender		
Female	33	30
Male	77	70
Surgery Type		
Subtotal gastrectomy	63	57
Total gastrectomy	47	43
Histology		
Adeno carcinoma	83	75
Signet cell carcinoma	21	19
Mucinous	3	2.7
Localization		
Cardia	26	24
Corpus	21	19
Antrum	61	56
Stage		
I	12	11
II	32	29
III	66	60
Metastatic/total lymph nodes		
<0.3	65	59
≥0.3	45	41
NLR		
<3	73	66
≥3	37	34

logical type, blood group, NLR, metastatic lymph node ratio were not found as effective factors in univariate analysis. The stage of the disease was the only factor effective on disease-free survival in univariate and multivariate analyzes. Disease-free survival was significantly shorter in patients with stage 3 in comparison with stages 1 and 2 (Table 2). Factors that significantly shorten survival in univariate analyzes were the size of the tumor greater than 4 cm, subtotal gastrectomy performed, age greater than 70, tumors located in proximal stomach, stage of the disease, metastatic lymph node ratio greater than 0.3 and NLR greater than 3. In the multivariate analysis, the type of surgery and age were not found to be significant factors. The factors effective on overall survival in multivariate analyzes are shown in Table 3.

While the significant effect of NLR below 3 was not shown, the values greater than 3 were effective on overall survival. (p:0.04, median survival: 20&35.3 month) (Fig. 1).

Table 2. The factors effective on Disease-Free Survival

	DFS (months)	p (univariate analysis)	p (multivariate analysis)
Stage			
I	40±4	0.08	0.01
II	37±2.5		
III	28±2.4		
Type of operation			
Subtotal	33±4	0.2	
Total	37±6		
Age			
<50	32±2	0.3	
≥50	38±6		
Gender			
Female	34±6	0.1	
Male	35±1		
Histology			
Adeno carcinoma	34±2.5	0.2	
Signetcell carcinoma	32±2		
Mucinous	35±4		
Localization			
Cardia	32±3	0.2	
Corpus	35±2		
Antrum	34±4		
Metastatic/total lymphnodes			
<0.3	32±6	0.3	
≥0.3	37±8		
NLR			
<3	34±6	0.4	
≥3	36±9		

Table 3. The factors effective on Overall survival (multivariate analysis)

	OS (months)	OR	95% CI	p
Stage				
I	51.8±6.5	9.7	3.89-6.46	0.001
II	38.4±4.3			
III	23±2.6			
Localization				
Cardia	19.9±3.9	6.4	1.21-2.77	0.016
Corpus	27±3.3			
Antrum	37±3.5			
LN ratio				
<0.3	35.3±3	4.1	1.43-2.56	0.04
≥0.3	20±2.8			
Tumor size				
<4 cm	41±3.9	5.1	1.93-3.04	0.002
≥4 cm	24.8±2.8			
NLR				
<3	35.3±3	3.9	1.43-2.56	0.04
≥3	20±2.8			

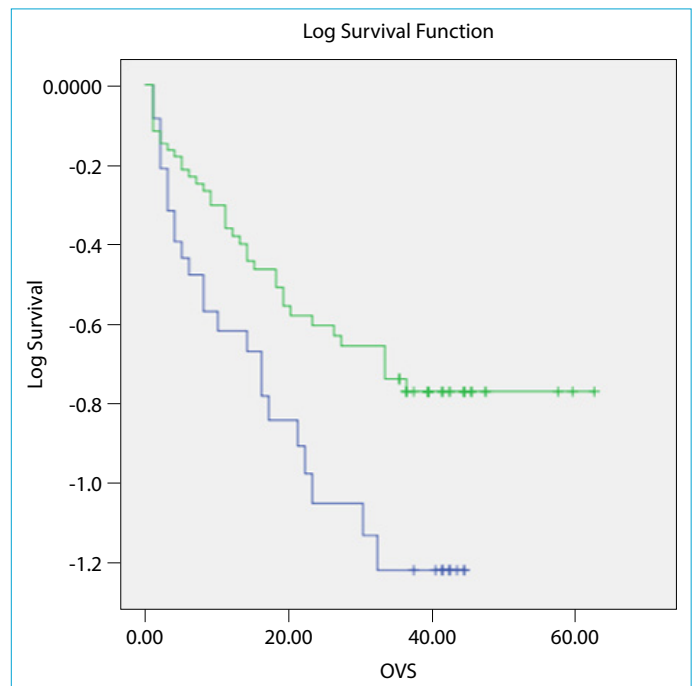


Figure 1. The effect of NLR on survival (month). 0: NLR value below 3, 1: NLR value greater than 3.

Discussion

Locoregional spread and biological characteristics of tumors are often used as predictive and prognostic markers. TNM staging is considered to be the most important prognostic factor in gastric cancer but it is known that tumors at the same stage and with similar biological characteristics can exhibit different clinical course. The use of immunologic and histological biomarkers in gastric cancer is ex-

pensive and limited. Markers like CEA, Human Epithelial Growth Factor Receptor-2 (HER2), p53 should be studied either in the tissue or the relationship between their levels and prognosis is not reliable. The degree of interaction between the tumor and the host, the level of inflammation produced by the tumor and the cellular and humoral response of the organism might be predictive and prognostic markers. Studies on the chronic inflammatory effect of gastric cancer have been previously reported in the literature.^[10] Tissue trauma secondary to tumor, hypoxia, and tissue necrosis are thought to be in the basis of this inflammatory effect.^[11] There are reports that non-steroidal anti-inflammatory drugs are protective against stomach cancer progression.^[12] *Helicobacter pylori* infection is another accusation in this regard.^[13] Neuroendocrinological and hematopoietic changes triggered by inflammation might increase tumor proliferation by suppressing immunity.^[14] At the core of this mechanism, there is increase in neutrophil count and decrease in lymphocyte count. It is known that neutrophils contribute to tumor progression by playing a role as angiogenetic and growth factor. Besides, neutrophils cause matrix metalloproteinase secretion from tumor cells, leading to an increase in proinflammatory cytokines and chemokines which plays a role in tumor progression.^[15] Reactive oxygen radicals resulting from neutrophil elevation reduce the barrier effect of the extracellular matrix and activated nuclear factors (like κ -B and STAT3) inhibit the apoptosis of tumor cells. Increased neutrophil levels suppress cytolytic activities of active T lymphocytes which are the cells that recognize tumor cells and kill them. Despite these effects of neutrophils favoring tumor progression, lymphocytes fight against the tumor by regulating antitumor immunity and cytotoxic tumor cell death.^[16] In this sense, NLR increase can be used as an indicator of increased systemic inflammation in the organism and decreased immunoreactivity. Although absolute neutrophil and lymphocyte values are influenced by physiological and pathological factors, NLR is usually stable and gives reliable results. In single center and retrospective studies, NLR has been shown to be an independent prognostic factor affecting survival. In a series of 601 patients with a mean follow-up of 49 months by Kim et al.,^[17] NLR with disease stage and age was determined as an effective prognostic factor for overall survival. In our study was not determined as a prognostic factor. In another series of 1030 patients with an average follow-up of 30 months, the rate of metastatic/excised lymph node in addition to NLR and disease stage appears to be a significant factor.^[18] In our study only stage is determined as a prognostic factor for DFS. On the other hand NLR (>3), tumor size (>4), LN ratio, localization and stage are determined as a prognostic factor for OS (Table 2, 3).

In a series of 291 patients reported from China, while 5-year survival was 17% in patients with high NLR, it was 43.6% ($p < 0.001$) in patients with low NLR.^[19] In a metaanalysis of 3709 patients from nine studies, NLR was found to be a factor for overall survival in patients with curative resection and disease-free survival in patients with palliative resection.^[20] In these studies, the cut-off values for the NLR range from 2-5.^[21] These values were obtained from median values, the values at 75 percentile, or by comparing the p values in the Kaplan-Meier test. In our study, the results were obtained by comparing the p values in the Kaplan-Meier test and the values above 3 were considered as high NLR values. In a meta-analysis by Sun et al.^[22] involving 19 studies and 5431 patients with cut-off values ranging from 1.4 to 5, meta-regression and subgroup analyzes (increasing values in quarter values) were used to find the ideal cut-off value. Accordingly, it was seen that the statistical results in studies with a cut-off value of 3 were more stable and close results. It was seen that, when the cut-off value is 3-4, the statistical values are reliable and no significant results are obtained in studies with cut-off values 5 and above. Also in this meta-analysis, while NLR was found to be an effective factor for overall, disease-free and progression-free survival, NLR was found to increase in direct proportion with the disease stage. In our study, while NLR was not detected as an effective factor on disease-free survival; stage, metastatic lymph node ratio, tumor size and localization were found as independent factors effective on overall survival. As a significant factor in multivariate analysis, NLR reflects the immune status of the organism, not the tumor aggressiveness or stage and it is an independent prognostic factor. The relation between tumor and inflammation may contribute to the development of different therapeutic targets in the future. Antiinflammatory drugs, immunotherapeutic vaccination to increase the efficacy of lymphocytes are being investigated in a protective and therapeutic way.^[23]

Our study has some limitation. First; the study is not multicentric study. The results are from only one center. Second; The number of patients are not enough, but beginning of the study we had 400 patients. Palliative interventions, emergent cases, histologies other than epithelial tumors, the cases with additional organ resection, neoadjuvant treated cases, the cases transfused with blood products during perioperative period and who were unable to complete adjuvant treatments and who could not be followed-up regularly were excluded from the study. The end we can reach only 110 patients's all of the record. Third; It is retrospective study. With the result of extensive prospective studies, simple, fast and cheap measurement of NLR may become a routine used marker in gastric cancer with aggressive disease progression, follow-up and treatment decision.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee (AOH-12.11.2015/7).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.A.U, L.D; Design – M.A.U, L.D.; Supervision – B.A, N.K; Materials – M.A.U, B.A; Data collection &/or processing – M.A.U, B.A, N.K; Analysis and/or interpretation – M.A.U, B.A; Literature search – M.A.U, N.K; Writing – M.A.U, L.D; Critical review – M.A.U, L.D.

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