

## Original Article



# Collective neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio symbolizes a new prognostic factor in the survival of gastric cancer patients

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## Abstract

**Background and aims:** Due to the high prevalence of gastric cancer and the lack of appropriate prognostic factors, most patients are diagnosed at advanced stages of the disease. Therefore, this study aimed to investigate the relationship between two prognostic factors: neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) to patient survival in gastric cancer patients diagnosed before surgery.

**Methods:** This retrospective study was performed on all gastric cancer patients referred to Kashani Hospital in Shahrekord during 2011-2016. Demographic and biological variables such as NLR and PLR were evaluated. Patient survival was calculated by subtracting the date of disease diagnosis (using endoscopy) from the date of death, and data were analyzed by SPSS version 16.

**Results:** In 100 studied patients, the mean age of patients was  $63.79 \pm 15.03$  (range: 10-92) years. 76% of patients were male and the rest were female. The duration of chronic gastrointestinal disease before cancer diagnosis ranged from one year to 12 years (mean:  $3.3 \pm 2.06$  years). The mean values of inflammatory markers for NLR were  $3.37 \pm 2.78$ , and the mean PLR was  $147.13 \pm 78.93$ . Patient survival after surgery until death or last follow-up ranged from 0.47 to 63.1 months (mean:  $18.29 \pm 13.53$  months). The mean survival in the survived and dead patients was  $16.89 \pm 11.44$  months and  $18.66 \pm 14.07$  months, respectively. Only NLR had a significant effect on survival ( $P < 0.001$ ) and PLR had no significant effect on survival ( $P = 0.646$ ).

**Conclusion:** With the increase of NLR by one point, the hazard rate of gastric cancer patients after surgery increased by 19%. In fact, the survival rate of gastric cancer patients after surgery decreased significantly with increasing NLR.

**Keywords:** Gastric cancer, Neutrophil, Lymphocyte, Platelet, Survival

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## Introduction

Gastric cancer is one of the leading causes of cancer deaths worldwide. Over a million cases of gastric cancer are diagnosed worldwide each year. Gastric cancer is the fifth leading cancer worldwide and the third leading cause of cancer deaths with an estimate of approximately 783 000 deaths in 2018 (1). About 75% of new cases of this cancer occur in developing countries. In Iran, more than 50 000 new cases of cancer are reported each year (2). Several factors contribute to cancer. Chronic inflammatory conditions caused by genetic mutations, autoimmune diseases, and exposure to environmental factors can increase the risk of developing cancer. Previous studies have demonstrated the association of inflammation and inflammatory reactions with atherosclerosis and thrombosis as well as with heart disease in renal disease patients (3-5). Regarding the association between these factors and cancer, epidemiological studies have indicated that more than 25% of cancer deaths are due to chronic inflammation (6). Numerous studies evidenced that

inflammation leads to the continuation and progression of cancer as well as complete changes in malignancies such as alterations in tumor tissue status, angiogenesis, and metastasis, preventing and suppressing the anti-cancer immune response (7). Although the systemic inflammatory response activity involves the body's various organs, the most important parameter to measure inflammation is the counts of white blood cells and acute-phase proteins. Specifically, white blood cell counts such as neutrophils, lymphocytes, and platelets, blood C-reactive protein (CRP) levels, and albumin as well as a neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been used as inflammatory parameters (3). There are numerous reports that a high density of neutrophils may stimulate tumor growth and metastasis and impair the immune system's antitumor response by suppressing lymphocytes. These observations suggest that high NLR in the peripheral blood of cancer patients may lead to tumor progression (8-10). However, little is known about the importance of NLR for the diagnosis of

gastric cancer (11,12). Thrombocytosis occurs due to the stimulation of megakaryocytes by inflammatory cytokines, and a high platelet count is known as an inflammatory marker. High platelet count is another parameter that helps predict patients' prognosis. Increased PLR has been reported as an independent factor in decreasing the life expectancy of patients with colon and pancreatic cancer (13,14). Neutrophils, however, are a stronger factor in inflammation and survival in cancer patients compared to thrombocytosis (15). Given the systemic nature of gastric cancer, poor prognosis, treatment despite surgery, radiotherapy, and chemotherapy, information about the diagnostic factors that predict the course of the disease is highly effective in adopting better treatments. Although the incidence of this cancer appears to be decreasing, due to the slow nature of the disease, it is extremely difficult to diagnose it, so nearly 50% of the cases are diagnosed in the advanced stages in Iran, and 5-year survival is extremely low (16,17). In Chaharmahal and Bakhtiari province, gastric cancer is highly prevalent. Knowledge about the patient's diagnostic factors makes the planning of treatment for patients more accurate and helps to use the standard treatments of choice for these patients. Given that NLR and PLR in many cancers are predictors of disease progression, invasion, and even lower treatment response, these measures need to be evaluated in gastric cancer patients so that their association with the disease prognosis and patient survival will be established. Therefore, the present study aimed to investigate the relationship of two prognostic factors NLR and PLR with patient survival in gastric cancer patients diagnosed before surgery.

### Materials and Methods

This is a retrospective study. All patients referred to Kashani Hospital from 21 March 2011 to 19 March 2016 for the treatment of gastric cancer and filed in the hospital were retrospectively studied. Patients whose disease was at a treatable stage were included. The exclusion criteria included patients suffering from more diseases and malignancies and having underlying systemic diseases such as diabetes and infectious comorbidities. To determine the stage of the disease, the Staging System and the American Joint Committee on Cancer (AJCC Staging Manual) method were used as follows:

- Early stage: Mucosal and submucosal involvement without the involvement of local lymph nodes (T1, T2, N0)
- Locally advanced stage (T3, T4, N+): Gastric metastasis with any distant metastasis (M1)

The survival duration of patients after surgery was evaluated. The NLR and PLR were calculated in patients undergoing surgery before the surgery. The correlation between these ratios and postoperative patient survival was investigated. The studied variables were of demographic and biological types. Demographic variables included the patient's age at diagnosis, gender, and place of residence.

Biological variables included the history of chronic gastrointestinal disease, the history of cancer in close or otherwise relatives, NLR, PLR, tobacco smoking, the type of treatment done, the degree of tumor differentiation, disease progression, type of histopathology, symptoms of the disease at diagnosis, and literacy. The data were collected from the medical records of patients and the latest physical conditions of the patients were investigated by telephone contact and registered in the prepared checklists. Patient survival was calculated by subtracting the date at diagnosis (using endoscopy) from the date at being censored and expressed in a month. In this study, surviving patients upon the completion of the study and missing persons at follow-up were censored, and all those who died during follow-up of death were registered. Data were analyzed using version 16 of SPSS software. Kaplan-Meier estimator was employed to evaluate cumulative survival rate, Cox regression model was used to compare survival rates, and factors affecting survival were considered at  $P < 0.05$  significance level.

### Results

A total of 100 gastric cancer patients who had undergone surgery were enrolled in the study (Figure 1). The age range of the patients was 10-92 (mean:  $63.79 \pm 15.03$ ) years, and 76 (76%) and 24 (24%) patients were male and female, respectively. Other characteristics of patients such as education level, place of residence, smoking status, the duration of being a smoker, the presence of gastrointestinal disease, and the duration of chronic gastrointestinal disease are listed in Table 1. The pathology test results confirmed the presence of a cancerous tumor for 99 (99%) patients with only one negative pathology test result. Furthermore, 5% of patients had no gastrointestinal disease, while 46% had gastrointestinal disease. The longest duration of the disease was four years ( $n=9$ ), followed by 3 years ( $n=15$ ) and 2 years ( $n=10$ ). The duration of chronic gastrointestinal disease before cancer diagnosis ranged from one year to 12 years (mean:  $3.3 \pm 2.06$  years). Table 2 presents the mean values of inflammatory markers

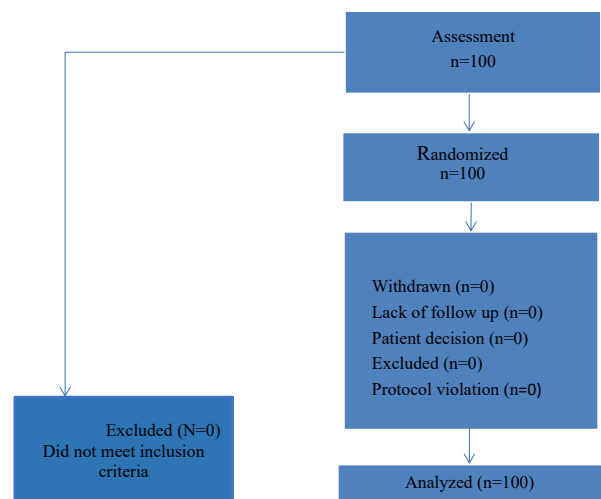


Figure 1. Consort Diagram of Included Population

in which the mean NLR was  $3.37 \pm 2.78$ , and the mean PLR was  $147.13 \pm 78.93$ . Moreover, patient survival after surgery until death or last follow-up ranged from 0.47 to 63.1 months (mean:  $18.29 \pm 13.53$  months). The mean survival in the survived and dead patients was  $16.89 \pm 11.44$  months and  $18.66 \pm 14.07$  months, respectively. Figure 2 illustrates the Kaplan-Meier survival function for our patients, and Table 3 presents the estimation of survival time by the Kaplan-Meier method. The Spearman correlation coefficient ( $r$ ) between NLR and PLR was 0.711 ( $P < 0.001$ ), indicating a significant direct correlation between the two indices. Using the univariate Cox proportional hazard model, both NLR and PLR had a significant effect on survival time. Using multiple Cox proportional hazard model, based on the backward stepwise (likelihood ratio) method, from the variables of age, gender, smoking, duration of smoking, education, place of residence, presence of gastrointestinal disease, PLR, and NLR, only NLR remained in the model (Table 4). The results indicated that in the presence of NLR, the variable of PLR has no effect on survival. In other words, the main variable affecting the survival of patients was NLR. With the increase of NLR by one point, the hazard rate of gastric cancer patients after surgery increased by 19%. More clearly, the survival rate of gastric cancer patients after surgery decreased significantly with increasing NLR. Furthermore, the Cox regression model showed no association between the survival of patients and age, gender, smoking, duration of smoking,

education, place of residence, presence of gastrointestinal disease, and PLR.

**Discussion**

Systemic inflammatory response activity in a variety of conditions, including cancer, can affect different organs of the body. The most important parameter to measure inflammation is the counts of white blood cells and acute-phase proteins. Specifically, white blood cell count such as neutrophils, lymphocytes, and platelets, blood CRP levels, albumin, NLR, and PLR have been used as inflammation parameters (3). The present study investigated the relationship of two prognostic factors (i.e., NLR and PLR) on survival in gastric cancer patients diagnosed before surgery in Shahrekord. The mean age of the studied patients was  $63.79 \pm 15.03$  (range: 10-92) years. Moreover, 76% of patients were male, and the rest were female. In the study by Biglarian et al on postoperative survival in patients with gastric cancer, 71.6% of patients were reported to be male with a mean age of 59.39 years, and the rest (28.6%) were female with a mean age of 56.22 years (18). In the study by Moghimi et al entitled “Modeling Survival Analysis Using Cox Model in Gastric Cancer Patients”, 68.6% of patients were male, and the mean age of the patients was 58.4 years (19). The results of the present study are consistent with the above-mentioned studies regarding gender and age distribution in gastric cancer patients. In the study by Biglarian et al, the mean and median survival of patients with gastric cancer were 32.56 and 28.3 months, respectively, and one, two, three, four, and five-year survival rates were reported to be 0.78, 0.53, 0.40, 0.32, and 0.15, respectively. Cox proportional hazard displayed that age at diagnosis, family history, and tumor size are significantly correlated with patients’ longevity (18). In the present study, the Cox regression model showed no relationship between age, gender, smoking, education, place of residence,

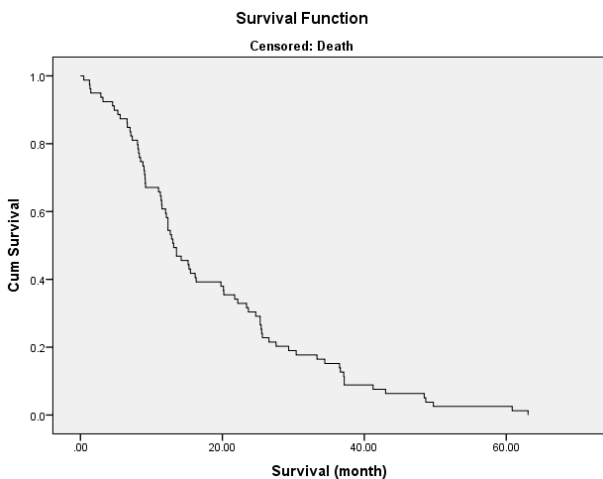


Figure 2. The Kaplan-Meier Survival Function for Gastric Cancer

Table 1. Some characteristics of gastric cancer patients

Variable	
Age (y), Mean $\pm$ SD	63.79 $\pm$ 15.03
Smoking duration (y), Mean $\pm$ SD	14.85 $\pm$ 15.17
Gastrointestinal disease duration (y), Mean $\pm$ SD	1.45 $\pm$ 1.90
Gastrointestinal disease presence, No. (%)	46 (46)
Gender (male), No. (%)	76 (76)
Place of residence (city), No. (%)	47 (47)
Education (Diploma and above), No. (%)	79 (79)

Note. SD: Standard deviation.

Table 2. Inflammatory markers of gastric cancer patients

Marker	Minimum	Maximum	Mean $\pm$ SD
NLR	0.58	16.80	3.37 $\pm$ 2.78
PLR	42.00	500.00	147.13 $\pm$ 78.93

Note. SD: Standard deviation; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

Table 3. Kaplan-Meier estimate of mean and median of survival of gastric cancer patients

Statistical Index	Estimate	SD	95% CI
Mean (month)	18.66	1.58	(15.55 - 21.76)
Median (month)	13.13	1.24	(10.71 - 15.56)

Note. SD: Standard deviation; CI: Confidence interval.

Table 4. The results of Cox proportional hazard model regarding gastric cancer survival

Variable	Coefficient	Standard error	P value	Hazard ratio	95% CI
NLR	0.177	0.035	<0.001	1.19	(1.12 - 1.28)

Note. CI: Confidence interval; NLR: Neutrophil-to-lymphocyte ratio.

duration of chronic gastrointestinal disease, and survival of patients. The mean NLR and PLR were  $3.37 \pm 2.78$  and  $147.13 \pm 78.93$ , respectively. Additionally, the Spearman correlation coefficient ( $r$ ) between NLR and PLR was 0.711 ( $P < 0.001$ ), indicating a significant direct correlation between the two indices. In evaluating the factors affecting survival in patients in the univariate model, the Cox proportional hazard of both NLR and PLR was found to have a significant effect on survival. In the present study, 54% of the studied patients had no gastrointestinal disease, while 46% had gastrointestinal disease. The longest duration of the disease was four years ( $n=9$ ), followed by 3 years ( $n=15$ ) and 2 years ( $n=10$ ). Moreover, patient survival after surgery until death or last follow-up ranged from 0.47 to 63.1 months (mean:  $18.29 \pm 13.53$  months). The mean survival in the survived and dead patients was  $16.89 \pm 11.44$  months and  $18.66 \pm 14.07$  months, respectively. After the inclusion of both NLR and PLR, only NLR was found to have a significant effect on patient survival. The results also indicated that in the presence of NLR, PLR does not affect survival. In other words, the main variable affecting the survival of patients was NLR. With the increase of NLR by one point, the hazard rate of gastric cancer patients after surgery increased by 19%; that is, with an increase in NLR, the survival rate of gastric cancer patients after surgery significantly decreased. Various studies have reported that NLR in patients with gastric cancer is prognostically valuable before surgery, and higher preoperative NLR, as a strong independent factor, is associated with poorer prognosis in gastric cancer patients (15,20). Other studies have also reported that comparably higher NLR is associated with lower survival in patients with malignant pleural mesothelioma (21). There are many reports that a high density of neutrophils may stimulate tumor growth and metastasis and impair the immune system's antitumor response by suppressing lymphocytes. These observations suggest that high NLR in the peripheral blood of cancer patients may lead to tumor progression (8-10). Regarding studies on the prognostic importance of PLR in cancer patients, Smith et al in a study on patients with pancreatic adenocarcinoma reported that the PLR ratio is prognostically important before surgery and is a more reliable marker for the prognosis of cancer compared to lymphocyte count alone (13). Gu et al also reported that a high PLR is significantly associated with overall survival but not with disease-free survival. High PLR also significantly predicted poor and low overall survival in whites, chemotherapy recipients, and patients with advanced cancer. In addition, the PLR over 160 was prognostically appropriate. High PLR was also associated with lymph node metastasis and carcinoembryonic antigen levels in gastric cancer (22). In other studies, increased PLR has been reported as an independent factor for the reduced longevity of patients with colon and pancreatic cancer (13,23). However, a study by Matowicka-Karna et al showed that gastric cancer progression is associated with a decrease in the

levels of interleukin-6 (IL-6) and interleukin-23 (IL-23) but is not associated with platelet count or morphological features (24). Accordingly, it is suggested to investigate the relationship between the levels of the two ILs and NLR and PLR in terms of survival in gastric cancer patients in additional studies. Dogan et al reported that in patients with metastatic gastric cancer,  $PLR > 160$  or  $NLR \geq 2.5$  is significantly associated with poorer survival in these patients (25). He et al also comparatively studied NLR and PLR and reported that NLR is more efficient than PLR as a prognostic marker for colon cancer (26). The results of the present study also indicated that NLR, as compared to PLR, is the main factor associated with the survival of gastric cancer patients. Therefore, according to the results of this study, the main variable affecting the survival of gastric cancer patients is NLR which can be used as a prognostic factor affecting the survival of these patients.

### Conclusion

The present results indicated that PLR has no effect on survival in the presence of NLR. The main variable affecting the survival of patients was NLR. With the increase in NLR by one point, the hazard rate of gastric cancer patients after surgery increased by 19%. In other words, the survival rate of gastric cancer patients after surgery decreased significantly with increasing NLR.

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### Authors' Contribution

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**Data curation:** Sareh Mohammadi.

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**Funding acquisition:** Sareh Mohammadi.

**Investigation:** Sareh Mohammadi, Mohammad Moazeni.

**Methodology:** Soleiman Kheiri.

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**Resources:** Zahra Lorigooini.

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**Validation:** Sareh Mohammadi.

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**Writing—original draft:** All authors.

**Writing—review & editing:** All authors.

### Competing Interests

The authors declare that they have no conflict of interests.

### Ethics Approval

All stages of experimentation were carried out according to the regulations of the Ethics Committee of Shahrekord University of Medical Sciences (Ethics code: IR.SKUMS.REC.1395.117).

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